ELSEVIER

Neuropsychologia 46 (2008) 614–623

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

The human hippocampal formation mediates short-term memory of colour–location associations

Carsten Finke [a], Mischa Braun [a], Florian Ostendorf [a], Thomas-Nicolas Lehmann [b], Karl-Titus Hoffmann [c], Ute Kopp [a], Christoph J. Ploner [a,*]

[a] *Klinik für Neurologie, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany*
[b] *Klinik für Neurochirurgie, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany*
[c] *Klinik für Strahlenheilkunde, Charité – Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany*

Received 14 June 2007; received in revised form 2 October 2007; accepted 10 October 2007
Available online 16 October 2007

Abstract

The medial temporal lobe (MTL) has long been considered essential for declarative long-term memory, whereas the fronto-parietal cortex is generally seen as the anatomical substrate of short-term memory. This traditional dichotomy is questioned by recent studies suggesting a possible role of the MTL for short-term memory. In addition, there is no consensus on a possible specialization of MTL sub-regions for memory of associative information. Here, we investigated short-term memory for single features and feature associations in three humans with post-surgical lesions affecting the right hippocampal formation and in 10 healthy controls. We used three delayed-match-to-sample tasks with two delays (900/5000 ms) and three set sizes (2/4/6 items). Subjects were instructed to remember either colours, locations or colour–location associations. In colour-only and location-only conditions, performance of patients did not differ from controls. By contrast, a significant group difference was found in the association condition at 5000 ms delay. This difference was largely independent of set size, thus suggesting that it cannot be explained by the increased complexity of the association condition. These findings show that the hippocampal formation plays a significant role for short-term memory of simple visuo-spatial associations, and suggest a specialization of MTL sub-regions for associative memory.

Keywords: Associative memory; Hippocampus; Long-term memory; Medial temporal lobe; Relational memory

1. Introduction

About 50 years ago, Scoville and Milner's reports of a memory loss after bilateral resection of the medial temporal lobe (MTL) in patient H.M. have identified this region (i.e. hippocampus, entorhinal cortex, perirhinal cortex and parahippocampal cortex) as a key structure for declarative memory (Scoville, 1954; Scoville & Milner, 1957). Despite a seemingly complete anterograde amnesia, further neuropsychological testing of H.M. revealed that memory for simple visual and verbal material was normal at delays of some seconds (Sidman, Stoddard, & Mohr, 1968; Wickelgren, 1968). In the following, studies of patients with MTL lesions (e.g. Aggleton, Shaw, & Gaffan, 1992; Buffalo, Reber, & Squire, 1998; Holdstock et al., 2000) and studies of primate models of amnesia (e.g. Alvarez, Zola-Morgan, & Squire, 1994; Buckley, Gaffan, & Murray, 1997; Meunier, Bachevalier, Mishkin, & Murray, 1993; Zola-Morgan, Squire, & Amaral, 1989; Zola-Morgan, Squire, Amaral, & Suzuki, 1989) have frequently shown a temporally graded anterograde amnesia, with relatively unimpaired memory of simple visual and spatial information at brief delays. Conversely, the discovery of stimulus-selective neuronal activity in prefrontal cortex during short-term memory tasks (Fuster & Alexander, 1971; Kubota & Niki, 1971) and behavioural deficits seen with prefrontal lesions (e.g. Funahashi, Bruce, & Goldman-Rakic, 1993; Fuster & Alexander, 1970) have fuelled the popular view in which short-term and long-term memory are believed to represent largely distinct memory systems with distinct anatomical substrates.

Recently, the validity of this dichotomy has been questioned (Ranganath & Blumenfeld, 2005). Several studies in human patients have demonstrated significant non-verbal memory

* Corresponding author at: Klinik für Neurologie, Charité – Universitätsmedizin Berlin, Campus Virchow-Klinikum, Augustenburger Platz 1, D-13353 Berlin, Germany. Tel.: +49 30 450 560 666;
fax: +49 30 450 560 901.
E-mail address: christoph.ploner@charite.de (C.J. Ploner).

0028-3932/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2007.10.004

deficits at short delays (e.g. Hannula, Tranel, & Cohen, 2006; Nichols, Kao, Verfaellie, & Gabrieli, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). However, these results were mainly obtained in patients with MTL damage due to global cerebral hypoxia or encephalitis. These disorders rarely produce pure amnesic syndromes (Caine & Watson, 2000; Hokkanen, Salonen, & Launes, 1996; Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004) and the resulting neuropathological changes frequently affect cerebral regions outside the MTL (Auer & Sutherland, 2002; Caine & Watson, 2000; Grubb et al., 2000). Hence, there remains uncertainty about the precise anatomical correlates of memory deficits in these patients (Stark, 2007). In addition, there is an ongoing debate on the degree of specialization of MTL sub-regions for different aspects of declarative memory (see Morris (2007) and Squire, Stark, and Clark (2004) for recent reviews). Current theories of hippocampal function propose a partial segregation of function between regions, with their respective contributions depending on the associations within and between items which have to be remembered (e.g. Brown & Aggleton, 2001; Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Mayes, Montaldi, & Migo, 2007). At present, there is only limited experimental evidence for such distinctions in human patients (Squire et al., 2004). In this context, recent studies of non-verbal short-term memory in patients with MTL lesions of various aetiologies have yielded equivocal results. Some studies found a selective impairment of associative short-term memory with MTL lesions (e.g. Hannula et al., 2006; Olson et al., 2006), whereas others found additional significant deficits in non-associative short-term memory tasks (e.g. Nichols et al., 2006; Owen et al., 1995).

Here, we investigated non-verbal short-term memory in three non-amnesic humans with well-defined post-surgical lesions affecting the right hippocampal formation. It was aimed to provide clear-cut anatomical and behavioural data on a possible role of the MTL for non-verbal short-term memory. A simple delayed matching-to-sample task was employed, where subjects had to remember sets of either colours, locations or colour–location associations for 900 or 5000 ms. These memory delays were chosen to be sufficiently long to be outside the temporal limits of iconic memory (Coltheart, 1980; Sperling, 1960) and sufficiently short to correspond to the delays used in classic primate lesion studies of short-term memory (e.g. Funahashi et al., 1993; Fuster & Alexander, 1970). We hypothesized that any short-term memory impairment in patients should manifest itself with a delay-dependent decrease in performance compared to controls. Our results show that lesions affecting the hippocampal formation yield selective deficits in maintenance of colour–location associations at 5000 ms memory delay, thus suggesting a specialization of MTL sub-regions for associative short-term memory.

2. Materials and methods

2.1. Subjects

The lesion group consisted of three patients (mean age 31 years) who had undergone resection of right temporal lobe structures for the treatment of epilepsy. All patients were well beyond the immediate post-operative period with a minimum of 22 months between resection and testing. All patients were right-handed and normal on neurological examination. All patients were free of additional neurological and psychiatric disorders.

Patient H.N. is a 42-year-old female. Since 1999, she had suffered from recurrent déjà vu-experiences and dream-like states lasting for a few seconds at a frequency of 3–4 per month. After a complex-focal seizure with secondary generalization in March 2004, she was admitted to our hospital. Magnetic resonance imaging (MRI) disclosed a right temporo-mesial lesion that was resected in June 2004. The lesion was histologically classified as a pilomyxoid astrocytoma. After surgery, H.N. experienced no further seizures. H.N. reported no mnestic or other cognitive deficits following resection. During testing, she was medicated with gabapentin 1200 mg/d.

Patient S.W. is a 19-year-old male. In 2000, he started experiencing atonic seizures at a frequency of about 5–6 per month. MRI disclosed a right temporo-mesial lesion. A medication with carbamazepine was initiated and the atonic seizures ceased. During the following years, S.W. reported no seizures and no cognitive impairments. In 2002, an increase of lesion size was seen on MRI and resection of the lesion was decided. Histology revealed a pilocytic astrocytoma. After surgery, S.W. experienced no further seizures and no mnestic or other cognitive impairment. During testing, S.W. was medicated with carbamazepine 300 mg/d.

Patient A.M. is a 32-year-old female. Since 1999, she had suffered from focal seizures with secondary generalization at a frequency of about one per month. A right temporo-mesial lesion was found on MRI. Despite extensive pharmacotherapy, frequency of seizures increased and lesion resection was eventually decided. The resection was performed in 2002 and the lesion was histologically classified as epidermoid. After surgery, the seizures ceased with the exception of a single seizure in 2003. A.M. reported no mnestic or other cognitive deficits following resection. During testing, A.M. was medicated with levetiracetam 2000 mg/d and lamotrigine 200 mg/d.

The control group consisted of 10 healthy adults (four males, range 19–57 years, mean 34.5 years) without any history of neurological or psychiatric disorders. Further demographic and neuropsychological characteristics of patients and controls are listed in Table 1. We found no significant differences between groups in terms of age, years of education, verbal IQ (as assessed by the MWT-B, a German equivalent to the National adult reading test, NART; Lehrl, 2005), non-verbal intelligence and reasoning (as assessed by sub-test no. 3 of LPS, a German equivalent to Raven's Progressive Matrices; Horn, 1983), forward and backward block tapping span, and immediate and delayed copying of the Rey-Osterrieth figure. The experiments were undertaken with the understanding and written consent of each subject. The study was approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki.

2.2. Lesion evaluation

MRI was performed in a 1.5 T scanner (Philips NT, The Netherlands, software release 11.0) with a circular polarized head coil. A three-dimensional gradient echo sequence (TR 15 ms, TE 5.4 ms, flip angle 30°, one excitation, acquisition matrix 256 × 256, field of view 256, slice thickness 1.0 mm) was used to obtain isotropic volume elements of 1 mm^3. The primary slice orientation was sagittal. Coronal reformatting was carried out perpendicular to the anterior commissure/posterior commissure line (AC–PC line), as defined on the mid-sagittal image. Covering the temporal lobe, 80 coronal sections with an individual thickness of 1.0 mm were reconstructed for each subject.

MR images were analyzed using the OsiriX open source imaging software (Rosset, Spadola, & Ratib, 2004). The rostro-caudal position of coronal sections relative to the AC was determined according to a modified Talairach coordinate system, where the section perpendicular to the AC is defined as 0 mm and sections caudal to this reference are assigned positive millimetric values (Mai, Assheuer, & Paxinos, 2004). For demonstration of lesions, we chose four coronal sections which show amygdala, hippocampus, entorhinal cortex, perirhinal cortex, parahippocampal cortex and infero-temporal cortex (Fig. 1). Since there was a significant variation in medio-lateral brain diameter, symmetry of ventric-

Table 1
Characteristics of patients and controls

	Age (years)	Education (years)	MWT-B (verbal IQ)	LPS-3 (*t*-value)	Block tapping span		Rey-Osterrieth figure	
					Forward	Backward	Immediate	Delayed
HF patients								
H.N.	42	12	118	52	9	9	17.0	16.0
S.W.	19	12	97	67	9	8	22.0	22.5
A.M.	32	13	104	55	8	8	20.5	22.5
Mean (S.E.M.)	31.0 (6.7)	12.3 (0.3)	106.3 (6.2)	58.0 (4.6)	8.7 (0.3)	8.3 (0.3)	19.8 (1.5)	20.3 (2.2)
Controls ($n = 10$)								
Mean (S.E.M.)	34.5 (4.8)	14.1 (0.5)	109.0 (3.4)	58.2 (2.2)	9.0 (0.8)	7.9 (0.2)	22.4 (2.0)	22.9 (1.7)
p-Value	0.69	0.05	0.69	0.94	0.57	0.47	0.69	0.57

MWT-B, Mehrfachwahl-Wortschatztest Version B (a German equivalent to the National adult reading test, NART); LPS-3, Leistungsprüfsystem sub-test no. 3, age-corrected score (a German equivalent to Raven's Progressive Matrices). *p*-values from group comparisons with Mann–Whitney tests.

ular spaces (patient A.M.), and AC–PC distance between patients, the positions of these four sections were determined individually by using landmarks rather than by using absolute distances. We first determined the individual position of the most rostral and the most caudal sections (rows A and D in Fig. 1). Then we divided the individual distance between these sections by three in each subject in order to determine the rostro-caudal positions of the other two sections (rows B and C in Fig. 1). Sections shown in row A of Fig. 1 are located 6 mm posterior to the fronto-temporal junction and slightly posterior to the AC. These sections show the amygdala, rostral entorhinal cortex, rostral perirhinal cortex and infero-temporal cortex (Insausti & Amaral, 2004; Insausti, Tuñón, Sobreviela, Insausti, & Gonzalo, 1995; Insausti et al., 1998; Mai et al., 2004). Sections in row D are located at the centre of the lateral geniculate nucleus. These sections show the hippocampus, parahippocampal cortex and infero-temporal cortex (Insausti & Amaral, 2004; Mai et al., 2004). The intermediate sections in rows B and C show the hippocampus, entorhinal cortex and perirhinal cortex (Insausti & Amaral, 2004; Insausti et al., 1995, 1998; Mai et al., 2004). The extent of MTL damage at each of the four levels is summarized in Table 2 for each patient. All three patients had damage to the right amygdala, anterior hippocampus, anterior entorhinal cortex and middle portions of the perirhinal cortex. The infero-temporal cortex, rostral perirhinal cortex, parahippocampal cortex and posterior hippocampus were normal in all patients.

2.3. Stimulus presentation

Subjects were seated in a darkened room in front of a 22 in. computer monitor. The head was positioned on a chinrest to ensure a constant viewing distance of 50 cm to the screen. Visual stimuli were programmed and presented with ERTS software, Version 3.32 (BeriSoft, Germany). All stimulus arrays were presented

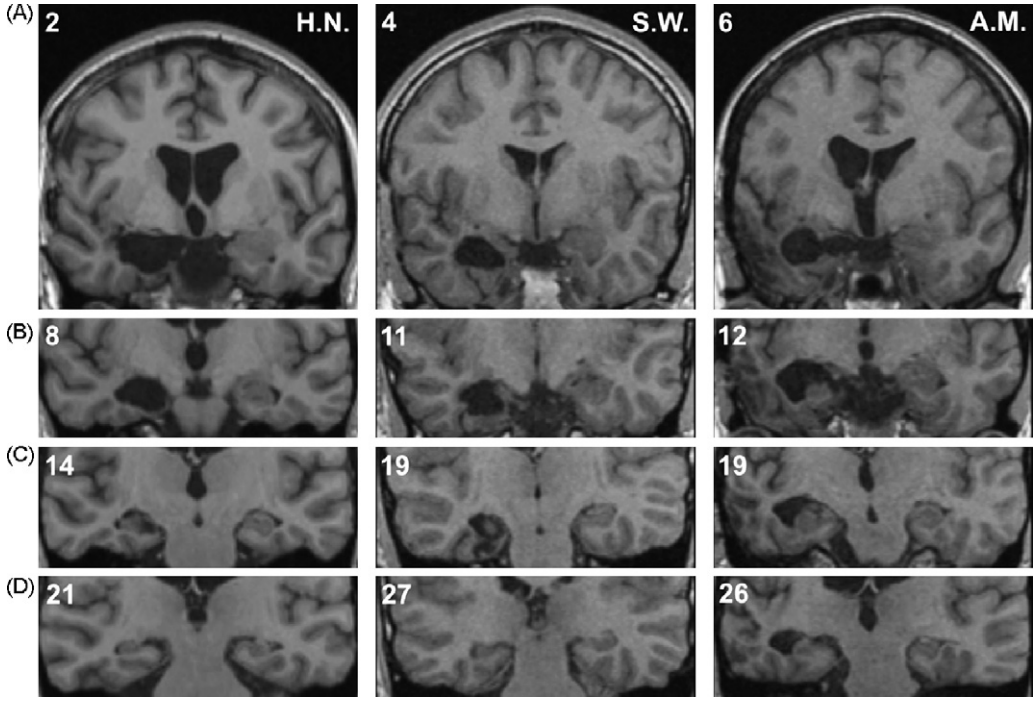

Fig. 1. Magnetic resonance imaging scans of patients H.N., S.W. and A.M. Four coronal sections perpendicular to the anterior commissure/posterior commissure line are arranged from rostral (row A) to caudal (row D). The caudal distance of each section from the anterior commissure is given in mm in the upper left corner of each section. Note correspondence of anatomical structures between patients in single rows. Note damage to right anterior medial temporal lobe structures in all three patients.

Table 2
Individual lesion analysis

	H.N.	S.W.	A.M.
A			
AMY	+	+	+
ERC	+	+	+
PRC	0	0	0
ITC	0	0	0
B			
HIP	+	+	+
ERC	+	+	+
PRC	+	+	+
ITC	0	0	0
C			
HIP	+	+	(+)
ERC	0	+	0
PRC	0	+	0
ITC	0	0	0
D			
HIP	0	0	0
PHC	0	0	0
ITC	0	0	0

Columns represent patients, rows A–D represent the four rostro-caudal levels of patients' magnetic resonance imaging scans shown in Fig. 1. See text for further details. AMY, amygdala; HIP, hippocampus; ERC, entorhinal cortex; PRC, perirhinal cortex; ITC, infero-temporal cortex; +, affected; 0, not affected.

within a central region of the screen, subtending 9.8° × 7.3° of visual angle. Stimuli were small squares, subtending 0.65° × 0.65° of visual angle (mean luminance 23 cd/m^2) on a light grey background (luminance 21 cd/m^2). Stimulus arrays consisted of two, four or six simultaneously presented squares. Manual responses were recorded by two response keys, positioned to the right and left of the column carrying the chinrest. Fixation was monitored at a sampling rate of 240 Hz by using video-oculography (iView Hi-Speed, SMI, Germany) in all patients and in seven controls.

2.4. Paradigms

Subjects were tested with three delayed-match-to-sample (DMS) tasks, testing either memory of colours, locations or colour–location associations (Fig. 2). The general design of the tasks was identical. A trial started with the appearance of a black central fixation dot for 1000 ms followed by the presentation of the sample array for 200 ms. The location of each square in the sample array was pseudo-randomly chosen from 48 possible locations with the minimal distance between two squares being at least 2.0° (centre to centre). Repetition of sample arrays was avoided in each task. The presentation of the sample array was followed by an unfilled memory delay of 900 or 5000 ms, during which subjects continued fixating. After the delay, a test stimulus appeared and subjects indicated by an unspeeded manual key press whether the test stimulus matched one of the stimuli presented in the sample array or not ("match", right index finger, 50% of trials; "non-match", left index finger, 50% of trials). No feedback was given. Test stimuli were presented for a maximum of 2000 ms, with presentation being terminated by the key press. Between trials, the screen was cleared for a variable inter-trial interval of 1000–3000 ms.

2.4.1. Colour task

Subjects were presented sample arrays consisting of coloured squares (Fig. 2, top row). Colours were chosen from a set of nine highly discriminable colours (red, orange, yellow, green, cyan, blue, violet, black, white). Each colour was used only once in a given sample array. After the delay, a coloured test square appeared in the centre of the screen. Subjects indicated whether or not its colour had been presented in the sample array.

2.4.2. Location task

Subjects were presented sample arrays consisting of dark grey squares (Fig. 2, middle row). After the delay, a dark grey test square appeared either at one of the locations occupied by a square in the sample array or at a different location. Subjects indicated whether or not the test square had been presented at a location previously occupied in the sample array.

2.4.3. Association task

As in the colour task, subjects were presented sample arrays consisting of coloured squares (Fig. 2, bottom row). After the delay, a coloured test square was presented at 1 out of 48 possible locations. In match-trials, the test stimulus

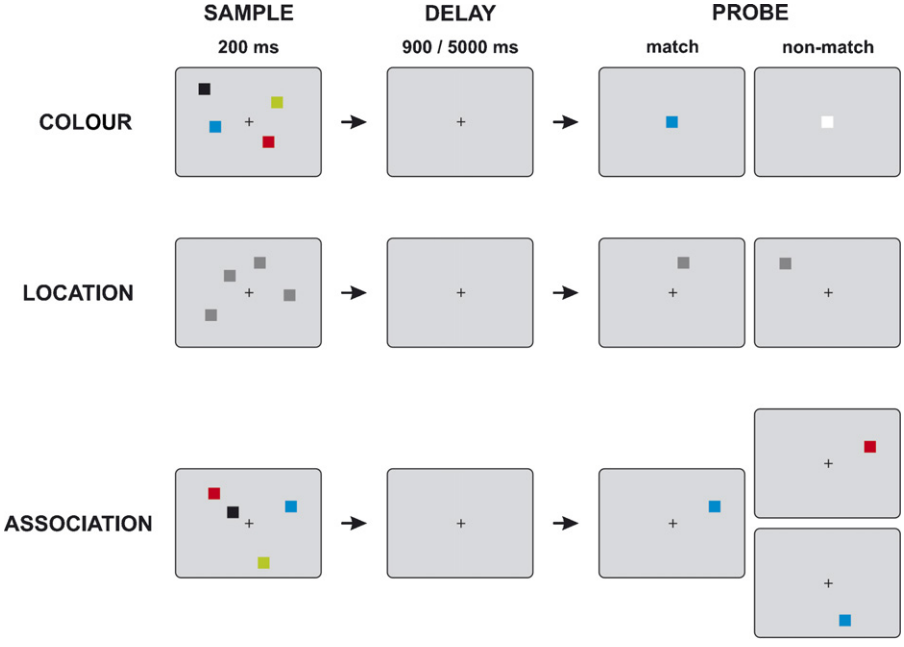

Fig. 2. Schematic of the three delayed-match-to-sample tasks. While fixating on a central fixation cross, subjects were presented an array of two, four or six squares. After a memory delay of 900 or 5000 ms, subjects were presented a single probe stimulus and indicated by a key press whether or not the probe matched one of the sample squares in colour (colour task), location (location task), or colour and location (association task).

Table 3
Individual patients' performance in the three delayed-match-to-sample tasks

	Colour (%)		Location (%)		Association (%)	
	900 ms	5000 ms	900 ms	5000 ms	900 ms	5000 ms
HF patients						
H.N.	83.3	84.0	91.0	86.8	79.9	76.4
S.W.	88.2	83.3	95.1	79.9	90.3	74.3
A.M.	91.7	81.3	83.3	72.2	83.3	73.6
Mean (S.E.M.)	87.7 (2.4)	82.9 (0.8)	89.8 (3.5)	79.6 (4.2)	84.5 (3.1)	74.8 (0.8)
Controls ($n = 10$)						
Mean (S.E.M.)	89.7 (1.2)	86.0 (1.4)	92.2 (1.8)	85.6 (2.0)	88.3 (1.1)	87.3 (0.9)
p-Value	0.57	0.16	0.57	0.22	0.22	<0.007

p-Values from group comparisons with Mann–Whitney tests.

matched one of the squares from the sample array both in colour and location. In non-match-trials, the test stimulus differed either in colour or location from squares presented in the sample array. Subjects indicated whether or not the test square matched a square from the sample array both in colour and location.

2.5. Procedure

Subjects were tested on two consecutive days. The experiment was run in a blocked design with separate administration of the three DMS tasks. On both days, subjects performed all three tasks with the order of the tasks being counterbalanced across subjects and days. Each task consisted of six blocks per day. Subjects started a task with two blocks of set size 2, followed by two blocks of set size 4, and two blocks of set size 6. A single block consisted of 24 trials arranged in pseudo-random order. Each block consisted of an equal number of trials with 900 and 5000 ms delay. In total, subjects performed 288 trials for each task. Subjects were given time to rest between blocks. Breaks of about 45 min. duration were scheduled between tasks to avoid fatigue. Prior to each block with a new set size, subjects performed 12 training trials.

2.6. Data analysis

Patients and controls kept fixation in the majority of trials. Eye movements exceeding 1° during sample array presentation and delay period were rare in both groups (group mean for sample presentation period: patients 3.1% of trials, controls 3.0%; $p = 0.83$; delay period: patients 1.9% of trials, controls 5.9%; $p = 0.18$). For each task, delay and set size, performance was expressed both in percent correct and d' scores (Macmillan & Creelman, 2005). Since we found no differences between results from statistical analyses using either measure of performance, percent correct scores are reported. As the number of subjects permitted no meaningful conclusions on the normality of the data distribution, non-parametric statistical analyses with Wilcoxon-tests, Mann–Whitney-tests and Friedman-ANOVAs were applied throughout (Altman, 1991).

3. Results

Individual results of patients are summarized in Table 3, group results are shown in Fig. 3. In the colour task (Fig. 3), no significant effect of the group factor was found in overall performance (collapsed over delays and set sizes; $p = 0.37$). The effects of delay (performance collapsed over set sizes; $p = 0.003$) and set size (performance collapsed over delays; d.f. = 2; $\chi^2 = 22.6$; $p < 0.001$) were significant, indicating that performance changed with delay and set size. On an average, performance dropped from 89.2% at 900 ms delay to 85.3% at 5000 ms delay and from 98.5% at set size 2 to 76.9% at set size 6. (900 ms; controls: 98.8%, 88.5% and 81.7% for set sizes 2, 4 and 6, respectively; patients: 98.6%, 90.3% and 74.3%; 5000 ms; controls: 98.8%, 85.6% and 73.8%; patients: 96.5%, 77.8% and 74.3%). Similar results were obtained in the location task (Fig. 3). The effect of the group factor was not significant in overall performance ($p = 0.29$), while effects of delay ($p = 0.002$) and set size (d.f. = 2; $\chi^2 = 14.9$; $p = 0.001$) were significant. Average performance dropped from 91.6% at 900 ms delay to 84.2% at 5000 ms delay and from 93.3% at set size 2 to 81.8% at set size 6 (900 ms; controls: 97.3%, 91.9% and 87.3% for set sizes 2, 4 and 6, respectively; patients: 95.1%, 90.3% and 84.0%; 5000 ms; controls:

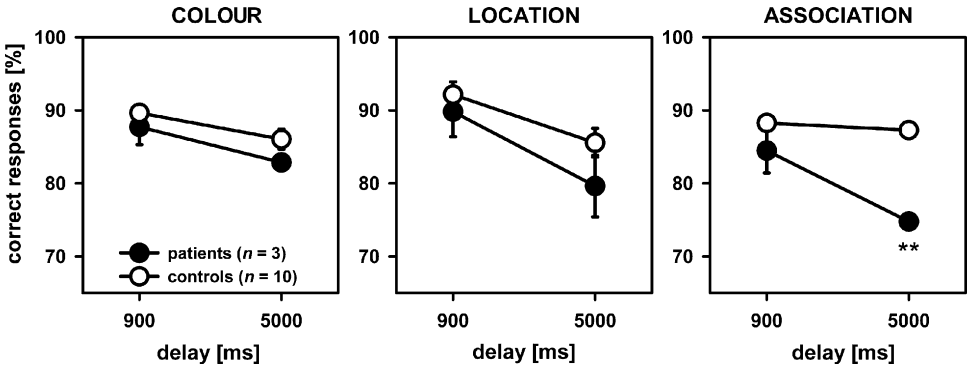

Fig. 3. Average performance of patients (black dots) and controls (white dots) in the three delayed-match-to-sample tasks. Mean correct responses in percent ±S.E.M. collapsed over set sizes, shown as a function of delay. Asterisks indicate significant difference between groups ($p = 0.007$).

90.2%, 87.9% and 78.5%; patients: 88.2%, 78.5% and 72.2%). Taken together, these results therefore suggest that short-term memory of colours and locations was intact in our patients, at least at memory delays of up to 5000 ms and set sizes of up to six to-be-remembered items.

A different picture emerged in the association task (Fig. 3). Here, a significant effect of the group factor was found in overall performance ($p = 0.007$). Comparing the performance of patients and controls, we found a significant difference in task performance between groups at 5000 ms memory delay (collapsed over set sizes; $p = 0.007$) but not at 900 ms ($p = 0.22$), suggesting that patients performed significantly worse compared to controls as the length of the memory delay increased from 900 to 5000 ms. However, it may be argued that this finding may simply be due to increased task difficulty of the association condition compared to the colour and location conditions. We therefore compared the controls' performance between the three tasks and found no significant effect of the factor task at both memory delays (900 ms: d.f. = 2; $\chi^2 = 5.3$; $p = 0.07$; 5000 ms: d.f. = 2; $\chi^2 = 1.9$; $p = 0.39$). Hence, greater task difficulty of the association task appears not to account for our findings. Although evidence from behavioural studies suggests that short-term memory stores integrated chunks of visuo-spatial information (Jiang, Olson, & Chun, 2000), it may further be argued that performance differences between groups at 5000 ms memory delay in the association task may be due to increased memory load (six colours + six locations) compared to the colour and location tasks. Patients may have failed to maintain large set sizes because of a deficit in short-term memory capacity. Additional analyses render this explanation unlikely. Like in the single-feature conditions, there was a significant effect of set size across groups in the association task (performance collapsed over delays; d.f. = 2; $\chi^2 = 26.0$; $p < 0.001$). However, the decrease in performance from set sizes 2 to 6 was very similar in both groups at both memory delays. At 900 ms delay, average performance dropped from set sizes 2 to 6 by 20.1% in patients and by 21.9% in controls ($p = 0.57$). At 5000 ms delay, performance dropped by 22.2% in patients and by 20.8% in controls ($p = 0.81$). With group average performance plotted as a function of set size separately for each delay (Fig. 4), curves are indeed largely running in parallel

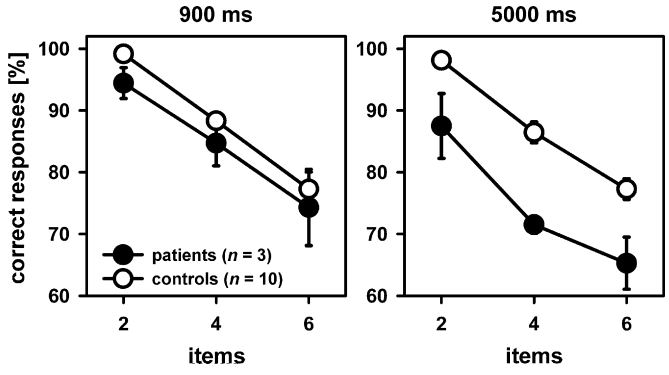

Fig. 4. Average performance of patients (black dots) and controls (white dots) in the association task. Mean correct responses in percent ±S.E.M., shown as a function of set size separately for both delays. Note that the two group average curves at 5000 ms delay are running in parallel.

at both delays (900 ms; controls: 99.2%, 88.3% and 77.3% for set sizes 2, 4 and 6, respectively; patients: 94.4%, 84.7% and 74.3%; 5000 ms; controls: 98.1%, 86.5% and 77.3%; patients: 87.5%, 71.5% and 65.3%). These analyses indicate that patients had a deficit in short-term memory of colour–location associations rather than a deficit in maintaining large set sizes. In the latter case, we would have expected an increasing difference in performance between groups with increasing set size.

4. Discussion

The present study shows that patients with well-defined unilateral lesions of the anterior MTL are significantly impaired in visuo-spatial short-term memory. With the tasks used here, this deficit appears to affect memory of colour–location associations selectively, while short-term representation of colours and locations is normal. In the following, we discuss how these findings relate to the anatomy of the MTL and current theories of hippocampal function.

4.1. Convergence of visual and spatial processing in the MTL

In our patients, the common lesion zone was restricted to the right anterior hippocampal formation, i.e. entorhinal cortex and anterior hippocampus proper, with additional involvement of middle portions of perirhinal cortex. This zone therefore corresponds closely to damage of the right MTL in patient H.M. (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997). Within the affected MTL structures, candidate sub-regions mediating memory of colour–location associations should receive afferents both from regions involved in processing spatial and visual information. For perirhinal cortex, the strongest neocortical inputs are from visual areas TE and TEO in infero-temporal cortex (Suzuki & Amaral, 1994a). Spatial information reaches perirhinal cortex only indirectly via projections from areas TF and TH in the parahippocampal cortex (Suzuki & Amaral, 1994a). The hippocampal formation in turn receives input both from perirhinal and parahippocampal cortex (Suzuki & Amaral, 1994b), with additional direct afferents to its subicular portion and CA1 from neocortical regions involved in visual and spatial cognition (Cavada & Goldman-Rakic, 1989; Goldman-Rakic, Selemon, & Schwartz, 1984; Rockland & Van Hoesen, 1999; Suzuki & Amaral, 1990; Yukie & Iwai, 1988). Although the hippocampal formation appears thus to be well positioned for visuo-spatial associative memory tasks, neurophysiological studies have shown neurons responding to combinations of visual and spatial information not only in the hippocampus but also in perirhinal/parahippocampal cortex (Rolls, Xiang, & Franco, 2005). Consistent with this finding, lesion studies in monkeys found deficient memory for object–location associations both after lesions of the hippocampus (Parkinson, Murray, & Mishkin, 1988) and the parahippocampal cortex (Malkova & Mishkin, 2003). By contrast, results from functional imaging studies in humans investigating memory of object–location and face–location associations have shown mostly right-sided activations of the anterior hippocampal formation, which are

congruent with the hippocampal part of the common lesion zone of our patients (Düzel et al., 2003; Köhler, Danckert, Gati, & Menon, 2005; Mitchell, Johnson, Raye, & D'Esposito, 2000; Piekema, Kessels, Mars, Petersson, & Fernandez, 2006). The apparent parallelism of these latter findings with our results must be interpreted with caution, as processing in the MTL of the comparatively complex visual material in these tasks may be different from processing of the simple colours in our experiment (Sato & Nakamura, 2003). Moreover, disconnection of caudal hippocampal regions remains an alternative explanation for memory deficits after anterior MTL resections (Beason-Held, Rosene, Killiany, & Moss, 1999; Corkin et al., 1997). Therefore, anatomical data support a role of the anterior MTL, in particular the anterior hippocampal formation, for visuo-spatial associative memory, but do not allow to definitely relate the observed deficits to a distinct sub-region within the common lesion zone of our patients.

4.2. Visuo-spatial short-term memory in patients with MTL lesions

How do our findings compare to visual short-term memory deficits in previous human lesion studies of the MTL? The claim that the MTL contributes significantly to visuo-spatial short-term memory is controversial, and unequivocal anatomical evidence for this hypothesis has been lacking in humans (Ranganath & Blumenfeld, 2005). Lesions in numerous studies of human patients either involved structures outside the MTL or were not precisely documented by structural brain imaging (e.g. Nichols et al., 2006; Owen et al., 1995). Another set of studies used patients with hippocampal dysfunction following global cerebral hypoxia (e.g. Hannula et al., 2006; Olson et al., 2006). Transient global hypoxia frequently leads to neuronal damage in the hippocampal formation, and this damage may be selective in some cases (e.g. Rempel-Clower, Zola-Morgan, Squire, & Amaral, 1996; Zola-Morgan, Squire, & Amaral, 1986). The study of the cognitive deficits of these patients has advanced our understanding of human hippocampal function considerably (Stark, 2007). However, in most patients, extra-hippocampal brain regions are also affected, including regions of cerebral cortex, basal ganglia and thalamus, some of which are involved in declarative memory too (Auer & Sutherland, 2002; Caine & Watson, 2000; Grubb et al., 2000). Consequently, isolated amnesic syndromes are rare and amnesia is often associated with variable executive and motor deficits (Caine & Watson, 2000; Lim et al., 2004). In the face of the limited sensitivity of current neuroimaging techniques to subtle neuronal damage, it has thus been stated that the study of amnesic patients after global hypoxia does not necessarily imply the study of selective hippocampal damage, even when the hippocampus is the only affected structure on MRI (Stark, 2007). This objection does not apply to the patients reported here, since they suffered from conditions which were confined to the right MTL, showed no additional cognitive deficits, and maintained fixation during stimulus presentation and memory delay similar to controls. We therefore think that our results provide clear evidence that the MTL significantly contributes to visuo-spatial memory at delays which are commonly considered short-term memory delays.

While the delay-dependency of our patients' deficit in the association task argues against the possibility of a perceptual impairment, the lack of a significant deficit at 900 ms memory delay does not necessarily mean that performance at this delay was entirely intact. It remains possible, that by increasing statistical power with a larger sample of patients, deficits may also emerge at delays as short as 900 ms. Moreover, it appears likely that our findings underestimate the real magnitude of the contribution of the MTL to short-term memory, since our patients' lesions were unilateral, while there is evidence for bilateral processing of visual memory in the human MTL (Hornak, Oxbury, Oxbury, Iversen, & Gaffan, 1997). In addition, the caudal hippocampus, parts of perirhinal cortex and the entire parahippocampal cortex were not included in our patients' lesions, i.e. structures which may also be involved in visuo-spatial associative memory (e.g. Malkova & Mishkin, 2003; Rolls et al., 2005). The incompleteness of the lesions may also explain why copying of the Rey-Osterrieth figure was not significantly impaired in our patients. Previous research suggests that both the right hippocampus and the parahippocampal cortex may contribute to performance in the Rey-Osterrieth complex figure test (Bohbot et al., 1998).

4.3. Associative and non-associative memory in patients with MTL lesions

Considering the connectivity of the MTL, influential theories of hippocampal function propose a partial division of labour between MTL sub-regions (see Squire et al. (2004) and Morris (2007) for recent reviews). A hypothesis central to several of these theories is, that the hippocampal formation is mainly concerned with associative representations, i.e. memory which integrates information from diverse cortical processing streams (e.g. Brown & Aggleton, 2001; Cohen & Eichenbaum, 1993; Eichenbaum & Cohen, 2001; Mayes et al., 2007). In this framework, the representation of non-associative information is believed to depend mainly on the adjacent perirhinal and parahippocampal cortices. While these theories complement the anatomical convergence of multiple distinct afferents through the latter regions into the hippocampal formation (Insausti & Amaral, 2004), human lesion studies have yielded inconsistent results. Hence, a clear functional specialization of the MTL in sub-regions processing either associations or non-associative information has been questioned (Squire et al., 2004). For example, in experiments where memory of single words was contrasted to memory of word pairs or associations between words and imagined scenes, some patients with amnesic syndromes secondary to global cerebral hypoxia scored significantly below controls both for single item memory and associative memory (Gold, Hopkins, & Squire, 2006; Gold, Smith et al., 2006; Stark & Squire, 2003), while in other studies relative sparing of item memory and a clear impairment in certain associative memory tasks was observed (Holdstock et al., 2002; Mayes et al., 2004). For visuo-spatial short-term memory, several studies of patients with unilateral post-surgical lesions

of the MTL and studies of patients with bilateral lesions following global hypoxia or encephalitis found an almost equivalent impairment in memory of visual or spatial items and of associations between them (Owen et al., 1995; Stark, Bayley, & Squire, 2002; Stark & Squire, 2003). By contrast, in two recent series of patients with MTL lesions of mixed aetiology, selective deficits in short-term memory of associations between complex visual and spatial information were found (Hannula et al., 2006; Olson et al., 2006). This finding is in line with the majority of recent functional imaging studies on this matter, which suggest that the hippocampus supports associative processing across domains (see Davachi, 2006 for a recent review). While differences in methodology and task design may explain some of the above-mentioned discrepancies, the strong heterogeneity of the literature further suggests that several interacting factors may influence the contribution of the MTL and its sub-regions to memory of items and associations.

In this context, the results reported here suggest that, at least for delays of up to some seconds, associative and non-associative memory are not equally supported by the anterior MTL. Alternative accounts, e.g. a general deficit in short-term memory capacity revealed in a condition with relatively large set sizes, appear unlikely, as patients showed no differential set size effect in the association task. In addition, performance of normal controls in the association condition was not inferior to performance in the single-feature conditions. Task difficulty does therefore not account for our findings. Rather, our results point to a predominant role of the anterior MTL, possibly the anterior hippocampal formation, for the short-term representation of associations between visual and spatial information. This function appears not to be limited to complex visual material, as has been speculated recently (Hannula et al., 2006), since it manifests itself already with the simple stimulus material of our tasks. However, facing the clear non-associative memory impairments in several previous human lesion studies (see above), it would be premature to infer that this specialization is absolute. It appears possible, that in patients with bilateral selective hippocampal lesions or in a larger sample of patients with unilateral hippocampal lesions, deficits in colour- or location-only conditions emerge which were undetected in the present study. Lastly, it remains to be investigated whether the associative memory deficit of our patients is confined to associations between information of different domains such as colours and locations or extends to other types of associations. Recent research suggests that only the former may critically depend on the hippocampal formation (Mayes et al., 2007).

5. Conclusion

The results of the present study substantiate recent doubts about a strict dichotomy of short-term and long-term memory (Ranganath & Blumenfeld, 2005). In addition, they call for an explanation that reconciles an involvement of the MTL in short-term memory with theories of hippocampal function which postulate an at least partial segregation in the representation of visuo-spatial items and associations in the MTL. Tasks and memory delays similar to those used here have previously been employed in several studies of short-term memory-related neuronal activity in fronto-parietal cortices. Particularly in prefrontal cortex, like in the MTL, there is both segregation and convergence of processing from diverse sensory modalities (Fuster, 1995; Goldman-Rakic, 1988; Miller & Cohen, 2001). For example, single-unit recordings from prefrontal neurons of monkeys performing object–location short-term memory tasks revealed neurons with delay-period activity related either to objects or locations but also a considerable number of neurons engaged in processing of both types of stimuli (Rainer, Asaad, & Miller, 1998; Rao, Rainer, & Miller, 1997). Similarly, functional imaging studies have revealed prefrontal activations with associative short-term memory tasks, which differed from activations in single-feature conditions (e.g. Munk et al., 2002; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000). While our results are consistent with the general claim that representations in short-term memory are distributed across a large-scale network that includes the MTL (Fuster, 1995; Goldman-Rakic, 1988; Miller & Cohen, 2001), the precise respective contributions of the frontal, parietal and medio-temporal nodes of this network are still under debate. The findings in our patients suggest that, within this network, the recruitment of the MTL also depends on the associative nature of to-be-remembered visuo-spatial material.

Acknowledgements

The authors wish to thank Markus Ploner, Bettina Schmitz and the reviewers for helpful comments on the manuscript. Supported by the Deutsche Forschungsgemeinschaft (Grant Pl 248/3-1), the Bundesministerium für Bildung und Forschung (grant 01GW0653), the Sonnenfeld-Stiftung and the Forschungsförderung of the Charité Berlin.

References

Aggleton, J. P., Shaw, C., & Gaffan, E. A. (1992). The performance of postencephalitic amnesic subjects on two behavioural tests of memory: Concurrent discrimination learning and delayed matching-to-sample. *Cortex*, *28*(3), 359–372.

Alvarez, P., Zola-Morgan, S., & Squire, L. R. (1994). The animal model of human amnesia: Long-term memory impaired and short-term memory intact. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(12), 5637–5641.

Altman, D. G. (1991). *Practical statistics for medical research*. London, United Kingdom: Chapman & Hall.

Auer, R. N., & Sutherland, G. R. (2002). Hypoxia and related conditions. In D. Graham & P. Lantos (Eds.), *Greenfield's neuropathology* (pp. 233–280). London: Hodder Arnold.

Beason-Held, L. L., Rosene, D. L., Killiany, R. J., & Moss, M. B. (1999). Hippocampal formation lesions produce memory impairment in the rhesus monkey. *Hippocampus*, *9*(5), 562–574.

Brown, M. W., & Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nature Reviews Neuroscience*, *2*(1), 51–61.

Bohbot, V. D., Kalina, M., Stepankova, K., Spackova, N., Petrides, M., & Nadel, L. (1998). Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. *Neuropsychologia*, *36*(11), 1217–1238.

Buckley, M. J., Gaffan, D., & Murray, E. A. (1997). Functional double dissociation between two inferior temporal cortical areas: Perirhinal cortex

versus middle temporal gyrus. *Journal of Neurophysiology*, *77*(2), 587–598.

Buffalo, E. A., Reber, P. J., & Squire, L. R. (1998). The human perirhinal cortex and recognition memory. *Hippocampus*, *8*(4), 330–339.

Caine, D., & Watson, J. D. (2000). Neuropsychological and neuropathological sequelae of cerebral anoxia: A critical review. *Journal of the International Neuropsychological Society*, *6*(1), 86–99.

Cavada, C., & Goldman-Rakic, P. S. (1989). Posterior parietal cortex in rhesus monkey. I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *The Journal of Comparative Neurology*, *287*(4), 393–421.

Cohen, N. J., & Eichenbaum, H. (1993). *Memory, amnesia and the hippocampal system*. Cambrigde, MA: MIT Press.

Coltheart, M. (1980). Iconic memory and visible persistence. *Perception & Psychophysics*, *27*(3), 183–228.

Corkin, S., Amaral, D. G., Gonzalez, R. G., Johnson, K. A., & Hyman, B. T. (1997). H.M.'s medial temporal lobe lesion: Findings from magnetic resonance imaging. *Journal of Neuroscience*, *17*(10), 3964–3979.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. *Current Opinion in Neurobiology*, *16*(6), 693–700.

Düzel, E., Habib, R., Rotte, M., Guderian, S., Tulving, E., & Heinze, H. J. (2003). Human hippocampal and parahippocampal activity during visual associative recognition memory for spatial and nonspatial stimulus configurations. *Journal of Neuroscience*, *23*(28), 9439–9444.

Eichenbaum, H., & Cohen, N. J. (2001). *From conditioning to conscious recollection: Memory systems of the brain*. Oxford, United Kingdom: Oxford University Press.

Funahashi, S., Bruce, C. J., & Goldman-Rakic, P. S. (1993). Dorsolateral prefrontal lesions and oculomotor delayed-response performance: Evidence for mnemonic "scotomas". *Journal of Neuroscience*, *13*(4), 1479–1497.

Fuster, J. M., & Alexander, G. E. (1970). Delayed response deficit by cryogenic depression of frontal cortex. *Brain Research*, *20*(1), 85–90.

Fuster, J. M., & Alexander, G. E. (1971). Neuron activity related to short-term memory. *Science*, *173*(997), 652–654.

Fuster, J. M. (1995). *Memory in the cerebral cortex*. Cambridge, MA: MIT Press.

Gold, J. J., Hopkins, R. O., & Squire, L. R. (2006). Single-item memory, associative memory, and the human hippocampus. *Learning & Memory*, *13*(5), 644–649.

Gold, J. J., Smith, C. N., Bayley, P. J., Shrager, Y., Brewer, J. B., Stark, C. E., et al. (2006). Item memory, source memory, and the medial temporal lobe: Concordant findings from fMRI and memory-impaired patients. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(24), 9351–9356.

Goldman-Rakic, P. S., Selemon, L. D., & Schwartz, M. L. (1984). Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience*, *12*(3), 719–743.

Goldman-Rakic, P. S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex. *Annual Review of Neuroscience*, *11*, 137–156.

Grubb, N. R., Fox, K. A., Smith, K., Best, J., Blane, A., Ebmeier, K. P., et al. (2000). Memory impairment in out-of-hospital cardiac arrest survivors is associated with global reduction in brain volume, not focal hippocampal injury. *Stroke*, *31*(7), 1509–1514.

Hannula, D. E., Tranel, D., & Cohen, N. J. (2006). The long and the short of it: Relational memory impairments in amnesia, even at short lags. *Journal of Neuroscience*, *26*(32), 8352–8359.

Hokkanen, L., Salonen, O., & Launes, J. (1996). Amnesia in acute herpetic and nonherpetic encephalitis. *Archives of Neurology*, *53*(10), 972–978.

Holdstock, J. S., Mayes, A. R., Cezayirli, E., Isaac, C. L., Aggleton, J. P., & Roberts, N. (2000). A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. *Neuropsychologia*, *38*(4), 410–425.

Holdstock, J. S., Mayes, A. R., Roberts, N., Cezayirli, E., Isaac, C. L., O'Reilly, R. C., et al. (2002). Under what conditions is recognition spared relative to recall after selective hippocampal damage in humans? *Neuropsychologia*, *12*(3), 341–351.

Horn, W. (1983). *Leistungsprüfsystem*. Göttingen, Germany: Hogrefe Verlag.

Hornak, J., Oxbury, S., Oxbury, J., Iversen, S. D., & Gaffan, D. (1997). Hemifield-specific visual recognition memory impairments in patients with unilateral temporal lobe removals. *Neuropsychologia*, *35*(9), 1311–1315.

Insausti, R., Tuñón, T., Sobreviela, T., Insausti, A. M., & Gonzalo, L. M. (1995). The human entorhinal cortex: A cytoarchitectonic analysis. *The Journal of Comparative Neurology*, *355*(2), 171–198.

Insausti, R., Juottonen, K., Soininen, H., Insausti, A. M., Partanen, K., Vainio, P., et al. (1998). MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *American Journal of Neuroradiology*, *19*(4), 659–671.

Insausti, R., & Amaral, D. G. (2004). Hippocampal formation. In G. Paxinos & J. Mai (Eds.), *The human nervous system* (pp. 871–915). Amsterdam, The Netherlands: Elsevier Academic Press.

Jiang, Y., Olson, I. R., & Chun, M. M. (2000). Organization of visual short-term memory. *Journal of Experimental Psychology. Learning, Memory and Cognition*, *26*(3), 683–702.

Köhler, S., Danckert, S., Gati, J. S., & Menon, R. S. (2005). Novelty responses to relational and non-relational information in the hippocampus and the parahippocampal region: A comparison based on event-related fMRI. *Hippocampus*, *15*(6), 763–774.

Kubota, K., & Niki, H. (1971). Prefrontal cortical unit activity and delayed alternation performance in monkeys. *Journal of Neurophysiology*, *34*(3), 337–347.

Lehrl, S. (2005). *Mehrfachwahl-Wortschatz-Intelligenztest*. Göttingen, Germany: Hogrefe Verlag.

Lim, C., Alexander, M. P., LaFleche, G., Schnyer, D. M., & Verfaellie, M. (2004). The neurological and cognitive sequelae of cardiac arrest. *Neurology*, *63*(10), 1774–1778.

Macmillan, N. A., & Creelman, C. D. (2005). *Detection theory*. Mahwah, NJ: Lawrence Erlbaum Associates.

Mai, J., Assheuer, J., & Paxinos, G. (2004). *Atlas of the human brain*. Amsterdam, The Netherlands: Elsevier Academic Press.

Malkova, L., & Mishkin, M. (2003). One-trial memory for object–place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. *Journal of Neuroscience*, *23*(5), 1956–1965.

Mayes, A. R., Holdstock, J. S., Isaac, C. L., Montaldi, D., Grigor, J., Gummer, A., et al. (2004). Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition. *Hippocampus*, *14*(6), 763–784.

Mayes, A., Montaldi, D., & Migo, E. (2007). Associative memory and the medial temporal lobes. *Trends in Cognitive Sciences*, *11*(3), 126–135.

Meunier, M., Bachevalier, J., Mishkin, M., & Murray, E. A. (1993). Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *Journal of Neuroscience*, *13*(12), 5418–5432.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.

Mitchell, K. J., Johnson, M. K., Raye, C. L., & D'Esposito, M. (2000). fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. *Brain Research Cognitive Brain Research*, *10*(1/2), 197–206.

Morris, R. (2007). Theories of hippocampal function. In P. Andersen, R. Morris, D. Amaral, T. Bliss, & J. O'Keefe (Eds.), *The hippocampus book*. Oxford, Uniterd Kingdom: Oxford University Press.

Munk, M. H., Linden, D. E., Muckli, L., Lanfermann, H., Zanella, F. E., Singer, W., et al. (2002). Distributed cortical systems in visual short-term memory revealed by event-related functional magnetic resonance imaging. *Cerebral Cortex*, *12*(8), 866–876.

Nichols, E. A., Kao, Y. C., Verfaellie, M., & Gabrieli, J. D. (2006). Working memory and long-term memory for faces: Evidence from fMRI and global amnesia for involvement of the medial temporal lobes. *Hippocampus*, *16*(7), 604–616.

Olson, I. R., Page, K., Moore, K. S., Chatterjee, A., & Verfaellie, M. (2006). Working memory for associations relies on the medial temporal lobe. *Journal of Neuroscience*, *26*(17), 4596–4601.

Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E., & Robbins, T. W. (1995). Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia*, *33*(1), 1–24.

Parkinson, J. K., Murray, E. A., & Mishkin, M. (1988). A selective mnemonic role for the hippocampus in monkeys: Memory for the location of objects. *Journal of Neuroscience*, *8*(11), 4159–4167.

Piekema, C., Kessels, R. P., Mars, R. B., Petersson, K. M., & Fernandez, G. (2006). The right hippocampus participates in short-term memory maintenance of object–location associations. *Neuroimage*, *33*(1), 374–382.

Prabhakaran, V., Narayanan, K., Zhao, Z., & Gabrieli, J. D. (2000). Integration of diverse information in working memory within the frontal lobe. *Nature Neuroscience*, *3*(1), 85–90.

Rainer, G., Asaad, W. F., & Miller, E. K. (1998). Memory fields of neurons in the primate prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(25), 15008–15013.

Ranganath, C., & Blumenfeld, R. S. (2005). Doubts about double dissociations between short- and long-term memory. *Trends in Cognitive Sciences*, *9*(8), 374–380.

Rao, S. C., Rainer, G., & Miller, E. K. (1997). Integration of what and where in the primate prefrontal cortex. *Science*, *276*(5313), 821–824.

Rempel-Clower, N. L., Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1996). Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. *Journal of Neuroscience*, *16*(16), 5233–5255.

Rockland, K. S., & Van Hoesen, G. W. (1999). Some temporal and parietal cortical connections converge in CA1 of the primate hippocampus. *Cerebral Cortex*, *9*(3), 232–237.

Rolls, E. T., Xiang, J., & Franco, L. (2005). Object, space, and object–space representations in the primate hippocampus. *Journal of Neurophysiology*, *94*(1), 833–844.

Rosset, A., Spadola, L., & Ratib, O. (2004). OsiriX: An open-source software for navigating in multidimensional DICOM images. *Journal of Digital Imaging*, *17*(3), 205–216.

Sato, N., & Nakamura, K. (2003). Visual response properties of neurons in the parahippocampal cortex of monkeys. *Journal of Neurophysiology*, *90*(2), 876–886.

Scoville, W. B. (1954). The limbic lobe in man. *Journal of Neurosurgery*, *11*(1), 64–66.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery and Psychiatry*, *20*(1), 11–21.

Sidman, M., Stoddard, L. T., & Mohr, J. P. (1968). Some additional quantitative observations of immediate memory in a patient with bilateral hippocampal lesions. *Neuropsychologia*, *6*(3), 245–254.

Sperling, G. (1960). The information available in brief visual presentations. *Psychological Monographs: General and Applied*, *74*(11), 1–29.

Squire, L. R., Stark, C. E., & Clark, R. E. (2004). The medial temporal lobe. *Annual Review of Neuroscience*, *27*, 279–306.

Stark, C. E., Bayley, P. J., & Squire, L. R. (2002). Recognition memory for single items and for associations is similarly impaired following damage to the hippocampal region. *Learning & Memory*, *9*(5), 238–242.

Stark, C. E., & Squire, L. R. (2003). Hippocampal damage equally impairs memory for single items and memory for associations. *Hippocampus*, *13*(2), 281–292.

Stark, C. E. (2007). Functional role of the human hippocampus. In P. Andersen, R. Morris, D. Amaral, T. Bliss, & J. O'Keefe (Eds.), *The hippocampus book*. Oxford, United Kingdom: Oxford University Press.

Suzuki, W. A., & Amaral, D. G. (1990). Cortical inputs to the CA1 field of the monkey hippocampus originate from the perirhinal and parahippocampal cortex but not from area TE. *Neuroscience Letters*, *115*(1), 43–48.

Suzuki, W. A., & Amaral, D. G. (1994a). Perirhinal and parahippocampal cortices of the macaque monkey: Cortical afferents. *The Journal of Comparative Neurology*, *350*(4), 497–533.

Suzuki, W. A., & Amaral, D. G. (1994b). Topographic organization of the reciprocal connections between the monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *Journal of Neuroscience*, *14*(3 Pt 2), 1856–1877.

Wickelgren, W. A. (1968). Sparing of short-term memory in an amnesic patient: Implications for strength theory of memory. *Neuropsychologia*, *6*(3), 235–244.

Yukie, M., & Iwai, E. (1988). Direct projections from the ventral TE area of the inferotemporal cortex to hippocampal field CA1 in the monkey. *Neuroscience Letters*, *88*(1), 6–10.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1986). Human amnesia and the medial temporal region: Enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience*, *6*(10), 2950–2967.

Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1989). Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. *Journal of Neuroscience*, *9*(3), 898–913.

Zola-Morgan, S., Squire, L. R., Amaral, D. G., & Suzuki, W. A. (1989). Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *Journal of Neuroscience*, *9*(12), 4355–4370.