Reorganization of associative memory in humans with long-standing hippocampal damage

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Conflicting theories have been advanced to explain why hippocampal lesions affect distinct memory domains and spare others. Recent findings in monkeys suggest that lesion-induced plasticity may contribute to the seeming preservation of some of these domains. We tested this hypothesis by investigating visuo-spatial associative memory in two patient groups with similar surgical lesions to the right medial temporal lobe, but different pre-operative disease courses (benign brain tumours, mean: 1.8 ± 0.6 years, n = 5, age: 28.2 ± 4.0 years; hippocampal sclerosis, mean: 16.8 ± 1.9 years, n = 9, age: 38.9 ± 4.1 years). Compared to controls (n = 14), tumour patients showed a significant delay-dependent deficit in memory of colour-location associations. No such deficit was observed in hippocampal sclerosis patients, which appeared to benefit from a compensatory mechanism that was inefficient in tumour patients. These results indicate that long-standing hippocampal damage can yield significant functional reorganization of the neural substrate underlying memory in the human brain. We suppose that this process accounts for some of the discrepancies between results from previous lesion studies of the human medial temporal lobe.

Keywords: associative memory; short-term memory; medial temporal lobe; hippocampus; plasticity

Abbreviations: ERC = entorhinal cortex; HIP = hippocampus; ITC = inferotemporal cortex; MTL = medial temporal lobe; PHC = parahippocampal cortex; PRC = perirhinal cortex

Introduction

The medial temporal lobe (MTL) has a pivotal role in the formation and retention of new memories. Much of our knowledge on memory functions of the MTL is based on lesion studies starting with patient H.M., who underwent bilateral resection of the MTL for the treatment of epilepsy in 1953 (Scoville, 1954; Scoville and Milner, 1957). However, the MTL is not a homogenous area but consists of anatomically distinct subregions, i.e. hippocampus, entorhinal cortex (ERC), perirhinal cortex (PRC) and parahippocampal cortex (PHC) (Insausti and Amaral, 2004; Amaral and Lavenex, 2007). Based on findings from neuropsychological, neurophysiological and functional imaging studies in humans and monkeys, several dichotomies have been proposed to conceptualize functional differences between the hippocampus and adjacent regions of the MTL (e.g. episodic versus semantic memory, associative versus non-associative memory, spatial versus non-spatial memory, recollection versus familiarity), and between MTL and remote neocortical regions (e.g. perception versus memory, short-term versus long-term memory) (Squire et al., 2004; Eichenbaum et al., 2007; Morris, 2007; Murray et al., 2007). At present, however, none of these theories has received unanimous experimental support in humans.

A major obstacle for establishing a unifying theory of normal MTL function is the lack of an ideal human model of its dysfunction. MTL lesions of various aetiologies, such as hypoxic brain damage, encephalitis, tumours and hippocampal sclerosis, have been used to investigate MTL function in humans. The problem with these approaches is twofold: first, lesions of these aetiologies only rarely yield well-demarcated damage of MTL sub-regions (Stark, 2007). Second, it is unclear whether compensatory mechanisms account for intact memory domains in some of these patients and thus obscure the contributions of MTL...
subregions to cognition in the normal brain. Indeed, discrepant findings of preserved semantic learning with infant to juvenile hippocampal damage (Vargha-Khadem et al., 1997, 2003) and impaired semantic learning with adult hippocampal damage (Reed and Squire, 1998; Manns et al., 2003) point to the possibility of significant brain reorganization after early MTL lesions (De Haan et al., 2006; Morris, 2007). Recent experimental work in monkeys has moreover demonstrated substantial functional recovery following neonatal lesions of the hippocampus (Banta et al., 2006; Lavenex et al., 2007b). However, there is currently no direct evidence of significant compensation for MTL damage in humans.

Here, we investigated a possible reorganization of the neural substrate underlying associative memory in two groups of human patients with surgical lesions to the right MTL. Both groups underwent comparable resections of MTL structures, albeit for distinct underlying aetiologies with different preoperative disease courses. The first group consisted of patients treated for benign brain tumour; the second group was treated for hippocampal sclerosis. Patients and controls were tested with three delayed match-to-sample (DMS) tasks requiring memory either of colours, locations or colour–location associations for 900 or 5000 ms. Contrary to the traditional view, which generally relates memory at delays of some seconds to regions outside the hippocampus, recent studies have shown that visuo-spatial associative memory tasks can be particularly sensitive to hippocampal dysfunction, even at delays that are commonly considered to tap short-term memory (Hannula et al., 2006; Olson et al., 2006; Hartley et al., 2007; Finke et al., 2008). Congruent with these findings, brain tumour patients showed a significant delay-dependent deficit in memory of colour–location associations. In contrast, patients with hippocampal sclerosis showed no such impairment. These results suggest that long-standing hippocampal damage can lead to functionally relevant reorganization of the neural substrate underlying associative memory in the human brain.

### Methods

#### Subjects

Patients were recruited from the Department of Neurosurgery at the Charité—Universitätsmedizin Berlin, Germany (Table 1). They had undergone resection of right temporal lobe structures for the treatment of epilepsy caused either by a benign brain tumour in the MTL (two females, three males, age 28.2 ± 4.0 years) or by hippocampal sclerosis (five females, four males, age 38.9 ± 4.1 years). Histopathology was independently determined by two neuropathologists, who agreed on the diagnosis in each case. Postoperatively, seizures had ceased in all patients and they were back in their social and professional lives. All patients were right-handed and normal on neurological examination. All patients were free of additional neurological or psychiatric disorders. By the time of testing, all patients received anticonvulsant medication (see Supplementary Table 1).

The control group consisted of 14 healthy subjects (eight females, six males, age 33.2 ± 3.5 years) without any history of neurological or psychiatric disorders. There were no significant differences between controls and the two patient groups in terms of age (Kruskal–Wallis test, d.f. = 2, \( \chi^2 = 3.8, P = 0.15 \)) and years of education (tumour patients 13.4 ± 0.9 years, hippocampal sclerosis patients 14.1 ± 0.7 years, controls 15.2 ± 0.6 years; d.f. = 2, \( \chi^2 = 3.8, P = 0.15 \)). In all subjects, verbal intelligence was assessed by the MWT-B, a German equivalent to the National Adult Reading Test (Lehrl, 2005). No significant difference of verbal IQ was found.

### Table 1 Patient data and individual lesion extents

<table>
<thead>
<tr>
<th>Tumour patients</th>
<th>Age (years)</th>
<th>Preoperative epilepsy (years)</th>
<th>Postoperative time (months)</th>
<th>Neuropathology</th>
<th>Lesion extent</th>
<th>HIP</th>
<th>ERC</th>
<th>PRC</th>
<th>PHC</th>
<th>ITC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.M.</td>
<td>32</td>
<td>3</td>
<td>44</td>
<td>Epidermoid tumour</td>
<td>+ + + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F.P.</td>
<td>24</td>
<td>1</td>
<td>5</td>
<td>Neuroepithelial tumour</td>
<td>+ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H.N.</td>
<td>42</td>
<td>&lt;1</td>
<td>22</td>
<td>Pilomyxoid astrocytoma</td>
<td>+ + + + + + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S.D.</td>
<td>24</td>
<td>3</td>
<td>56</td>
<td>Pigmented astrocytoma</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S.W.</td>
<td>19</td>
<td>2</td>
<td>47</td>
<td>Pilocytic astrocytoma</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>28.2 (4.0)</td>
<td>1.8 (0.6)</td>
<td>34.8 (9.3)</td>
<td>Epidermoid tumour</td>
<td>+ + + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sclerosis patients</th>
<th>Age (years)</th>
<th>Preoperative epilepsy (years)</th>
<th>Postoperative time (months)</th>
<th>Neuropathology</th>
<th>Lesion extent</th>
<th>HIP</th>
<th>ERC</th>
<th>PRC</th>
<th>PHC</th>
<th>ITC</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.R.</td>
<td>29</td>
<td>18</td>
<td>36</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C.N.</td>
<td>48</td>
<td>18</td>
<td>3</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C.S.</td>
<td>25</td>
<td>9</td>
<td>8</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>E.R.</td>
<td>45</td>
<td>10</td>
<td>66</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M.O.</td>
<td>35</td>
<td>17</td>
<td>6</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M.I.</td>
<td>27</td>
<td>11</td>
<td>18</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N.W.</td>
<td>30</td>
<td>20</td>
<td>69</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R.W.</td>
<td>54</td>
<td>24</td>
<td>36</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V.R.</td>
<td>57</td>
<td>24</td>
<td>10</td>
<td>Hippocampal sclerosis</td>
<td>++ ++ ++ + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>38.9 (4.1)</td>
<td>16.8 (1.9)</td>
<td>28.0 (8.5)</td>
<td>Epidermoid tumour</td>
<td>+ + + + +</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**P-value:** 0.08, 0.001, 0.61

HIP = hippocampus; ‘0’ indicates an unaffected sub region, ‘+’ a rostro-caudal lesion extent of ≤ 20 mm, ‘++’ ≤ 40 mm, and ‘+++’ >40 mm. 

*P*-values from group comparisons with Mann–Whitney tests.
between groups (tumour patients 108.6 ± 5.3, hippocampal sclerosis patients 107.8 ± 3.6, controls 113.4 ± 3.8; d.f. = 2, \( \chi^2 = 0.7, P = 0.69 \)). Non-verbal intelligence was assessed by sub-test no. 3 of LPS, a German equivalent to Raven’s Progressive Matrices (Horn, 1983). Again, no significant differences in LPS-scores (t-values) were found between groups (tumour patients 59.6 ± 3.5, hippocampal sclerosis patients 58.2 ± 2.4, controls 60.5 ± 1.9; d.f. = 2, \( \chi^2 = 0.3, P = 0.85 \)). Informed consent was obtained from each subject before participation in the study, which was approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki.

**Lesion evaluation**

In patients, structural magnetic resonance imaging (MRI) was performed with a three-dimensional gradient echo sequence to obtain isotropic volume elements of 1 mm\(^3\). Covering the temporal lobe, 80 coronal sections were perpendicular to the anterior commissure/posterior commissure line (AC–PC line) with an individual thickness of 1.0 mm were reconstructed. Individual lesion extent was then determined from rostral to caudal sections by using landmarks proposed by Insausti *et al.* (1995, 1998), Insausti and Amaral (2004) and derived from Mai *et al.* (2004). Lesions were rated independently by two neurologists with extensive experience in reconstruction of cerebral lesions. During anatomical analysis, both raters were blind to the aetiology of the lesions. Extrapolating anatomical data from monkeys (Suzuki and Amaral, 1994), we assumed that on caudal sections the ITC borders the PHC laterally.

**Hippocampus**

Since the right anterior hippocampus had been removed in all patients, the rostral limit of the hippocampus was determined in the intact left MTL. Its identification was guided by the rostral end of the temporal horn of the lateral ventricle, which generally coincides with the rostral limit of the hippocampal head. The posterior limit of the hippocampus was not determined, as lesions never extended caudally beyond the hippocampus.

**Entorhinal cortex**

The ERC was located in the rostral parahippocampal gyrus, beginning 2 mm caudal of the first section showing the fronto-temporal junction. The caudal limit of the ERC was located anterior to the rostral pole of the lateral geniculate nucleus. Medially, the transition from ERC to the anterior hippocampus was not determined, as there was damage to both structures in all patients.

**Perirhinal cortex**

The PRC covers much of the rostral collateral sulcus. It borders the ERC rostrally, laterally and with a narrow strip of cortex caudally. Its rostral limit coincides with the rostral end of the collateral sulcus. The caudal limit of the PRC coincides with the rostral pole of the lateral geniculate nucleus. Medially, the transition from PRC to ERC was located in the medial bank of the collateral sulcus.

**Parahippocampal cortex**

The PHC covers the caudal parahippocampal gyrus. Its rostral limit was determined on the first section showing the lateral geniculate nucleus. The posterior limit of the PHC was not determined, as lesions never extended caudally beyond the PHC.

**Inferotemporal cortex**

The ITC borders the cortices of the MTL laterally. Its rostral limit is marked by the most rostral portions of the inferior and superior temporal sulci, about 8–10 mm anterior of the PRC. Laterally, the transition between the PRC and ITC occurs in the lateral edge of the collateral sulcus. Since there is no clear definition of the caudal borders of the ITC, its caudal limit could not be determined with certainty. Extrapolating anatomical data from monkeys (Suzuki and Amaral, 1994), we assumed that on caudal sections the ITC borders the PHC laterally.

**Stimulus presentation**

Stimuli were programmed and presented with ERTS software, version 3.32 (BeriSoft, Germany). Subjects were seated in a darkened room at a fixed distance of 50 cm to a 22-in. computer monitor. Stimulus arrays were presented in the 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. The location of each square in the sample array was pseudo-randomly chosen from 48 possible locations with a minimal distance of 2.0° between the centres of squares. Repetition of sample arrays was avoided. Manual responses were recorded by two response keys. Fixation maintenance was monitored at a sampling frequency of 240 Hz by using high-speed video-octolography (View Hi-Speed, SMI, Germany) in most subjects. Due to corrected refraction anomalies, fixation control could not be performed in 1 out of 5 tumour patients (20%), 2 out of 9 hippocampal sclerosis patients (22%) and 3 out of 14 controls (21%).

**Paradigms and procedure**

Subjects were tested with three DMS tasks, requiring short-term memory either of colours, locations or colour–location associations (Fig. 1) (Finke *et al.*, 2008). While subjects fixated on a small central dot, a sample array was presented for 200 ms. After an unfilled memory delay of unpredictable length (900 or 5000 ms), the probe stimulus appeared for up to 2000 ms. Subjects indicated by an unspeeded manual key-press whether this probe stimulus matched one of the sample squares in colour (colour task, Fig. 1A), location (location task, Fig. 1B) or colour and location (association task, Fig. 1C). In the colour and association tasks, stimuli were red, orange, yellow, green, cyan, blue, violet, black or white. Each colour was used only once in a given sample array. In the location task, all stimuli were dark grey. The experiment was run in a blocked design on two consecutive days in a counter-balanced order of 18 blocks per day. The different tasks were administered in separate blocks of 24 trials in pseudo-random distribution with an equal number of short/long delays and match/non-match trials. In total, subjects performed 288 trials for...
enlightened both in percent correct and \( P = 0.50 \). For each task and memory delay, performance was of the sample stimuli in colour (indicated by a key press whether or not the probe matched one (900 or 5000 ms), a single probe stimulus appeared and subjects six squares. After a memory delay of unpredictable length fixation cross, subjects were presented an array of two, four or location task; \( P_{2} = 1.4, P = 0.23 \). Although performance appeared to decline slightly more rapidly in tumour patients, the two patient groups did not differ significantly (900 ms: \( P = 0.36, 5000 \text{ms: } P = 0.36 \)). Patients were doing worse than controls (900 ms: \( P = 0.02, 5000 \text{ms: } P = 0.004; \text{Fig. 3B} \)), while no significant differences in \( \Delta \text{ delay} \) were found across groups (controls: \(-4.0\%\), tumours: \(-4.4\%\), hippocampal sclerosis: \(-6.6\%\); d.f. = 2, \( \chi^2 = 2.9, P = 0.23 \)). A similar pattern of results was obtained in the location task. The overall performance differed between groups (d.f. = 2, \( \chi^2 = 7.5, P = 0.02 \)). Although performance appeared to decline slightly more rapidly in tumour patients, the two patient groups did not differ significantly (900 ms: \( P = 0.36, 5000 \text{ms: } P = 0.36 \)). Patients were doing worse than controls (900 ms: \( P = 0.02, 5000 \text{ms: } P = 0.004; \text{Fig. 3B} \)), while no significant differences in \( \Delta \text{ delay} \) were found across groups (controls: \(-6.6\%\), tumours: \(-12.8\%\), hippocampal sclerosis: \(-6.9\%\); d.f. = 2, \( \chi^2 = 4.5, P = 0.11 \)). These results therefore suggest the existence of a delay-independent performance deficit of similar magnitude in both patient groups. However, compared with controls, both patient groups did not show a disproportionate performance decrease across the delays tested.

A different picture emerged in the association task. As in the first two tasks, the overall performance differed between groups (d.f. = 2, \( \chi^2 = 14.5, P = 0.001 \)) with the controls showed partial resections of the right MTL with damage of the amygdala, anterior hippocampus, ERC and parts of PRC in all patients (Fig. 2, Table 1). Several patients showed additional involvement of the PHC and inferotemporal cortex (ITC) (Fig. 2, Table 1).

Although speed was not emphasized in instructions, we first looked at general differences of reaction times (RTs) between groups. Average RTs for correct responses were 964 ms in tumour patients, 1049 ms in hippocampal sclerosis patients and 977 ms in controls. For none of the investigated memory tasks, significant differences of RTs between groups were found (collapsed over delays; Kruskal–Wallis test, d.f. = 2, \( \chi^2 = 2.5, P \geq 0.29 \)). For analysis of response accuracy in the memory tasks, absolute performance differences between controls and patient groups were analysed. In order to identify possible memory deficits, we then determined individual differences in accuracy between 900 and 5000 ms delay (’\( \Delta \text{ delay} \)). Performance decreases were assigned negative values. As memory builds and maintains representations over time, it was reasoned that deficits of memory should be time dependent, i.e. worsen significantly as the delay proceeds from 900 to 5000 ms (Smith and Milner, 1989; Butters et al., 1995; Wixted, 2004; Jonides et al., 2008).

Group results from the three memory tasks are summarized in Fig. 3; individual results are summarized in Table 2 of the Supplementary data. In the colour task, the overall performance differed significantly between groups (collapsed over delays; Kruskal–Wallis test, d.f. = 2, \( \chi^2 = 11.3, P = 0.004 \)). Both patient groups performed inferior to controls at delays of 900 and 5000 ms (Fig. 3A). Post hoc comparisons showed no significant difference between both patient groups (900 ms: \( P = 0.80, 5000 \text{ms: } P = 0.80 \)) but confirmed a difference between patients and controls at both delays (900 ms: \( P = 0.008, 5000 \text{ms: } P < 0.001 \). There was no significant difference in \( \Delta \text{ delay} \) between groups (controls: \(-4.0\%\), tumours: \(-4.4\%\), hippocampal sclerosis: \(-6.6\%\); d.f. = 2, \( \chi^2 = 2.9, P = 0.23 \)). A similar pattern of results was obtained in the location task. The overall performance differed between groups (d.f. = 2, \( \chi^2 = 7.5, P = 0.02 \)). Although performance appeared to decline slightly more rapidly in tumour patients, the two patient groups did not differ significantly (900 ms: \( P = 0.36, 5000 \text{ms: } P = 0.36 \)). Patients were doing worse than controls (900 ms: \( P = 0.02, 5000 \text{ms: } P = 0.004; \text{Fig. 3B} \)), while no significant differences in \( \Delta \text{ delay} \) were found across groups (controls: \(-6.6\%\), tumours: \(-12.8\%\), hippocampal sclerosis: \(-6.9\%\); d.f. = 2, \( \chi^2 = 4.5, P = 0.11 \)). These results therefore suggest the existence of a delay-independent performance deficit of similar magnitude in both patient groups. However, compared with controls, both patient groups did not show a disproportionate performance decrease across the delays tested.

A different picture emerged in the association task. As in the first two tasks, the overall performance differed between groups (d.f. = 2, \( \chi^2 = 14.5, P = 0.001 \)) with the controls.

![Fig. 1 Schematic of the three DMS tasks. (A) colour task; (B) location task; (C) association task. While fixating on a central fixation cross, subjects were presented an array of two, four or six squares. After a memory delay of unpredictable length (900 or 5000 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 colour (A), location (B) or colour and location (C).](image-url)
doing better than both patient groups (900 ms; tumours: $P < 0.03$, hippocampal sclerosis: $P = 0.05$; 5000 ms; tumours: $P < 0.001$, hippocampal sclerosis: $P = 0.005$). However, the three performance curves separated clearly at 5000 ms delay (Fig. 3C). As expected from previous studies (Hannula et al., 2006; Olson et al., 2006; Finke et al., 2008), tumour patients showed a marked decline in performance across delays, indicating a profound impairment in memory of non-verbal associative information. In contrast, this deficit was not observed in hippocampal sclerosis patients, whose performance curves ran largely in parallel to controls. A direct statistical comparison of tumour and hippocampal sclerosis patients yielded no difference at 900 ms ($P = 0.70$), but a highly significant performance difference at 5000 ms delay ($P = 0.007$). In addition, and contrary to the first two tasks, $\Delta$ delay differed markedly across groups (controls: 0.4%, hippocampal sclerosis: $-2.5\%$, tumours: $-10.7\%$; d.f. = 2, $\chi^2 = 10.3$, $P = 0.006$), with significant differences between both patient groups ($P = 0.01$), between tumour patients and controls ($P = 0.001$), but not between hippocampal sclerosis patients and controls ($P = 0.18$). This is particularly remarkable, as all patients had undergone similar surgical resections of the right MTL and the resulting lesions tended to be even larger in the hippocampal sclerosis group (Table 1). Facing the high degree of lesion overlap between groups, these findings therefore suggest that visuo-spatial associative memory in tumour patients relied on the right MTL, whereas this function was effectively supported by regions outside the right MTL in hippocampal sclerosis patients.

Irrespective of the aetiology- and delay-dependent impairment in the association task, average performance of both patient groups was inferior to controls in all three tasks at both delays (Fig. 3). A similar deficit has repeatedly

Fig. 2 Example lesions from two subjects. Magnetic resonance imaging scans from patient F.P. (resected benign brain tumour) and patient M.T. (resected hippocampal sclerosis). Four coronal sections perpendicular to the anterior commissure–posterior commissure line are arranged from rostral (A) to caudal (D); (A) scan at the level of the amygdala, entorhinal cortex, perirhinal cortex and inferotemporal cortex; (B) scan at the level of the anterior hippocampus, entorhinal cortex, perirhinal cortex and inferotemporal cortex; (C) scan at the level of the middle portion of the hippocampus, entorhinal cortex, perirhinal cortex and inferotemporal cortex; (D) scan at the level of the posterior hippocampus, parahippocampal cortex and inferotemporal cortex. Note the damage to right amygdala, anterior and middle hippocampus, entorhinal cortex and perirhinal cortex in both patients. The posterior hippocampus, parahippocampal cortex and inferotemporal cortex are spared in patient F.P. and affected in patient M.T.
been reported in patients with unilateral MTL lesions (e.g. Owen et al., 1995; Piekema et al., 2007) and implies the possibility of an additional performance deficit associated with the removal of extra-hippocampal temporal lobe structures. Since our stimulus material was neither complex nor characterized by a high degree of feature ambiguity, a perceptual deficit associated with PRC damage is unlikely to account for this delay-independent impairment (Lee et al., 2005; Murray et al., 2007). We therefore further analysed individual performance in colour and location tasks at 900 ms delay. These task conditions are neither confounded by the aetiology-dependent impairment in the association task nor by memory processes operating from 900 to 5000 ms delay. To investigate the neural substrates of the delay-independent deficits, we identified those patients who performed worst in these two tasks (below two standard deviations of the control mean; patients S.D., V.R., R.W. and C.N.; colour: $P = 0.01$, location: $P = 0.02$, difference with controls). All four patients had comparatively large lesions with damage to ITC and PHC. Then, we analysed performance of two groups of patients with intact ITC and PHC, respectively. Patients with intact ITC (patients H.N., A.M., S.W. and F.P.) and intact PHC (patients H.N., A.M., S.W., F.P., C.S. and M.O.) did not perform differently from controls (ITC, colour: $P = 0.16$, location: $P = 0.23$; PHC, colour: $P = 0.09$, location: $P = 0.24$). Since in all patients with lesions of the PHC there was also significant damage to the ITC, it is not possible to further relate the delay-independent performance deficits to a distinct sub-region of the temporal lobe. However, lesion studies and single-neuron recordings have implicated both the ITC and PHC in processing of simple visual and spatial information (Heywood et al., 1988; Huxlin et al., 2000; Sato and Nakamura, 2003). We therefore speculate that extra-hippocampal lesions may have contributed to the observed aetiology- and delay-independent performance deficits.

**Discussion**

The present study shows that memory deficits in patients with surgical lesions of the MTL critically depend on the preoperative disease course. Our findings further suggest that long-standing hippocampal damage induces significant reorganization of the neural substrate underlying memory in the human brain. These results have implications for the interpretation of behavioural studies in humans with lesions of the MTL.

In the patients investigated here, surgical treatment and time since resection were similar. Different preoperative disease courses are therefore the likeliest explanation for different short-term memory performance between groups. Theoretically, in hippocampal sclerosis patients, the long duration of preoperative symptoms may have allowed for functional reorganization that had not yet developed in brain tumour patients. Alternatively, recovery from hippocampal damage in this group may have occurred because onset of hippocampal pathology fell within a period of postnatal maturation that allows for compensatory processes, which may be less efficient in the adult brain. This hypothesis is supported by current theories of temporal lobe epilepsy with hippocampal sclerosis, which postulate a combination of an early incident, followed by a latent period and the ultimate development of epilepsy in the majority of these patients (Baulac et al., 2004; Sadler, 2006; Walker et al., 2007). When the onset of seizures is taken as the point in time at which significant pathology must have definitely been present in the MTL, it is however not sure which period of postnatal brain development our patients’ initial lesions can be dated back to. Average age at seizure onset in our patients with hippocampal sclerosis was 19.6 years and reliable information about perinatal incidents or febrile convulsions during childhood was not available. Since it is likely that hippocampal pathology had antedated seizure onset by several years, our data contribute little to the definition of a critical period for adaptive changes to

![Fig. 3 Group results. Average performance of controls (white circles), tumour patients (grey circles) and hippocampal sclerosis patients (black circles) in the three DMS tasks. Mean correct responses in percent ± SEM, shown as function of delay.](image-url)
diseases affecting the MTL. Moreover, early age at injury and longer duration since initial lesion are no mutually exclusive explanations for the lack of memory impairment after resection of longstanding hippocampal pathology. Recent findings in monkeys however suggest that the age at injury represents a decisive factor. When tested with a spatial relational memory task sensitive to hippocampal dysfunction, monkeys with hippocampal lesions acquired at 6–9 years of age were impaired, whereas monkeys with neonatal hippocampal lesions performed normally (Banta Lavenex et al., 2006; Lavenex et al., 2007b). The post-lesion delays were actually shorter in the group with neonatal lesions, thus suggesting the existence of a postnatal time window during which memory functions may be allocated to extrahippocampal brain regions that normally do not sub-serve this function (Lavenex et al., 2007b). Although there are only limited data on the time-course of the development of the primate hippocampus (De Haan et al., 2006; Lavenex et al., 2007a), this hypothesis appears to be an attractive explanation for the observed performance differences in our study and suggest that patients with brain tumours were not able to overcome their mnemonic deficits, because by the time of their initial hippocampal lesion the critical developmental period had passed.

From our findings it may further be concluded that cognitive deficits in patients with lesions acquired during hippocampal development may allow for limited inferences on hippocampal function in the adult brain. For example, the pattern of memory deficits in patients with developmental amnesia, a disorder acquired during infancy to puberty and characterized by impaired episodic memory with preserved semantic memory, may be interpreted as reflecting a functional dissociation between these types of memory with only the former depending on the hippocampus and the latter on adjacent neocortical regions (Vargha-Khadem et al., 1997, 2003). This syndrome is however at odds with reports from patients with hippocampal damage sustained in adulthood, in which these types of memory were found to be equally affected (Reed and Squire, 1998; Manns et al., 2003; but see Verfaellie et al., 2000; McKenna and Gerhand, 2002). An alternative explanation therefore suggests that in cases of early hippocampal injury, semantic but not episodic memory functions can increasingly be supported by extrahippocampal cortex (Vargha-Khadem et al., 2003; De Haan et al., 2006). Electrophysiological and imaging studies in a case of developmental amnesia (‘Jon’) have pointed to the existence of corresponding adaptive processes (Düzel et al., 2001; Maguire et al., 2001). The findings in our study provide behavioural evidence for such reorganization processes and may thus offer a way to reconcile seemingly inconsistent findings of preserved and affected memory domains in early-onset and late-onset cases of amnesia (De Haan et al., 2006).

The observation of significant compensation for hippocampal damage also prompts a reconsideration of inferences from classic neuropsychological findings, which gave reason for the popular view that the MTL is mainly involved in long-term memory. Normal performance of the famous patient H.M. in several short-term memory tasks (Sidman et al., 1968; Wickelgren, 1968) as well as the temporally graded amnesia observed in numerous subsequent lesion studies (Aggleton et al., 1992; Bufalfo et al., 1998; Holdstock et al., 2000) have frequently been taken as evidence against a significant contribution of the hippocampus to short-term memory (Squire et al., 2004). Recent results from imaging and behavioural studies in humans have however challenged this traditional short-/long-term memory dichotomy (Ranganath and Blumenfeld, 2005; Jonides et al., 2008). In direct support of the hypothesis that short- and long-term memory are not architecturally separable systems, patients with adult hippocampal damage have repeatedly shown profound deficits in tasks requiring associative memory at delays of some seconds (Hannula et al., 2006; Olson et al., 2006; Hartley et al., 2007; Finke et al., 2008). On a first glance, these findings seem to contradict results from a study with short-term memory tasks very similar to those used here, where patients with resected hippocampal sclerosis only showed minor impairments (Piekema et al., 2007). Similar contradictions have been reported for a classic test of object-location memory, where patients with selective hippocampal resections for the treatment of epilepsy with hippocampal sclerosis performed near to normal (Smith and Milner, 1989), and patients with post-anoxic selective hippocampal lesions sustained in adulthood were severely impaired (Cave and Squire, 1991). Thus, facing H.M.’s long preoperative disease course and the significant reduction in seizure frequency after hippocampal removal (Corkin, 1984, 2002), it appears possible that the temporal pattern of memory deficits in H.M. and at least some of the studies in patients with long-standing hippocampal damage was modified by compensatory processes similar to those observed in our study. This interpretation does not exclude the possibility that the temporal properties of hippocampus-dependent memory deficits interact with the type of information that has to be remembered (Kesner and Hopkins, 2006). Simple, non-associative information like the colours and locations in our experiments may still be maintained across delays of some seconds even in patients with uncompensated hippocampal dysfunction and impaired associative short-term memory. Conversely, it appears possible that distinct stimulus configurations may reveal memory deficits at delays much shorter than 5000 ms in such patients. This speculation is supported by the observation of perceptual impairments for complex visuo-spatial material in patients with adult hippocampal lesions (Lee et al., 2005; Murray et al., 2007). Although it must further be conceded that the pattern of performance deficits in our patients may be different at delays shorter than 900 ms or longer than 5000 ms, it is obvious from our findings that temporal criteria are not sufficient to define the respective contributions of hippocampal and extra-hippocampal regions to
memory (Ranganath and Blumenfeld, 2005; Jonides et al., 2008). The performance differences between our two patient groups rather suggest that reorganization of the neural substrates of memory partly accounts for the seeming preservation of short-term memory in classic human lesion studies of the MTL.

The deficient short-term memory for colour–location associations in our patients with resected brain tumours is in line with theories that postulate a relative specialization of the hippocampal formation for processing of associative or relational information (see Cohen and Eichenbaum, 1993; Brown and Aggleton, 2001; Eichenbaum and Cohen, 2001; Mayes et al., 2007 for reviews). Similar to our results, several recent studies have found memory deficits in patients with hippocampal lesions that were largely confined to associative visuo-spatial material (Hannula et al., 2006; Olson et al., 2006; Hartley et al., 2007; Finke et al., 2008). However, there have also been reports of impaired non-associative short-term memory in patients with hippocampal damage (Owen et al., 1995; Stark et al., 2002; Nichols et al., 2006). Facing such inconsistencies, a functional specialization of the hippocampus for processing of associative information has repeatedly been questioned (Squire et al., 2004, 2007). Our findings do not reconcile these divergent results, but the observed delay-independent performance deficit in associative and non-associative memory tasks in both patient groups suggests that hippocampus-independent impairments may significantly contribute to behavioural deficits in patients with lesions of the MTL. It can therefore be concluded that both brain reorganization and the selectivity of hippocampal damage critically determine the relative contributions of delay-dependent and delay-independent deficits to performance in distinct patient groups. Differential efficacy of compensatory processes as well as differences in extra-hippocampal lesion extent may therefore partially account for the mixed results in previous studies on associative memory in humans with lesions of the MTL.

Conclusion

The traditional approach to establish causal brain–behaviour relationships is cognitive testing in subjects with focal lesions affecting a cerebral region of interest. Despite considerable progress in functional imaging of the MTL, much of our knowledge on the function of the human hippocampal formation is still based on such studies employing various diseases including global cerebral hypoxia, encephalitis, resected hippocampal sclerosis or brain tumours. The findings in our patients however show that inferences on normal hippocampal function may be distorted by compensatory processes, which operate with distinct efficacy in distinct patient groups. A correct interpretation of lesion studies therefore necessitates consideration of the temporal properties of the underlying pathologies. To date, there is no generally accepted unifying theory of hippocampal function in humans. We suppose that at least some of the controversies that pervade the literature, can be explained by taking into account compensatory processes such as those demonstrated here. Comparative studies of brain activation across early- and late-onset cases of hippocampal damage may clarify the mechanisms of neurobehavioural plasticity with human hippocampal lesions.

Supplementary material

Supplementary material is available at Brain online.

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