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Visuo-spatial memory deficits following medial temporal lobe damage: A comparison of three patient groups

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ABSTRACT

The contributions of the hippocampal formation and adjacent regions of the medial temporal lobe (MTL) to memory are still a matter of debate. It is currently unclear, to what extent discrepancies between previous human lesion studies may have been caused by the choice of distinct patient models of MTL dysfunction, as disorders affecting this region differ in selectivity, laterality and mechanisms of post-lesional compensation. Here, we investigated the performance of three distinct patient groups with lesions to the MTL with a battery of visuo-spatial short-term memory tasks. Thirty-one subjects with either unilateral damage to the MTL (postsurgical lesions following resection of a benign brain tumor, 6 right-sided lesions, 5 left) or bilateral damage (10 post-encephalitic lesions, 10 post-anoxic lesions) performed a series of tasks requiring short-term memory of colors, locations or color–location associations. We have shown previously that performance in the association task critically depends on hippocampal integrity. Patients with postsurgical damage of the MTL showed deficient performance in the association task, but performed normally in color and location tasks. Patients with left-sided lesions were almost as impaired as patients with right-sided lesions. Patients with bilateral post-encephalitic lesions showed comparable damage to MTL sub-regions and performed similarly to patients with postsurgical lesions in the association task. However, post-encephalitic patients showed additional impairments in the non-associative color and location tasks. A strikingly similar pattern of deficits was observed in post-anoxic patients. These results suggest a distinct cerebral organization of associative and non-associative short-term memory that was differentially affected in the three patient groups. Thus, while all patient groups may provide appropriate models of medial temporal lobe dysfunction in associative visuo-spatial short-term memory, additional deficits in non-associative memory tasks likely reflect damage of regions outside the MTL. Importantly, the choice of a patient model in human lesion studies of the MTL significantly influences overall performance patterns in visuo-spatial memory tasks.

1. Introduction

Lesion studies on human and non-human primates have greatly contributed to our understanding of the medial temporal lobe (MTL) and its role in conscious memory (Eichenbaum, 2013; Morris, 2007; Squire and Wixted, 2011; Stark, 2007). While in non-human primates an animal model of amnesia with selective bilateral lesions to MTL structures was developed (Mishkin, 1978; Zola-Morgan et al., 1982), such an ideal model of MTL dysfunction is not available for humans. Hence, human MTL function has been studied in patients with MTL damage caused by various disorders, including encephalitis, hypoxic brain damage, tumors, hippocampal sclerosis, and brain surgery. These lesion models have

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unequivocally demonstrated that the MTL is indispensable for conscious memory in humans (Eichenbaum, 2013; Morris, 2007; Squire and Wixted, 2011; Stark, 2007). However, there is a continuing debate on the precise contributions of the MTL and its subregions to distinct memory domains and to cognition beyond memory such as perception, decision making and imagination of the future (Henke, 2010; Ranganath, 2010; Shohamy and Turk-Browne, 2013; Squire and Wixted, 2011). The current lack of a unifying framework for the role of the MTL in memory and other cognitive functions may also be due to the fact that human lesion models of MTL dysfunction differ considerably with respect to the temporal properties, selectivity, extent and laterality of lesions (Stark, 2007). In addition, only very few patients with autoptically verified selective bilateral lesions to the MTL have been reported (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996). In many cases, significant uncertainties remain about the functional status of brain regions in- and outside the MTL (Squire and Wixted, 2011; Stark, 2007). Beside differences in assessment of memory between studies, these factors may significantly influence performance in cognitive tasks. For example, we have shown recently that the temporal properties of disorders affecting the MTL critically determine a subjects' performance in visuo-spatial short-term memory tasks, even in patients with otherwise similar lesion characteristics (Braun et al., 2008; Finke et al., 2013). Although previous studies in other domains such as motor function and language have repeatedly demonstrated a significant influence of disease type on behavioral performance (e.g. Anderson et al., 1990; Haaland and Delaney, 1981), systematic investigations on how mechanisms of MTL damage may account for the partly divergent findings in human lesion studies of memory have only rarely been reported.

Here, we have investigated the role of disease characteristics for behavioral performance in memory tasks. Patients with MTL lesions or MTL dysfunction acquired in the context of three different disorders (benign brain tumor, herpes encephalitis, global cerebral hypoxia) were tested with a set of tasks that included testing for short-term memory of colors, locations and color–location associations. Consistent with the hypothesis that the hippocampus is particularly involved in associative binding (Henke, 2010; Ranganath, 2010; Aggleton et al., 2012; Yonelinas, 2013), patients with damage to the hippocampal formation have previously shown selective deficits in memory of color–location associations, while performance in the other tasks was normal (Braun et al., 2008, 2011; Finke et al., 2008). In the present study, deficient associative memory in all patients suggests that all patient groups may provide appropriate models of hippocampal dysfunction. However, the presence of presumably MTL-independent deficits in non-associative memory tasks appears to depend significantly on disease characteristics.

2. Methods

2.1. Subjects

Thirty-one patients were recruited from the Department of Neurology and the Department of Nephrology and Medical Intensive Care Medicine at the Charité-Universitätsmedizin Berlin, Germany (6 patients with right-sided MTL lesions following resection of a benign brain tumor, 5 patients with left-sided MTL lesions following resection of a benign brain tumor, 10 patients with MTL lesions following herpes simplex encephalitis and 10

Table 1
Patient characteristics.

Patient	Diagnosis	Sex	Age	Delay (months) since lesion	Clinical notes/Histopathology	Anticonvulsant medication/centrally acting drugs
1	R-MTL	F	42	22	Pilomyxoid astrocytoma	Gabapentin 900 mg/d
2	R-MTL	F	32	44	Epidermoid tumor	Lamotrigine 200 mg/d
3	R-MTL	M	19	47	Pilocytic astrocytoma	None
4	R-MTL	M	24	5	Neuroepithelial tumor	Lamotrigine 200 mg/d
5	R-MTL	M	24	56	Pigmented astrocytoma	None
6	R-MTL	F	23	21	Ganglioglioma	Levetiracetam 2 g/d
7	L-MTL	M	22	8	DNET tumor WHO I	Oxcarbazepine 1800 mg/d
8	L-MTL	F	35	113	Ganglioneuroma	None
9	L-MTL	F	45	84	Oligo-astrocytoma WHO II	None
10	L-MTL	F	49	2	Ganglioglioma	Levetiracetam 3 g/d; lamotrigine 25 mg/d
11	L-MTL	M	38	18	Cavernous Haemangioma	Levetiracetam 2 g/d
12	HSE	M	33	100	Herpes 1 PCR positive	Phenytoin 500 mg/d
13	HSE	F	61	24	Herpes 1 PCR positive	Carbamazepine 600 mg ret./d
14	HSE	M	35	96	Herpes 1 PCR positive	None
15	HSE	F	69	28	Herpes 1 PCR positive	None
16	HSE	F	54	96	Herpes 1 PCR positive	Levetiracetam 3 g/d; oxcarbamazepine 1200 mg/d; escitalopram 20 mg/d
17	HSE	M	32	6	Herpes PCR neg./HSV IgM in CSF positive	Doxepin 100 mg/d
18	HSE	M	68	3	Herpes 1 PCR positive	Levetiracetam 2 g/d
19	HSE	M	49	5	Herpes 1 PCR positive	Levetiracetam 2 g/d
20	HSE	F	67	14	Herpes 1 PCR positive	None
21	HSE	M	53	2	Herpes 1 PCR positive	Citalopram 20 mg/d; opipramol 150 mg/d
22	GCH	M	27	95	CPC score 2, no hypothermia	None
23	GCH	M	69	36	CPC score 1, therapeutic hypothermia	None
24	GCH	M	57	30	CPC score 1, therapeutic hypothermia	None
25	GCH	M	57	33	CPC score 2, therapeutic hypothermia	None
26	GCH	M	35	36	CPC score 1, therapeutic hypothermia	None
27	GCH	M	54	23	CPC score 1, therapeutic hypothermia	None
28	GCH	M	68	11	CPC score 1, no hypothermia	None
29	GCH	F	62	10	CPC score 2, therapeutic hypothermia	None
30	GCH	M	60	8	CPC score 2, therapeutic hypothermia	None
31	GCH	F	52	5	CPC score 1, therapeutic hypothermia	Lorazepam 0,5 mg/d; citalopram 20 mg/d