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

Nazli Esfahani-Bayerl [a,1], Carsten Finke [a,b,1], Mischa Braun [a], Emrah Düzel [c,d,e], Hauke R. Heekeren [f,g], Martin Holtkamp [a,h], Dietrich Hasper [i], Christian Storm [i], Christoph J. Ploner [a,*]

[a] Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany
[b] Berlin School of Mind and Brain, Humboldt-Universität, Berlin, Germany
[c] Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University Magdeburg, Magdeburg, Germany
[d] German Center for Neurodegenerative Diseases (DZNE) Site, Magdeburg, Germany
[e] Institute of Cognitive Neuroscience, University College London, London, United Kingdom
[f] Department of Education and Psychology, Freie Universität Berlin, Berlin, Germany
[g] Cluster of Excellence "Languages of Emotion", Freie Universität Berlin, Berlin, Germany
[h] Epilepsy-Center Berlin-Brandenburg, Evangelisches Krankenhaus Königin Elisabeth Herzberge, Berlin, Germany
[i] Department of Nephrology and Medical Intensive Care Medicine, Charité – Universitätsmedizin Berlin, Berlin, Germany

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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

* Correspondence to: Department of Neurology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
E-mail address: christoph.ploner@charite.de (C.J. Ploner).
[1] Equal contribution.

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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

patients following global cerebral hypoxia in the context of cardiac arrest; Table 1). All patients were right-handed and normal on neurological examination. Mean delay between MTL lesion/cardiac arrest and testing was 34.9 ± 6.2 months and did not differ significantly between groups (right MTL tumor resection, 32.5 ± 7.9 months; left MTL tumor resection, 32.5 ± 7.9 months; herpes encephalitis 37.4 ± 13.4 months; global cerebral hypoxia 28.7 ± 8.3 months; $p=0.96$, Kruskal–Wallis-test). Patients with additional neurological or psychiatric disorders and patients older than 70 years were excluded. In all subjects, verbal and non-verbal intelligence were assessed using the MWT-B, a German equivalent to the National Adult Reading Test (Lehrl, 2005) and the sub-test no. 3 of LPS, a German equivalent to Raven's Progressive Matrices (Horn, 1983). Spatial working memory was tested with Corsi Block Tapping test forward and backward. Visuo-spatial abilities were tested with the Rey–Osterrieth Complex Figure test. Informed consent was obtained from all subjects before participation in the study, which was approved by the local Ethical Committee and conducted in conformity with the Declaration of Helsinki.

2.1.1 Postsurgical MTL lesions

Eleven patients with resections of right or left medial temporal lobe structures for the treatment of epilepsy caused by a benign brain tumor were recruited (5 patients with left MTL tumor (L-MTL); 3 females, age 37.8 ± 4.7 years; 6 patients with right MTL tumor (R-MTL), 3 females, age 27.3 ± 3.4 years, see Fig. 1 for exemplary MRI). In all patients, tumors affected the resected portion of the hippocampus preoperatively. Duration of preoperative epilepsy was 25.8 ± 5.5 months and did not differ significantly between groups (right MTL tumor resection, 24.2 ± 5.7 months; left MTL tumor resection, 27.8 ± 10.8 months; $p=1.0$). In all patients, 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 fully integrated in their social and professional lives. The time since tumor resection and behavioral testing did not differ significantly between L-MTL and R-MTL patient groups ($p=0.96$).

2.1.2 Herpes simplex encephalitis

Ten patients with bilateral MTL damage following herpes simplex encephalitis (HSE) were recruited (4 females, age 52.1 ± 4.6 years, see Fig. 1 for exemplary MRI). Diagnosis in all patients was established based on the guidelines of the German Society of Neurology (Diener and Putzki, 2008), i.e. typical clinical presentation, cerebral MR imaging results and inflammatory CSF response with positive herpes simplex virus type 1-PCR.

2.1.3 Global cerebral hypoxia

Ten patients with global cerebral hypoxia (GCH) following cardiac arrest and cardiopulmonary resuscitation were recruited (2 females, age 54.1 ± 4.3 years, see Fig. 1 for exemplary MRI). Eight patients underwent therapeutic hypothermia (33 °C for 24 h) according to ERC guidelines. Only patients with cerebral performance category (CPC) scores of 1 ("good cerebral performance") or 2 ("moderate cerebral disability") at hospital discharge and without additional neurological and cerebrovascular comorbidities were included (Safar, 1981). All patients reported memory deficits sufficiently severe to interfere with activities of daily living in a questionnaire that was based on the Memory Assessment Clinics Self-rating Scale (MAC-S) (Crook and Larrabee, 1990, 1992) and adapted for German language.

2.1.4 Controls

Healthy subjects without any history of neurological or psychiatric disorders were recruited as control subjects. As the three patient groups differed significantly with respect to age ($p < 0.001$, Kruskal–Wallis test), two different control groups were used. Control group 1 (Con1) consisted of 10 subjects (8 females, age 34.5 ± 4.8 years) and was matched to L-MTL and R-MTL patient groups. No significant differences between L-MTL and R-MTL patient groups and control group 1 were observed regarding age ($p=0.44$), years of education ($p=0.08$), verbal IQ ($p=0.67$), non-verbal IQ ($p=0.48$), spatial working memory ($p \geq 0.44$) and visuo-spatial abilities ($p \geq 0.35$; Table 2). Control group 2 (Con2) consisted of 10 subjects (5 females, age 48.8 ± 2.7 years) and was matched to HSE and GCH patient groups. There were no significant differences between HSE and GCH patient groups and control group 2 regarding age ($p=0.34$), years of education ($p=0.12$), verbal IQ ($p=0.06$), non-verbal IQ ($p=0.29$) and spatial working memory ($p \geq 0.33$). Testing of visuospatial abilities with the Rey–Osterrieth Complex Figure test showed no significant group differences for figure copying (p 0.42) and immediate reproduction ($p=0.28$), but a significant group difference for delayed reproduction ($p=0.03$; Table 2). Post-hoc testing revealed that this

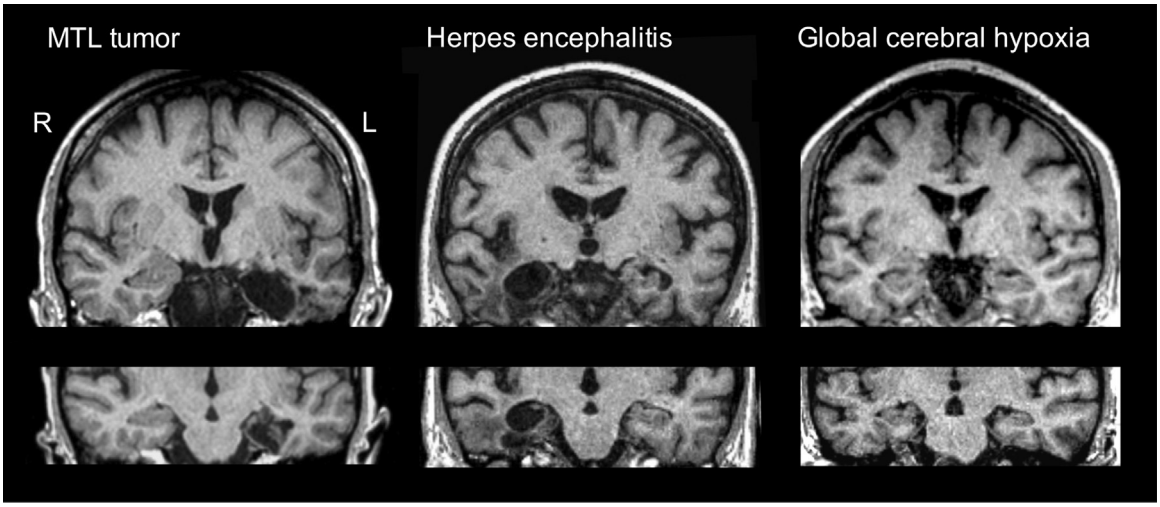

Fig. 1. Exemplary coronal MRIs from subjects of the three investigated patient groups. R, right; L, left. Top row, sections at the level of the hippocampal head; bottom row, sections at the level of the hippocampal body. Left, patient with lesion following left-sided resection of a benign brain tumor. Note damage to left hippocampus and adjacent regions of the MTL. Middle, patient with lesions following herpes encephalitis. Note complete loss of the right hippocampus and adjacent cortex of the MTL, substantial damage to right inferotemporal/lateral temporal cortex and underlying white matter and atrophy of the left hippocampus. Right, patient with a history of global cerebral hypoxia. Note moderate atrophy of the hippocampus bilaterally.

Table 2
Socio-demographic and neuropsychological data of patient and control groups.

Group		Age	YOE	TSL	MWT (Verbal IQ)	LPS (Nonverbal IQ)	BTfw	BTbw	ROCF copy	ROCF immediate	ROCF delayed
R-MTL		27.3 ± 3.4	13.7 ± 0.8	32.4 ± 7.9	107.2 ± 4.5	31.2 ± 3.8	8.7 ± 0.4	8.5 ± 0.4	34.5 ± 0.6	19.8 ± 1.1	19.4 ± 1.4
L-MTL		37.8 ± 4.7	16.1 ± 1.0	45.0 ± 22.5	103.2 ± 5.3	29.0 ± 1.9	8.4 ± 0.7	8.0 ± 0.3	34.8 ± 0.5	26.1 ± 3.2	25.5 ± 3.4
Con 1		34.5 ± 4.8	14.1 ± 0.5	n.a.	109.0 ± 3.4	26.8 ± 1.6	9.0 ± 0.8	7.9 ± 0.2	35.3 ± 0.3	22.4 ± 2.0	22.9 ± 1.7
	p* value	0.44	0.08	0.89	0.67	0.48	0.72	0.44	0.41	0.43	0.35
HSE		52.1 ± 4.6	17.0 ± 1.5	37.4 ± 13.4	105.8 ± 3.0	22.5 ± 2.0	6.9 ± 0.4	6.6 ± 0.5	35.1 ± 0.3	19.2 ± 3.0	16.5 ± 2.3
GCH		54.1 ± 4.3	13.6 ± 0.6	26.7 ± 8.3	114.1 ± 5.9	22.7 ± 2.2	7.1 ± 0.6	6.7 ± 0.5	35.4 ± 0.2	24.7 ± 1.9	24.1 ± 2.2
Con 2		48.1 ± 3.2	16.4 ± 1.1	n.a.	119.2 ± 3.9	27.4 ± 1.9	7.8 ± 0.7	7.3 ± 0.5	35.6 ± 0.3	25.6 ± 2.4	25.9 ± 2.2
	p* value	0.34	0.12	0.91	0.06	0.29	0.33	0.36	0.42	0.28	0.03

BTfw, block tapping forward; BTbw, block tapping backward; IQ, intelligence quotient; LPS, Leistungsprüfsystem (German equivalent to Raven's Progressive Matrices); MWT, Mehrfachwahl-Wortschatztest (German equivalent to the National Adult Reading Test); n.a., not applicable; ROCF, Rey–Osterrieth Complex Figure Task; TSL, time since lesion (months); YOE, years of education.

* Kruskal–Wallis-test; group averages are means ± SEM.

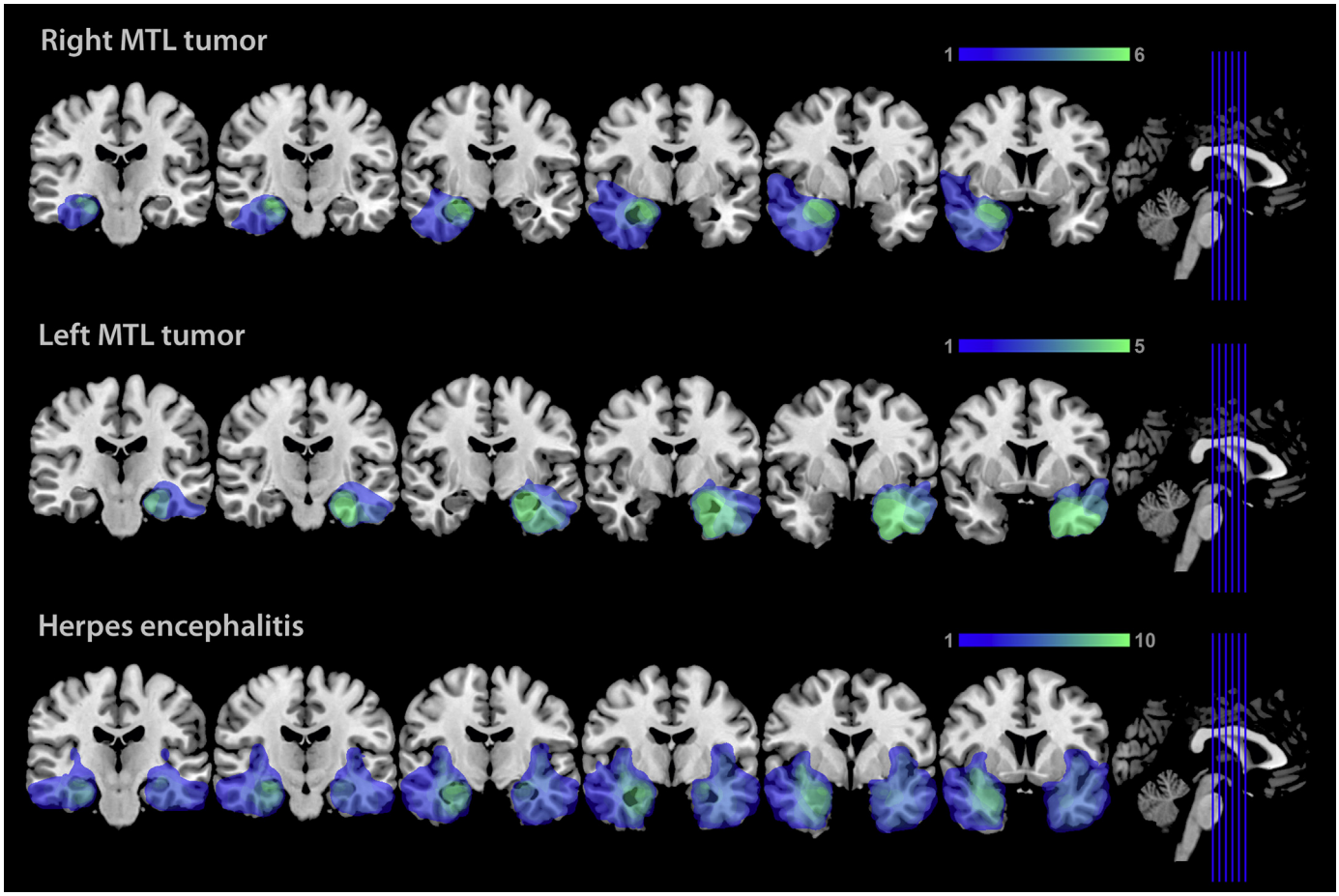

Fig. 2. Reconstruction of focal lesions. Six coronal brain sections are arranged from caudal to rostral separately for R-MTL-, L-MTL- and HSE-patients. Blue, maximum lesion extent; light green, maximum lesion overlap. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

deficit was selective for HSE patients ($p=0.02$ difference with Con2; Mann–Whitney test), while GCH patients performed normally ($p=0.82$ difference with Con2).

2.2. Cerebral imaging

In all L-MTL, R-MTL and HSE patients, whole-brain anatomical MRI data were collected on a 1.5 T Siemens Vision scanner using a standard 3D 1 mm isotropic magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence. Lesion boundaries were delineated on every coronal slice of the individual MPRAGE images using MRIcron (www.mricro.com/mricron; Rorden et al., 2007). The individual image and lesion shapes were then spatially normalized to the Montreal Neurological Institute (MNI) brain template using the unified segmentation and normalization approach provided with SPM8 (www.fil.ion.ucl.ac.uk/spm; Ashburner and Friston, 2005) see Fig. 2 for a lesion overlay). This method has been shown to provide a better and more reliable matching of lesioned brains to a standard template than commonly used alternatives, such as standard non-linear approaches with cost-function

masking (Crinion et al., 2007). In GCH patients, cerebral imaging was available for six patients only. MRI scans were obtained in three patients. In six patients, MRI studies were not conducted because of implanted pacemakers/cardioverter-defibrillators. One patient refused MRI because of claustrophobia. For three of these non-MRI patients, CT scans were available that did however not allow for detailed lesion analysis.

2.3. Lesion evaluation

After delineation of lesions and calculation of total lesion volumes on normalized MRIs, we determined rostro-caudal damage to individual MTL-sub-regions in all L-MTL, R-MTL and HSE patients by using a semi-quantitative method that is based on identification of anatomical landmarks and lesion boundaries (Braun et al., 2008, 2011). For patients with lesions resulting from surgery (R-MTL- and L-MTL-patients) and necrosis (HSE-patients), we deem this the most appropriate approach, since volumetry of MTL-sub-regions is not feasible for structures that are damaged completely or in which borders to adjacent structures cannot be identified with certainty. MTL-sub-regions were determined from rostral to caudal sections by using landmarks proposed by Insausti et al. (1995, 1998), Insausti and Amaral (2011) and derived from Mai et al. (2007). Lesion to these regions were rated independently by three neurologists with extensive experience in reconstruction of cerebral lesions. During analysis, raters were blind to individual behavioral performance. All raters agreed on affected temporal lobe structures and lesion extent in each patient.

MTL-sub-regions were identified as follows:

Hippocampus: Where appropriate, the rostral limit of the hippocampus was determined in the intact left or right anterior MTL. Its identification was guided by the rostral limit of the temporal horn of the lateral ventricle, which generally coincides with the rostral limit of the hippocampal head. The hippocampus was identified on the following slices of the normalized MR scans and rostro-caudal extent of hippocampal damage was determined.

Entorhinal cortex: The ERC was located in the rostral parahippocampal gyrus, beginning 2 mm caudally to 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.

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 generally coincides with

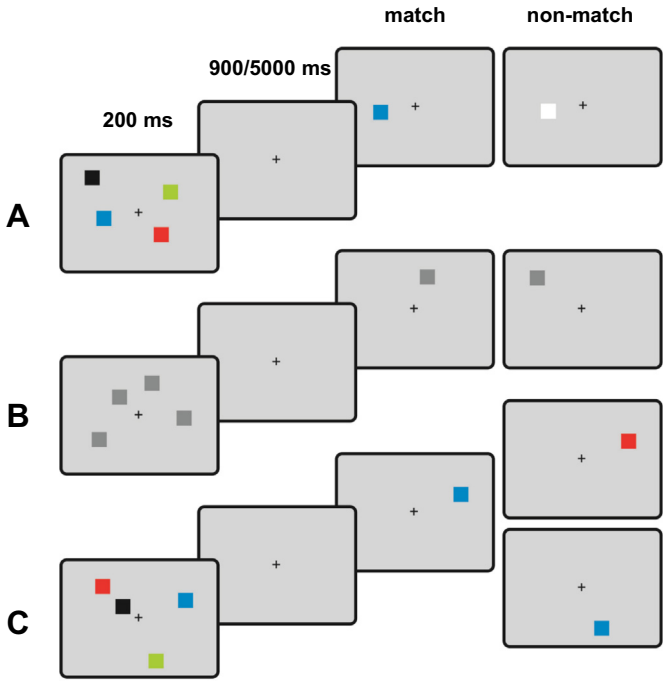

Fig. 3. Schematic of the short-term memory tasks. (A) color task; (B) location task; (C) association task. While fixating on a central fixation cross, subjects were presented an array of two, four or six squares. After a memory delay of unpredictable length (900 or 5000 ms), a single probe stimulus appeared and subjects indicated by a key press whether or not the probe matched one of the sample stimuli in color (A), location (B) or color and location (C). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
Lesion analysis.

Patient	Group	L-HIP	L-ERC	L-PRC	L-PHC	L-VOL	R-HIP	R-ERC	R-PRC	R-PHC	R-VOL
1	R-MTL	0	0	0	0	0	+	+	+	0	20.3
2	R-MTL	0	0	0	0	0	+	+	+	0	33.1
3	R-MTL	0	0	0	0	0	++	++	++	0	10.4
4	R-MTL	0	0	0	0	0	+	++	++	0	14.6
5	R-MTL	0	0	0	0	0	+++	++	++	+	55.4
6	R-MTL	0	0	0	0	0	+++	++	+	+	10.7
7	L-MTL	+++	+	++	+	43.6	0	0	0	0	0
8	L-MTL	++	++	++	+	40.8	0	0	0	0	0
9	L-MTL	+	++	++	0	39.2	0	0	0	0	0
10	L-MTL	++	++	++	+	26.9	0	0	0	0	0
11	L-MTL	++	++	++	++	34.7	0	0	0	0	0
12	HSE	+	+	0	0	3.1	++	++	++	++	77.7
13	HSE	+	0	+	0	37.2	++	+	++	0	16.5
14	HSE	+	0	0	0	0.2	++	0	0	0	0.7
15	HSE	++	0	0	0	4.2	++	++	++	++	47.9
16	HSE	++	+	++	0	17.2	++	++	++	++	68.5
17	HSE	+++	++	++	++	73.2	+	0	+	0	1.1
18	HSE	++	++	++	+	30.7	++	+	0	+	5.7
19	HSE	+++	++	++	+	40.5	+	0	0	0	0.7
20	HSE	+	+	++	0	34.8	+	+	0	0	3.4
21	HSE	++	++	++	+	32.1	++	++	++	+	63.8

R, right; L, left; HIP, hippocampus; ERC, entorhinal cortex; PRC, perirhinal cortex; PHC, parahippocampal cortex; VOL, lesion volume (ml); 0, region unaffected; +, rostrocaudal lesion extent ≤ 20 mm; ++, ≤ 40 mm; +++, > 40 mm.

Table 4
Group performance in color-, location-, and association memory tasks.

Group		Color		Location		Association	
		900 ms	5000 ms	900 ms	5000 ms	900 ms	5000 ms
R-MTL		86.5 ± 1.6	83.6 ± 2.3	92.2 ± 2.1	80.8 ± 3.2	83.6 ± 2.2	74.3 ± 2.8
L-MTL		86.5 ± 1.7	84.2 ± 3.2	91.0 ± 1.8	85.4 ± 2.5	83.8 ± 2.6	79.4 ± 2.9
Con 1		86.8 ± 1.3	82.6 ± 2.1	91.5 ± 1.6	86.3 ± 1.3	86.5 ± 1.1	84.6 ± 2.0
	p value*	0.218	0.486	0.843	0.324	0.091	0.005
HSE		77.7 ± 2.3	74.3 ± 1.4	81.1 ± 2.9	77.6 ± 2.8	78.8 ± 1.5	71.0 ± 2.6
GCH		81.3 ± 1.9	77.7 ± 2.3	84.9 ± 2.7	78.3 ± 3.0	79.6 ± 3.0	74.4 ± 3.6
Con 2		89.7 ± 1.2	86.0 ± 1.4	92.2 ± 1.8	85.6 ± 2	88.3 ± 1.1	87.3 ± 0.9
	p value*	0.011	0.037	0.022	0.036	0.014	0.006

* Kruskal–Wallis-test; group averages are means ± SEM.

the rostral end of the collateral sulcus. However, the rostral end of the collateral sulcus could not be clearly identified in all patients as it was either included in the lesions or had lost contour sharpness in normalized MR scans due to its small size. Therefore, we used a fixed distance of 2 mm rostral of the first section showing the fronto-temporal junction as described by Insausti et al. (1998). The caudal limit of the PRC coincides with the rostral pole of the lateral geniculate nucleus.

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.

After identification of lesion boundaries, we quantified individual rostro-caudal lesion extent for each of the affected MTL sub-regions by using a grading system (Table 3; Braun et al., 2008; 2011), where '0' always indicates an unaffected sub-region, '+' a lesion extent of ≤20 mm, '++' ≤40 mm and '+++' >40 mm.

2.4. Paradigms and procedure

Subjects were tested with three established delayed-match-to-sample (DMS) tasks, assessing either memory of colors, locations or color–location associations (Braun et al., 2008, 2011; Finke et al., 2008, 2013; see Fig. 3). Subjects were seated in a darkened room at a distance of 50 cm to a 22-in. computer monitor. While subjects fixated on a small central dot, a sample array was presented for 200 ms in the central region of the screen. Stimuli were small squares on a light gray background. Stimulus arrays consisted of two, four or six simultaneously presented gray or colored squares. The location of each square in the sample array was pseudo-randomly chosen from 48 possible locations. After an unfilled memory delay of unpredictable length (900 or 5000 ms), a probe stimulus appeared for up to 2000 ms and subjects indicated by an un-speeded manual key press whether this probe stimulus matched one of the sample squares in color, location, or color and location. The experiment was run in a blocked design on two consecutive days in a counterbalanced 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 each task. Before the start of data recording in a new task, all participants were given standardized written instructions and an equal number of training trials.

2.5. Data analysis

Throughout the manuscript, group averages of all variables are given as means ± SEM. For each task, delay and set size, performance was expressed both in percent correct and *d′* scores (Macmillan and 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 tests were applied through-out for comparison of performance measures, semi-quantitative damage scores and lesion volumes (Altman, 1991).

3. Results

3.1. Lesion analysis

Results are summarized in Fig. 2 and Table 3. Reconstruction of lesions demonstrated damage to the right hippocampal formation (i.e. hippocampus and entorhinal cortex) and right perirhinal cortex in all R-MTL patients and damage to the right parahippocampal cortex in two patients. Outside the MTL, there was additional involvement of the right inferior and lateral temporal cortex in one R-MTL patient. In the L-MTL group, lesions affected the left hippocampal formation and left perirhinal cortex in all patients and parts of the left parahippocampal cortex in four patients. Outside the MTL, there was damage at least of anterior portions of inferior and lateral temporal cortex in all L-MTL patients. There were no significant differences in damage to each MTL-subregion and in total lesion volume between these two patient groups ($p \geq 0.126$, Mann–Whitney test).

In HSE patients, lesions were always bilateral and involved the hippocampus on both sides in all cases. Lesions outside the hippocampus were strongly asymmetric. Entorhinal cortex and perirhinal cortex were at least unilaterally affected in almost all cases (in 9/10 patients) and parahippocampal cortex in most cases (in 7/10 patients). With the exception of one patient, at least on the more severely affected side, lesions regularly extended further into inferior and lateral temporal cortex (in 9/10 patients) and insular cortex (in 9/10 patients). However, on average, damage to right and left MTL-subregions and right and left lesion volumes did not differ significantly across the entire group of HSE patients ($p \geq 0.396$, Wilcoxon signed ranks test).

There were no significant differences in total lesion volume and damage to each MTL-subregion between R-MTL patients and right-sided lesions of HSE patients ($p \geq 0.263$, Mann–Whitney test) and between L-MTL patients and left-sided lesions of HSE patients ($p \geq 0.206$, Mann–Whitney test). In GCH patients with available neuroimaging, no focal lesions of the MTL or of other brain regions were observed. Among those with available MRI ($n=3$), the hippocampus appeared atrophic in two cases.

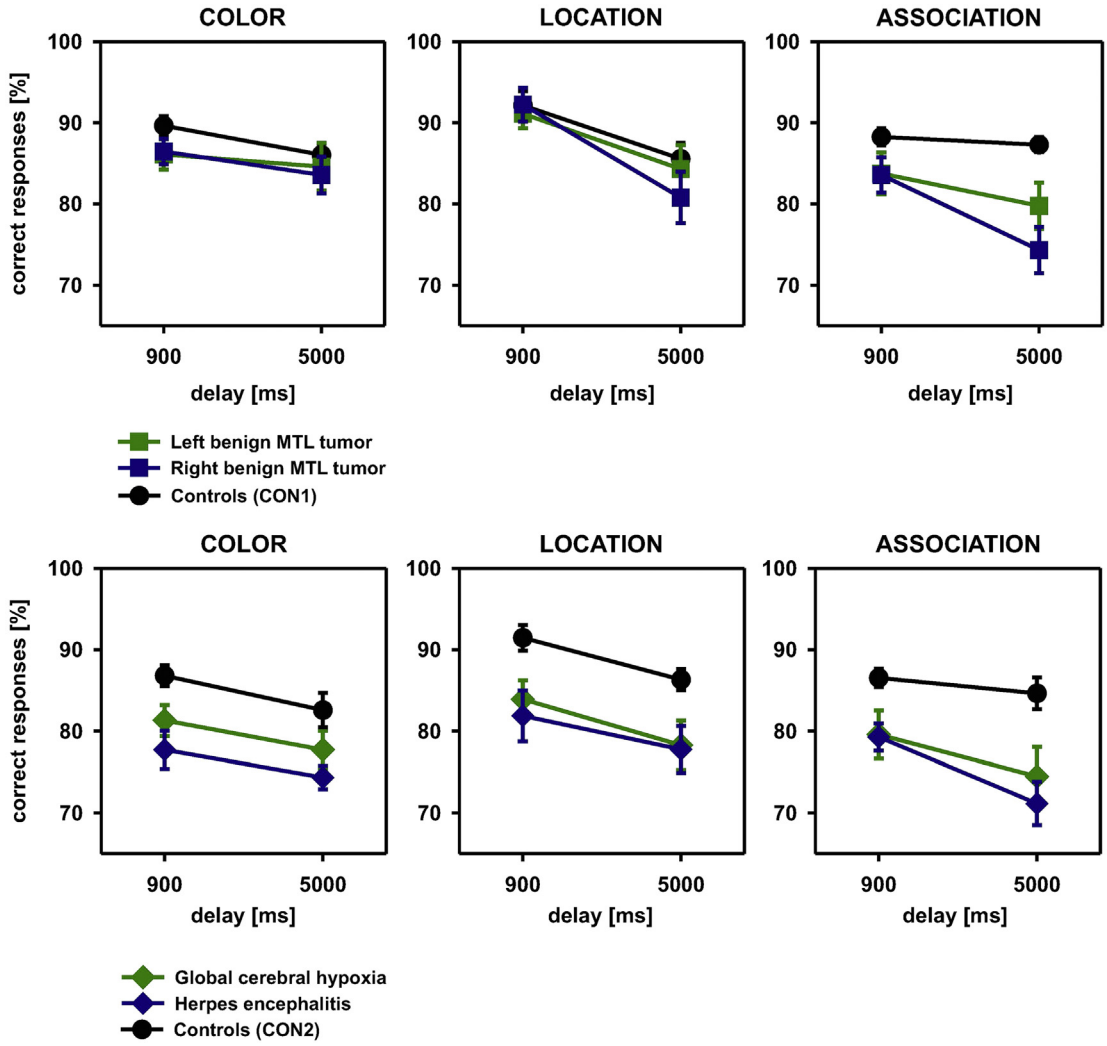

Fig. 4. Results. Group mean performances ± SEM in three short-term memory tasks at 900 and 5000 ms delay. Note similar performance across groups in the association task at 5000 ms delay. Note performance differences in color and location tasks between patients with unilateral damage and patients with bilateral damage at both delays.

3.2. Behavioral results

Group behavioral results are summarized in Table 4 and in Fig. 4. No significant performance differences were observed between R-MTL and L-MTL patients and controls (Con 1) for both delays of the color and the location tasks (all $p > 0.2$, Kruskal–Wallis test) and for the 900 ms delay of the association task ($p = 0.09$). In contrast, performance differed significantly between these three groups in trials of the association task with a delay of 5000 ms ($p < 0.005$). Post hoc comparisons revealed significantly worse performance of both patient groups relative to controls at 5000 ms delay (R-MTL, $p < 0.001$; L-MTL, $p < 0.05$, Mann–Whitney test). Although R-MTL patients performed slightly worse than L-MTL patients, these differences did not achieve statistical significance ($p = 0.18$). The magnitude of the deficit did not correlate with the length of hippocampal removal ($p \geq 0.86$, Spearman-Rho). R-MTL and L-MTL patients' impairments in the association task were equally present across set sizes, with performance decreasing from set size 2 to set size 6 by 24.1 ± 4.0% in R-MTL patients, by 23.0 ± 3.0% in L-MTL patients and by 21.3 ± 1.8% in controls ($p = 0.69$ difference between groups, Kruskal–Wallis-test).

By contrast, in HSE and GCH patients and control subjects (Con 2), significant performance differences were observed for both delays (900 and 5000 ms) in all three tasks (color, location, and association task; all $p < 0.038$). Further post-hoc analyses showed that HSE patients performed worse than controls at both delays of all three tasks (all $p < 0.023$). Theoretically, this may either be due to the mere bilaterality of lesions in HSE-patients or to other disease-related factors. To address this issue, we analyzed the role of laterality on performance and calculated an asymmetry index (AI) for each HSE-patient (larger lesion volume/smaller lesion volume). The average AI was 18.8 ± 7.6 (range 2.0–66.6). We next divided patients in those with less asymmetric lesions (AI < 10, $n = 5$, mean AI = 3.4 ± 7.6) and those with more asymmetric lesions (AI > 10, $n = 5$, mean AI = 34.2 ± 11.8; $p = 0.008$ difference between groups). We found no significant differences between groups for performance in the color-, location- and association-tasks at all delays ($p \geq 0.31$ for all comparisons). Moreover, AI values did not correlate with performance in the color-, location- and association-tasks ($p \geq 0.24$ for all correlations, Spearman-Rho). Thus, these analyses do not suggest that bilaterality of lesions mainly accounts for additional behavioral impairments in HSE patients.

We further tested whether asymmetry of lesions in HSE-patients influenced performance in our experimental tasks and divided patients in those with predominately right-sided lesions ($n = 5$) and those with predominately left-sided lesions ($n = 5$).

There was a tendency for a difference in the location task with slightly inferior performance of HSE-patients with predominately right-sided lesions that however did not achieve significance (900 ms delay, $p=0.06$; 5000 ms delay, $p=0.095$). All other comparisons were far from significance ($p \geq 0.22$ for all comparisons), suggesting largely symmetric deficits, despite asymmetry of lesions. Furthermore, the magnitude of the deficits did not correlate with the rostro-caudal lesion extent of right or left hippocampal damage ($p \geq 0.12$, for all correlations, Spearman-Rho). By contrast, when we further analyzed performance in the delayed reproduction of the Rey–Osterrieth complex figure test (Section 2.1.4), patients with predominately right-sided lesions showed a significant deficit in ($p=0.01$), while patients with predominately left-sided lesions were not significantly impaired ($p=0.17$). However, when HSE-patients with predominately right-sided lesions were compared to those with predominately left-sided lesions, there was no significant difference ($p=0.22$). These analyses indicate that the significant group difference between HSE-patients and controls in delayed reproduction of the Rey–Osterrieth complex figure test was mainly driven by HSE-patients with predominately right-sided lesions, but that this asymmetry was not very strong.

In GCH patients, performance in our short-term memory tasks showed a striking similarity to HSE patients, with performance inferior to that of controls in all comparisons (all $p < 0.035$), except for the color task at 5000 ms delay ($p=0.17$). Between GCH and HSE patients, there was no performance difference in any of the tasks (all $p > 0.28$). Both groups showed a similar set-size dependency of their deficits in the association task, with performance decreasing from set size 2 to set size 6 by $18.0 \pm 4.7\%$ in HSE patients, by $17.9 \pm 3.7\%$ in GCH patients and by $21.7 \pm 1.8\%$ in controls ($p=0.75$ difference between groups; Kruskal–Wallis-test). Likewise, set-size effects in the color and location tasks did not differ between groups (color task: performance decreasing from set size 2 to set size 6 by $17.7 \pm 3.4\%$ in HSE patients, by $19.4 \pm 2.8\%$ in GCH patients and by $22.4 \pm 1.7\%$ in controls, $p=0.53$ difference between groups; location task: performance decreasing from set size 2 to set size 6 by $14.9 \pm 2.5\%$ in HSE patients, by $16.6 \pm 2.4\%$ in GCH patients and by $12.5 \pm 1.6\%$ in controls, $p=0.44$ difference between groups). Since we used two different control groups, performance differences between HSE, GCH, R-MTL and L-MTL patients may theoretically result from age-dependent performance measures in our memory tasks. However, memory performance of the two control groups (Con 1 and Con 2) did not differ significantly for both memory delays in all of the three tasks (all $p > 0.14$).

4. Discussion

The present study investigated performance of three different patient groups with damage to the MTL in a battery of visuo-spatial short-term memory tasks. Damage was either caused by surgery for a benign brain tumor, herpes encephalitis or global cerebral hypoxia. When tested with an associative visuo-spatial memory task that has previously been shown to be sensitive to hippocampal integrity, all patient groups showed deficits that were quantitatively and qualitatively similar, regardless of the underlying disorder and laterality of lesions. Performance in non-associative tasks however differed significantly between groups. Significant impairments were only observed in patients with a history of herpes encephalitis or global cerebral hypoxia. In the following, we will discuss how these findings relate to the choice of distinct patient models in studies of human memory and to the organization of visuo-spatial memory in the normal brain.

4.1. Laterality of MTL lesions

Ever since Milner's first observations of material-specific memory deficits following unilateral resection of the MTL (Milner, 1966), it has become a widely accepted view that verbal memory functions are lateralized to the left MTL and visuospatial memory to the right MTL (see Saling (2009) and Willment and Golgy (2013) for reviews). While numerous subsequent patient and imaging studies have supported a hemispheric asymmetry for verbal memory, the findings on visuospatial memory are much more heterogeneous. A number of recent studies on patients with MTL pathology reported at best a slight hemisphere bias or no asymmetry at all, when patients were tested with visuospatial memory tasks that presumably precluded verbal strategies (e.g. Glikmann-Johnston et al., 2008; Jeyaraj et al., 2013; McConley et al., 2008; Shehzad et al., 2009; Wagner et al., 2009). A major obstacle for a conclusive interpretation of these divergent results is the fact, that most of these studies mainly included patients with medial temporal lobe epilepsy due to hippocampal sclerosis (HS). By combining lesion and fMRI studies, it has been shown that HS is a complex neurodevelopmental network disorder that induces significant reorganization of memory within and across hemispheres, both between right and left MTLs and between MTL and remote cortical areas (Bonelli et al., 2013; Braun et al., 2008; Düzel et al., 2006; Figueiredo et al., 2008; Finke et al., 2013). Thus, lateralization of memory deficits in HS patients may also reflect hemispheric asymmetries in efficacy of compensation in addition to lateralization of memory in the normal brain. Ideally, a patient model for lateralization of memory functions should therefore consist of humans with selective lesions of the MTL acquired in adulthood (Squire and Wixted, 2011; Stark, 2007). Here, we have used operated unilateral benign brain tumors as a lesion model of MTL dysfunction. Although it is not possible to precisely define the onset of the disorder, onset of epilepsy in our patients preceded tumor resection by two years on average only. This time course suggests that preoperative compensatory processes with a consecutive neurodevelopmental bias in behavioral results are less likely than in operated HS patients (Braun et al., 2008; Finke et al., 2013). The findings of similar visuo-spatial memory performance in patients with left- and right-sided lesions in our cohort thus strongly point to significant visuo-spatial memory functions of the left MTL, with only slight asymmetry between hemispheres. Furthermore, they support the notion that verbal and non-verbal memory are not simple opposites in terms of their respective patterns of cerebral organization (Saling, 2009). This does of course not exclude the possibility of verbal strategies contributing to memory performance in our tasks. These strategies would however not satisfactorily explain the impairments observed in our patients.

Previous patient studies have frequently used single subject groups consisting of a combination of bilateral, strongly lateralized or unilateral MTL-lesioned patients (e.g. Barrash et al., 2000; Hartley et al., 2007; Olson et al., 2006). Since there have been no systematic comparisons of behavioral deficits with unilateral and bilateral lesions of the MTL, their comparability has been an open issue. Facing these ambiguities, bilaterality of lesions has been considered to be a more appropriate model of MTL dysfunction (Squire and Wixted, 2011; Stark, 2007). Surprisingly, the findings in our study suggest that – at least for associative visuospatial memory - uni- and bilateral lesions yield similar performance deficits, thus pointing to strong interactions between both MTLs. Indeed, recent fMRI studies demonstrated a high degree of functional connectivity between the left and right MTL and moreover identified bilateral functional networks comprising both MTLs engaged in memory processing (Campo et al., 2012, 2013; Peer et al., 2014; Wang et al., 2010). In healthy subjects, the strength of

interhemispheric hippocampal connectivity correlated with individual memory performance (Wang et al., 2010). Importantly, disruption of a single node of the memory network, e.g. in unilateral hippocampal sclerosis, caused bilateral alterations of functional connectivity that were correlated with impaired memory performance (Campo et al., 2012, 2013). In the light of these results, our data support a view in which both MTLs may form nodes of a bi-hemispherial network for associative visuo-spatial memory, with network disruption in either hemisphere causing similar performance decrements. Alternatively, similar performance in patients with uni- and bilateral hippocampal damage may also result from the categorical output variables of our tasks ('match' vs. 'non-match'). Provided that visuo-spatial stimuli are dependent on lateralized processing and on hemifield representations involving mainly the contralateral MTLs (Hornak et al., 2002; Ploner et al., 2000), contralesional mnemonic 'scotomas' may be sufficient to cause significant performance decrements for stimuli which are presented across both visual hemifields. This hypothesis however does not exclude the possibility that memory of stimuli that are easy to verbalize or memory of abstract and less action-oriented representations than those required in our study still show significant hemispheric asymmetry (Barkas et al., 2010). The difference in performance of HSE-patients with predominately right- and left-sided lesions in delayed reproduction of the Rey–Osterrieth complex figure may support this hypothesis.

It should be conceded here, that similar effects of uni- and bilateral lesions of the hippocampal formation on associative memory in our patients do not imply that unilateral lesions fully disrupt integrity of the proposed bi-hemispherial network for associative visuo-spatial memory. Despite significant impairment, performance in the association task was clearly above chance level in all investigated patient groups, suggesting that residual hippocampal function was present in all patients. Moreover, our patients' performance in the Rey–Osterrieth Complex Figure task was not or only moderately impaired. It has been shown previously, that patients with neuropathologically verified bilateral lesions of the hippocampus can show severe deficits in delayed reproduction of the figure (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996). Although impairments in the task may result from lesions in several regions of the brain (Shin et al., 2006), these seemingly divergent results are best reconciled by the hypothesis that hippocampal damage was incomplete in our patients. Notwithstanding this important constraint, our data show that patients with right or left unilateral damage to the MTL acquired in adulthood may provide a model for hippocampal dysfunction in associative visuo-spatial memory that is just as appropriate as patients with bilateral lesions.

4.2. Selectivity of MTL lesions

Compared to our R-MTL and L-MTL patients, HSE patients showed significant deficits in non-associative tasks that were less clearly delay-dependent than the associative deficits. These distinct temporal properties likely point to cognitive domains that were additionally affected in HSE-patients and that contributed to performance deficits in non-associative memory tasks. Analysis of rostro-caudal extent of lesions, in particular of the hippocampus, further showed that differences between these groups cannot fully be explained by the magnitude of hippocampal damage. The more so, as entorhinal damage was substantial in all patients. Since most of the communication between extrahippocampal regions and the hippocampus passes through the entorhinal cortex, caudal hippocampal portions were likely to be largely de-afferented and de-efferented in most patients, leading to a memory deficit that is not further accentuated by posterior hippocampal damage (Corkin et al., 1997). Thus, deficits in non-associative tasks may either result from bilaterality of lesions or from additional damage to brain regions outside the MTL. As lesion etiology, laterality and extent are not independent variables, it is difficult to unequivocally relate these findings exclusively to one of these factors. However, the results from our laterality analyses in HSE patients suggest that bilaterality may not be decisive for additional non-associative deficits. Our findings are thus in line with results from classic studies of visuo-spatial memory in patients with unilateral anterior temporal lobe resections, showing that while object-location memory appears to depend on integrity of the body of the hippocampus, particularly on the right side, memory of non-associative details of visual scenes is likely to be mediated by temporal neocortex (Pigott and Milner, 1993; Smith and Milner, 1989). They further parallel previous observations of our group in a sample of patients with postsurgical unilateral lesions of the MTL, where deficits in non-associative task critically depended on lesion to temporal regions outside the hippocampal formation and perirhinal cortex (Braun et al., 2008). It is nevertheless difficult to definitely isolate the neuronal substrate for these additional deficits in HSE-patients, since lesions extending into the white matter may affect a multitude of fascicular connections (e.g. inferior longitudinal fasciculus, fronto-occipital fasciculus, uncinate fasciculus), causing cognitive impairments that cannot simply be related to a single temporal region and that are difficult to reconstruct from routine MRI (Hodgetts et al., 2015; Lockhart et al., 2012; Rémy et al., 2015). Moreover, secondary auto-immune mechanisms in the chronic stage of the disease may cause cognitive impairments that are not necessarily accompanied by brain lesions on routine structural MRI (Prüss et al., 2012). Thus, future studies with diffusion tensor imaging should clarify the contribution of white matter disruption to impairments in non-associative memory tasks in HSE patients.

The pattern of memory deficits in our GCH patients showed considerable overlap with the impairment seen in HSE patients. Like in many other studies on amnesic patients following resuscitation from cardiac arrest, implanted pacemakers in our GCH patients precluded cerebral MRI by the time of testing. The significant deficits in non-associative tasks nevertheless suggest significant damage to regions outside the hippocampus as well. Indeed, neuropathologically verified postanoxic lesions selective to the hippocampus are rare exceptions (Zola-Morgan et al., 1986; Rempel-Clower et al., 1996). Among the cognitive deficits seen in cardiac arrest survivors that achieve functional independence after rehabilitation, memory deficits predominate in many patients (Alexander et al., 2011; Mateen et al., 2011; Moulaert et al., 2009). In the absence of detailed imaging data, inferences from experimental studies on these patients are frequently based on the assumption that memory deficits following resuscitation may reflect hippocampal damage. However, neuropathological studies indicate that neuronal injury is much more widespread in many patients and may include neocortex, basal ganglia, thalamus and cerebellum (Caine and Watson, 2000; Björklund et al., 2014). Studies with diffusion-weighted and structural MRI further support the notion that the majority of cardiac arrest patients have significant extrahippocampal injury (Allen et al., 2006; Grubb et al., 2000; Mlynash et al., 2010), with memory deficits in some studies correlating more closely with whole-brain volumes than with hippocampal volumes (Grubb et al., 2000). Our findings support these observations by showing that even in the absence of overt damage to cortex outside the MTL in routine imaging protocols, covert damage to these regions may significantly contribute to the overall pattern of impairment in memory tasks (Squire and Wixted, 2011; Stark, 2007). This may also explain why the magnitude of anoxic hippocampal damage does not necessarily correlate with the severity and pattern of memory deficits in patients

with hippocampal atrophy following cardiac arrest (Holdstock et al., 2008). Although we have no detailed anatomical group information for our GCH patients, comparison of memory impairments to the other patient groups suggests that significant residual hippocampal function was present in all patients and thus additional deficits in non-associative tasks in GCH patients are unlikely to result from particularly severe hippocampal injury.

4.3. MTL lesions and associative memory

A long-standing discussion concerns a possible division of labor between MTL sub-regions, with a particular focus on the hippocampal formation vs. adjacent neocortex. Several dichotomies have been proposed to conceptualize these functional differences (e.g. familiarity vs. recollection, associative vs. non-associative, items vs. relationships, item vs. context; see Eichenbaum et al. (2007), Mayes et al. (2007), Ranganath (2010) and Squire and Wixted (2011) for reviews). Most human lesion studies agree on a role of the hippocampus for relational or associative information (e.g. Stark et al., 2002; Stark and Squire, 2003; Olson et al., 2006, Gold et al., 2006, Finke et al., 2008, Hannula et al., 2006, 2015). However, exceptions have been reported (Jeneson et al., 2010). What the studies differ in is the extent to which non-associative or item memory depends on integrity of the hippocampus. Several authors found equivalent deficits of item or non-associative memory (e.g. Hopkins et al., 1995; Gold et al., 2006; Stark et al., 2002, Stark and Squire, 2003; Holdstock et al., 2008), others predominately relational or associative deficits (e.g. Olson et al., 2006; Finke et al., 2008; Hannula et al., 2006, 2015). While some of these divergent findings may be explained by differences in sensitivity of tasks (Hannula et al., 2015), a possible role of disease-related factors has only rarely been investigated. In one of the few studies on this subject, Yonelinas et al. (2002) investigated familiarity and recollection for verbal material in patients resuscitated from cardiac arrest and in patients with unilateral post-surgical/post-ischemic lesions. Both patient groups suffered from similar impairments in recollection (assumed to be hippocampus-mediated), but differed in impairments in familiarity (presumably mediated by extrahippocampal regions). More recently, Hannula et al. (2015) have investigated visuo-spatial relational and item memory with an eye-movement memory task and visual scenes in patients following global cerebral hypoxia (assumed to have predominantly hippocampal damage) and herpes encephalitis/closed head injury (proven substantial hippocampal and extra-hippocampal damage). Much like our post-hypoxic and post-encephalitic patients, both patient groups exhibited impairments in relational memory and in item memory (albeit to a slightly lesser degree), despite methodological differences to our study that used much simpler stimulus material. Moreover, item memory deficits in this study appeared to correlate with the degree of parahippocampal atrophy on MRI.

We do of course not claim that these few studies together with our findings resolve debates about dichotomies in the MTL, which is an issue that requires extensive consideration of multiple experimental, clinical and imaging findings in humans and animals. The more so, as our tasks differ from those that are commonly used in neuroscience and neuropsychological studies of the MTL. These tasks mostly do not require fixation, stimuli are often presented for much longer durations, and frequently consist of complex objects, faces, scenes or other semantically meaningful materials. In contrast, the stimuli used in the current study consisted of relatively simple features, such as colors and locations. Our inferences are thus limited to associative visuo-spatial short-term memory. Comparison of our data to the few studies that did investigate the role of disease characteristics nevertheless reveals similarities across results with a particular sensitivity of non-associative tasks to extra-hippocampal damage.

4.4. Conclusion

Although we are cautious to prematurely generalize our findings on other memory domains, the findings reported here may have implications for patient studies of MTL-dependent visuo-spatial short-term memory. MTL lesions acquired during adulthood may provide a valid model for dysfunction of hippocampus-dependent associative visuo-spatial short-term memory, largely regardless of lesion etiology, laterality and selectivity. However, the choice of a distinct patient model may significantly determine non-associative contributions to visuo-spatial short-term memory deficits in MTL-lesioned patients, presumably reflecting additional damage of brain regions outside the MTL. Thus, disease characteristics appear to be particularly critical for those studies that focus on possible differential contributions of hippocampus and extrahippocampal cortex to visuo-spatial short-term memory.

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