J Neurol (2015) 262:2214–2224
DOI 10.1007/s00415-015-7831-3

ORIGINAL COMMUNICATION

Relevance of hippocampal integrity for memory outcome after surgical treatment of mesial temporal lobe epilepsy

Juri-Alexander Witt[1] · Roland Coras[2] · Johannes Schramm[3] · Albert J. Becker[4] · Christian E. Elger[1] · Ingmar Blümcke[2] · Christoph Helmstaedter[1]

Received: 21 May 2015 / Revised: 17 June 2015 / Accepted: 18 June 2015 / Published online: 3 July 2015

Abstract Surgical treatment of unilateral mesial temporal lobe epilepsy (mTLE) particularly bears the risk of episodic memory decline. The present study investigates the role of the ipsilateral hippocampal integrity for postoperative change in material-specific memory performance. In 104 patients who had undergone epilepsy surgery for unilateral mTLE, we analyzed pre- to postoperative changes of verbal and figural memory as a function of segmental neuronal cell densities of the resected hippocampus (cornu ammonis, CA1–4; internal and external limb of the dentate gyrus, DG). Results were controlled for side of surgery and hemispheric dominance. Surgery caused significant memory decline, especially with regard to verbal memory after left temporal resections. Seizure freedom (65 % Engel Ia) did not affect memory outcome. Higher neuronal cell densities of the resected left hippocampus were associated with greater declines in verbal memory parameters ($r = -0.27$ to $r = -0.39$, $p < 0.05$), especially when excluding patients with atypical hemispheric dominance ($r = -0.34$ to $r = -0.60$, $p < 0.05$; significant correlations across all hippocampal subfields). There were no systematic correlations between neuronal cell densities of the resected right hippocampus and memory changes. The results emphasize the role of the structural and functional integrity of the hippocampus within the left dominant hemisphere for the degree of verbal memory decline after temporal lobe surgery. Presurgical verbal memory performance may be taken as a marker of ipsilateral left hippocampal integrity and may contribute to individual risk–benefit evaluations before epilepsy surgery. Finally, more precise neuropsychological markers of right hippocampal integrity are needed.

Keywords Epilepsy surgery · Neuropsychology · Hippocampus · Outcome · Cognition

Introduction

Pharmacoresistant mesial temporal lobe epilepsies (mTLE) represent the most frequent indication for epilepsy surgery. Given the essential role of the limbic system for declarative memory functions [1], the surgical treatment for mTLE particularly bears the risk of memory decline. According to a recent meta-analysis [2], the risk of significant deteriorations in verbal memory is 44 % for epilepsy surgeries within the left temporal lobe and 20 % for right temporal lobe resections, whereas significant declines in nonverbal memory functions are to be expected after 21–23 % of temporal lobe surgeries.

Three major factors have been identified as determinants of the cognitive and mnestic outcome after surgical treatment of mTLE [3–5]: (1) the functional integrity of the resected tissues (also termed "functional adequacy"), (2) cognitive reserve capacities, and (3) postsurgical seizure control.

Electronic supplementary material The online version of this article (doi:10.1007/s00415-015-7831-3) contains supplementary material, which is available to authorized users.

✉ Juri-Alexander Witt
juri-alexander.witt@ukb.uni-bonn.de

[1] Department of Epileptology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany

[2] Department of Neuropathology, University Hospital of Erlangen, Erlangen, Germany

[3] Department of Neurosurgery, University of Bonn, Bonn, Germany

[4] Department of Neuropathology, University of Bonn, Bonn, Germany

Postoperative seizure freedom can lead to a functional recovery of brain regions that were secondarily affected by the active epilepsy [3, 6, 7].

Cognitive reserve capacities refer to the efficiency and plasticity of the brain to counteract iatrogenic negative effects of epilepsy surgery [8]. Higher reserve capacities are reflected by better presurgical functioning as well as by higher intelligence and education. Finally, a younger age and female sex are associated with greater functional plasticity [9–11]. In this regard age at onset and duration of epilepsy need to be considered, reflecting time windows and critical phases for reorganization processes [8].

In this context the functional integrity of the structures which are going to be resected has a major impact on the cognitive outcome of epilepsy surgery [12]. A postoperative decline is to be expected when the resection area still subserves cognitive functions. The cognitive deterioration after surgical removal of non-lesional tissue in MRI- and histopathology-negative patients with TLE may serve as proof of principle [13]. Consequently, the severity and extent of the underlying pathology can represent an estimate of the functional integrity of the to-be-resected structures. One approach to quantify pathology in mesial temporal lobe epilepsy is the analysis of neuropathological specimens, i.e. semi-quantitative measurements of hippocampal cell loss. In two studies by Hermann et al. verbal (and in the earlier study also nonverbal) memory decline after left temporal lobe epilepsy surgery was greater in patients with absent or mild (Wyler I or no HS) versus severe (Wyler II–IV) hippocampal pathology [14, 15]. This differential outcome was not observed in patients with right temporal lobe resections. Similar findings were reported by Rausch and Babb [16] and by Sass et al. [17] who performed a median split on quantified neuron densities within the resected hippocampus to distinguish patients with severe versus mild to moderate hippocampal pathology. Both studies focused on verbal memory and again solely the left hippocampal integrity was relevant for the postsurgical memory outcome. Two other studies [18, 19] directly correlated neuronal cell densities of hippocampal specimens with postoperative memory changes, indicating that greater decline in verbal memory is associated with higher neuron densities in CA1 (cornu ammonis). The study by Zaidel et al. [19] in addition also found significant correlations between verbal memory changes and cell loss in CA4 and the dentate gyrus, while the subfields CA2 and CA3 had not been investigated.

Despite different methodological approaches, all cited studies emphasize the importance of the hippocampal integrity for verbal memory change after left temporal lobe surgery. The role of the structural integrity of the right hippocampus for postsurgical memory change remains unclear.

Previous studies often had small and heterogeneous samples, partially with mixed samples of mesial and lateral TLE, and they used memory tests with different sensitivities to mesial temporal lobe pathologies [20, 21]. In the current study, we examined postoperative memory change as a function of neuronal cell densities within hippocampal subfields in a large sample of patients with solely mesial temporal lobe epilepsy (mTLE), employing verbal and figural memory tests with proven sensitivity to mesiotemporal pathology. Since our previous study in the same sample had revealed that the overall integrity (rather than specific subfields) of the resected hippocampus is an important determinant of preoperative memory performance [22], we again analyzed the mean neuronal cell loss across all subfields.

According to the functional adequacy theory, we expected a positive correlation between the degree of postsurgical memory declines and neuronal cell densities. In addition, moderating effects of the side of surgery and the individual pattern of hemispheric dominance for language and verbal memory were assumed [22, 23].

Methods

Patients

The analyses were based on 104 consecutive patients who underwent surgical treatment of unilateral mesial temporal lobe epilepsy at the neurosurgery department of the University of Bonn [22]. The comprehensive presurgical evaluation with non-invasive and/or invasive procedures revealed seizure onset in the mesial temporal lobe in all patients [24]. The resection of the hippocampus was clinically indicated in every case. All procedures were conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Bonn Medical Center. Informed written consent was obtained from all patients.

Inclusion criteria comprised a chronological age of at least 16 years, complete data on neuronal cell densities for all hippocampal subfields, and complete pre- and postsurgical neuropsychological assessments on verbal and figural memory.

Side of surgery was balanced with 53 left (51 %) and 51 right (49 %) temporal lobe resections. The most frequent type of surgery was selective amygdalohippocampectomy (80 %), followed by standard two-third resection of the temporal lobe (8 %), resection of the temporal pole plus

amygdalohippocampectomy (7 %), and extended lesionectomy plus amygdalohippocampectomy (6 %).

Demographic and clinical characteristics of the study sample are given in Table 1. More detailed information on the antiepileptic treatment at the time of the pre- and postsurgical assessment is provided in Supplementary Table 1. There were no significant differences in demographic and clinical characteristics between patients with left versus right temporal lobe surgeries.

The sample was composed of 54 female (52 %) and 50 male patients (48 %) with a mean age of 38.2 ± 12.8 (standard deviation). The average age at onset of epilepsy was 15.5 ± 12.5 years, the mean duration of epilepsy 22.7 ± 13.9 years. Prior to surgery, patients suffered from 8.9 ± 11.4 seizures per month. At the time of the postsurgical neuropsychological assessment, i.e. 12.9 ± 3.7 months after surgery, 65 % had been completely seizure free (Engel Ia/ILAE Ia; Table 1). This was accompanied by a significantly reduced mean number of concurrent AEDs ($t = 3.818$, $p < 0.001$; Table 1).

As part of the presurgical evaluation, 47 % of the patients underwent assessment of language dominance (32 % language fMRI, 17 % Wada; 2 % both). In patients without determination of language dominance, atypical hand dominance in left mTLE (4 %) or a neuropsychological suppression pattern (i.e. intraindividual profile with significantly better verbal than nonverbal memory performance despite left mesial temporal lobe epilepsy) (4 %) served as markers of atypical dominance regarding language or material-specific memory functions [25–27]. Despite typical language dominance as revealed by fMRI or Wada, the intraindividual material-specific memory profile of 4 patients with left mTLE (4 %) indicated a selective memory transfer [28, 29]. All in all, 16 patients (30 %) of those with left mesial temporal lobe epilepsy presented with markers of an atypical dominance for language or material-specific memory functions.

Pre- and postoperative memory assessment

Neuropsychological examinations of verbal and nonverbal memory functions were conducted as part of the presurgical evaluation and again around 1 year after surgery. To minimize practice effects parallel versions of the memory tests were employed at the postoperative assessment.

Verbal memory performance was assessed using the Verbaler Lern- und Merkfähigkeitstest (VLMT) [30], a modified German version of the Rey Auditory Verbal Learning Test—RAVLT [31]. The VLMT is the most frequently applied verbal learning and memory test in German epilepsy centers [32]. The test requires serial learning and immediate recall of 15 words in five consecutive learning trials, free recall after distraction as well as free recall and recognition of the target words after a 30-min delay. Analyses were based on learning performance (total number of words learned in five trials), delayed free recall, and recognition performance (corrected for false-positive answers). The test has been shown to be sensitive to left temporal lobe dysfunction, left mesiotemporal pathology and left-sided temporal lobe surgery [33–36].

Nonverbal figural memory was assessed by the revised version of the Diagnosticum für Cerebralschädigung (DCS-R) [37]. The test requires learning and reconstruction of 9 abstract designs in 5 consecutive trials. After a retention interval of 30 min, recognition memory is tested. The considered measures were the number of correctly learned designs over 5 learning trials and recognition performance (corrected for false-positive answers). The test has been shown to be sensitive to right temporal lobe dysfunction, right mesiotemporal pathology, and also to right-sided temporal lobe surgery [36–39].

Postoperative changes were determined by the difference between pre- and postsurgical scores (postoperative raw score minus preoperative raw score, i.e. positive values indicate gains, negative values indicate losses, and a value of zero indicates no change). To evaluate significant intraindividual changes, both memory tests provide practice-corrected reliable change indices (RCI) based on 100–142 reassessed healthy controls.

At the time of the neuropsychological assessments, the examiner was not aware of the neuropathological results.

Neuropathological examination

Hippocampal specimens were microscopically examined at the Department of Neuropathology, University Hospital of Erlangen. Neuropathological investigators were blinded to pre- and postoperative neuropsychological results.

En bloc specimens of the hippocampus were dissected into 5 mm thick slices along the anterior-posterior axis. Only tissue from the mid-hippocampal body was selected for this study to warrant unequivocal recognition of all subfields of the hippocampal pyramidal cell layer as well as the granule cell layer. The tissue was fixed overnight in 4 % formalin and routinely processed into liquid paraffin. Four-µm sections were stained with hematoxylin and eosin (HE) for histopathological inspection. Hippocampal pyramidal neurons and granule cells of the DG were specifically detected using immunohistochemistry for the neuronal core antigen NeuN (A60, Chemicon, Temecula, USA, dilution 1:1000, pre-treated with microwave) and an automated staining apparatus using the streptavidin–biotin method (Ventana; Strasbourg, France) and 3,3′-

Table 1 Demographic and clinical characteristics and neuronal cell densities of the resected hippocampus

	Total ($N = 104$)	Left mTLE ($N = 53$)	Right mTLE ($N = 51$)	
Sex				
Female	54 (48 %)	27 (51 %)	27 (53 %)	ns
Male	50 (52 %)	26 (49 %)	24 (47 %)	
Age (years)				
M (SD)	38.2 (12.8)	39.8 (12.8)	37.0 (12.8)	ns
Range	16–67	16–67	16–66	
Onset of epilepsy (age in years)				
M (SD)	15.5 (12.5)	14.6 (13.2)	16.5 (11.7)	ns
Range	0–58	0–58	0–48	
Duration of epilepsy (years)				
M (SD)	22.7 (13.9)	25.2 (13.4)	20.1 (14.0)	ns
Range	0–57	2–57	0–57	
Presurgical seizure types				
Simple-partial	41 (39 %)	23 (43 %)	18 (35 %)	ns
Complex-partial	102 (98 %)	52 (98 %)	50 (98 %)	
Secondarily generalized	72 (69 %)	39 (74 %)	33 (65 %)	
Presurgical seizure frequency (seizures per month)	($N = 99$)	($N = 49$)	($N = 50$)	
M (SD)	8.9 (11.4)	8.4 (10.7)	9.4 (12.1)	ns
Range	0–60	1–60	0–60	
Postsurgical seizure freedom				
Engel Ia/ILAE Ia	68 (65 %)	36 (68 %)	32 (63 %)	ns
Epilepsy surgery				
SAH	83 (80 %)	44 (83 %)	39 (77 %)	ns
TPR + AHE	7 (7 %)	4 (8 %)	3 (6 %)	
Extended LE + AHE	6 (6 %)	2 (4 %)	4 (8 %)	
Standard ATLR	8 (8 %)	3 (6 %)	5 (10 %)	
Neuronal cell densities (neurons/mm^2)				
CA1				
M (SD)	91.2 (87.5)	94.6 (96.8)	87.7 (77.5)	ns
Range	0–416	0–416	8–328	
CA2				
M (SD)	231.9 (86.4)	237.0 (90.0)	226.5 (83.1)	ns
Range	0–424	0–424	16–392	
CA3				
M (SD)	129.4 (80.5)	135.5 (90.3)	123.1 (69.2)	ns
Range	0–408	0–408	29–292	
CA4				
M (SD)	77.7 (69.2)	82.6 (78.2)	72.6 (58.8)	ns
Range	0–252	0–252	8–220	
DGint				
M (SD)	1408.3 (727.0)	1470.2 (850.0)	1343.9 (573.7)	ns
Range	250–3420	250–3420	660–3140	
DGext				
M (SD)	1628.8 (755.9)	1621.9 (843.9)	1635.9 (660.4)	ns
Range	170–4000	170–4000	590–3360	
Presurgical number of AEDs				
M (SD)	2.1 (0.7)	2.1 (0.7)	2.0 (0.7)	ns
Range	0–3	0–3	1–3	

Table 1 continued

	Total ($N = 104$)	Left mTLE ($N = 53$)	Right mTLE ($N = 51$)	
Postsurgical number of AEDs				
M (SD)	1.7 (0.7)	1.6 (0.7)	1.8 (0.8)	ns
Range	0–4	0–3	0–4	

mTLE mesial temporal lobe epilepsy, *M* mean, *SD* standard deviation, *TBI* traumatic brain injury, *SAH* selective amygdalohippocampectomy, *TPR* temporal pole resection, *AHE* amygdalohippocampectomy, *LE* lesionectomy, *ATLR* anterior temporal lobe resection, *CA* cornu ammonis, *DG* dentate gyrus, *int* internus, *ext* externus, *AEDs* antiepileptic drugs, *ns* no significant difference

diaminobenzidine as chromogen as well as hematoxylin counterstaining.

One representative hippocampal specimen was chosen from each subject for semi-quantitative neuronal cell counts. Semi-quantitative measurements of neuronal cell numbers were performed with a microcomputer imaging system (ColorView II CCD camera, AnalySIS imaging software, Stuttgart, Germany) equipped to a BX51 microscope (Olympus, Japan). Only NeuN-immunoreactive neuronal cell bodies were tagged on the computer screen and counted separately within hippocampal sectors CA1, CA2, CA3 and CA4 in four randomly placed visual fields at 20× objective magnification (Fig. 1). We separately examined granule cells of the external (DGext) and internal (DGint) limb at 40× objective magnification in ten randomly placed visual fields (Fig. 1). The hippocampal subfield specific quantification method was previously described to match data obtained from stereological cell counts and to be suitable for clinico-pathological correlations when using formalin-fixed and paraffin-embedded surgical human tissue specimens [40–42]. Differentiation of human hippocampal subfields followed the first international classification system for hippocampal sclerosis [42]. Subfield specific analyses were based on absolute cell densities. However, to determine the overall integrity of the hippocampus, neuronal cell counts (neurons/mm^2) were in the first instance transformed into standard-scores (mean = 100, standard deviation = 10) according to control values obtained from autopsy brains. Finally, since principal component analysis of segmental neuronal cell loss within the hippocampus had revealed a single factor structure [22], the mean standardized neuronal cell density across all hippocampal subfields was calculated. This index was termed "hippocampal integrity index" (HCI).

Statistical analyses

Repeated measures multivariate analyses of variances (MANOVA) were used to analyze pre- to postoperative memory change. Correlation analyses (Pearson) were applied to investigate the relationship between neuropsychological and neuropathological data.

Results

Neuronal cell densities

The neuronal cell densities of the resected hippocampal specimens are presented in Table 1. The most affected subfield was CA1 with a mean neuronal cell loss of 72 % followed by CA4 (67 %), CA3 (58 %), DGint (58 %), DGext (51 %) and finally CA2 with the least cell loss (42 %). The pattern of neuronal cell loss was not different for left and right hippocampal specimens.

Pre- to postoperative change of memory performance

The pre- and postsurgical mean memory performance of patients with left versus right mTLE is illustrated in Fig. 2. A repeated measures MANOVA with the between-subject factors "side of surgery" and "postsurgical seizure freedom" revealed a significant impact of surgery on memory performance ($F = 3.31, p = 0.003$) and a related interaction effect of the side of surgery ($F = 2.72$, $p = 0.013$), but not of seizure control ($F = 0.96, p = 0.468$). In the total sample, all memory parameters showed a postoperative decline. When considering the side of surgery, patients with left hemispheric resections showed greater deteriorations in verbal learning ($F = 12.53$, $p = 0.001$) and recognition ($F = 8.60$, $p = 0.004$) than those with right-sided operations. Regarding verbal delayed free recall a trend into the same direction was observed ($F = 3.91, p = 0.051$). Changes in figural memory were not dependent on the side of surgery.

Significant changes of memory performance on an individual level are summarized in Table 2. According to RCIs, 42–62 % of the patients deteriorated in verbal memory functions after left-sided surgery versus 9–13 % after right temporal resections. The respective numbers for figural memory were 9–11 % versus 10–20 % after surgical treatment of left versus right mTLE. However, regarding the decline of figural learning performance floor effects need to considered in 26 % of patients with left mTLE and 45 % of patients with right mTLE. In those patients significant postsurgical deteriorations in figural learning could

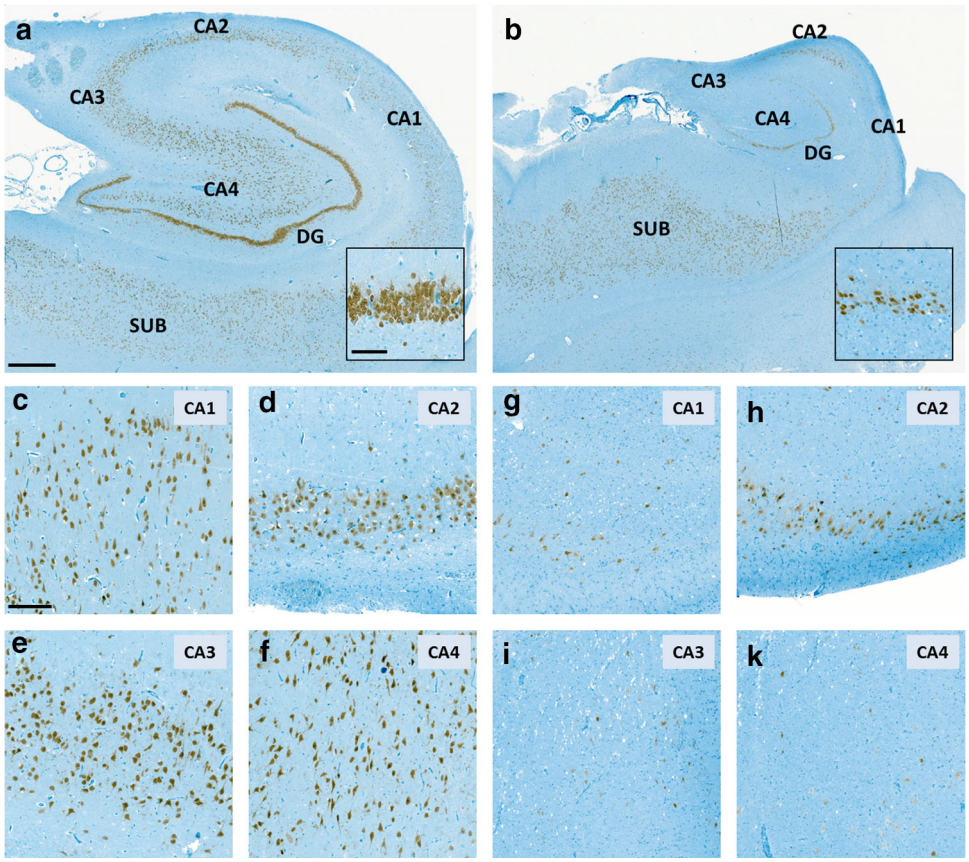

Fig. 1 Surgical specimen of **a** a non-pathological human hippocampus (control) as compared with **b** severe hippocampal sclerosis (HC). The *figure* shows the different anatomic subregions of the hippocampus including cornu ammonis (CA) sectors *CA1–CA4* as well as the dentate gyrus (DG). **a** NeuN immunohistochemistry of the hippocampus highlighting the subiculum (*SUB*), the sectors of the Cornu ammonis (*CA1–CA4*) and the dentate gyrus (*DG*) without evidence for segmental cell loss. *Inset* in **a** higher magnification of the dentate gyrus. Regular package density of the granule cell layer without signs of granule cell loss or dispersion. **c–f** Higher magnification (of **a**) of the Cornu ammonis sectors with regular pyramidal cell densities. **b** NeuN immunohistochemistry evidencing neuronal cell loss in sectors *CA1–CA4*. *Inset* in **b** higher magnification of the dentate gyrus with areas of severe granule cell depletion. **g–k** Higher magnification (of **b**) of the cornu ammonis sectors with severe pyramidal cell loss in all subfields (*CA1*, *CA3* and *CA4* more severe than *CA2*). **a**, **c**, **d** specimen with no hippocampal sclerosis. **b**, **g–k** specimen with hippocampal sclerosis (ILAE HS Type 1). Of note **a** and **b** are of same magnification, indicating also the 'shrinkage' of the hippocampal body in a specimen with hippocampal sclerosis. *Scale bar* in **a** 1 mm, applies also for **b**. *Scale bar inset* in **a** 100 µm, applies also for *inset* in **b**. *Scale bar* in **c** 200 µm, applies also for **d–k**

no longer be demonstrated, because of the already severely impaired presurgical performance.

Postsurgical memory change as a function of neuronal cell densities

Correlation analyses indicated significant relationships between neuronal cell counts of the left hippocampus and the postsurgical decline of all three verbal memory parameters. Higher cell densities were associated with greater deteriorations. Correlation coefficients ranged from $r = -0.27$ to $r = -0.39$ (Table 3). Among the hippocampal subfields only CA3 and DGext were unrelated to verbal memory change. Solely one significant correlation was found between neuronal cell loss of CA4 and figural (recognition) memory ($r = -0.31$, $p < 0.05$).

In the subgroup of patients with left mTLE and no evidence of atypical hemispheric dominance ($N = 37$) markedly higher correlations between hippocampal cell loss and change in verbal memory indices were observed, ranging from $r = -0.34$ to $r = -0.60$ (Table 4). In that subgroup, changes in verbal learning and delayed free recall were correlated with cell counts of all hippocampal segments. The hippocampal integrity index (HCI) explained up to 34 % of the observed variance in verbal memory change.

Segmental cell loss within the right hippocampus showed no significant correlations with verbal memory change. Regarding figural memory, only one significant correlation could be discerned: higher cell counts within CA3 were associated with greater declines in figural recognition.

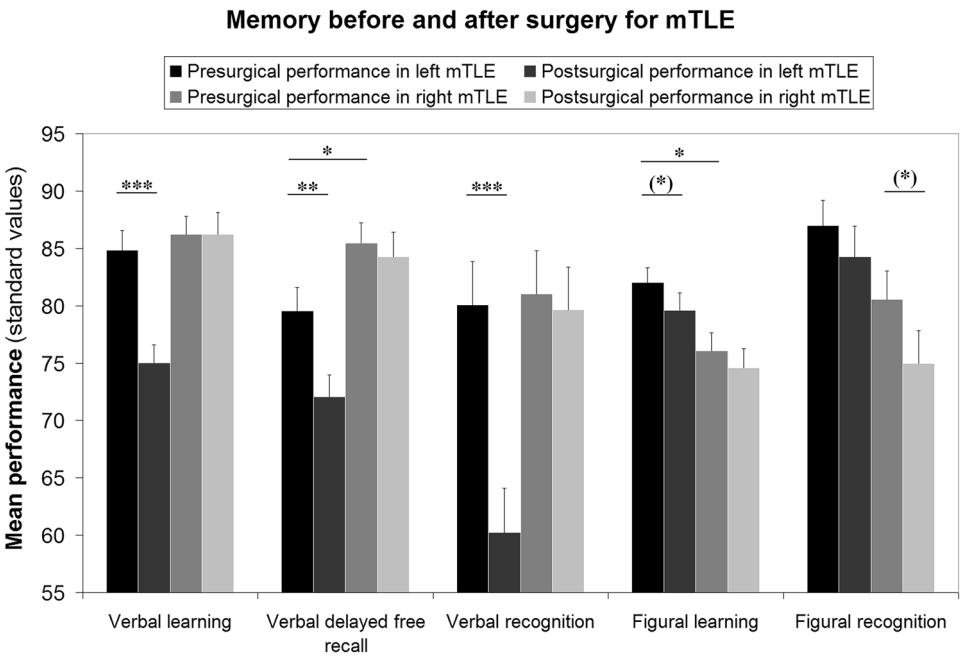

Fig. 2 Standardized pre- and postsurgical memory performance of patients who underwent left- versus right-sided surgery for mesial temporal lobe epilepsy (mTLE). Memory parameters were standardized according to a co-normalization sample of 488 healthy volunteers (mean = 100, standard deviation = 10), applying a correction for age. Higher values reflect better performance. Values <90 indicate below average performance compared to the healthy normative sample. (*) $p < 0.10$, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 2 Frequencies of significant individual changes after temporal lobe surgery according to reliable change indices

	Total ($N = 104$)	Left mTLE ($N = 53$)	Right mTLE ($N = 51$)	
Verbal learning				
Improvement	7 (7 %)	1 (2 %)	6 (12 %)	$\chi^2 = 8.70$
Deterioration	37 (36 %)	25 (47 %)	12 (24 %)	$p = 0.013$
Verbal delayed free recall				
Improvement	12 (12 %)	4 (8 %)	8 (16 %)	ns
Deterioration	37 (36 %)	22 (42 %)	15 (29 %)	
[Floor effect]	6 (6 %)	5 (9 %)	1 (2 %)	
Verbal recognition				
Improvement	13 (13 %)	4 (8 %)	9 (18 %)	$\chi^2 = 8.98$
Deterioration	50 (48 %)	33 (62 %)	17 (33 %)	$p = 0.011$
Figural learning				
Improvement	13 (13 %)	7 (13 %)	6 (12 %)	ns
Deterioration	10 (10 %)	5 (9 %)	5 (10 %)	
[Floor effect]	37 (36 %)	14 (26 %)	23 (45 %)	
Figural recognition				
Improvement	20 (19 %)	10 (19 %)	10 (20 %)	ns
Deterioration	16 (15 %)	6 (11 %)	10 (20 %)	

Floor effects (i.e. already severely impaired presurgical performance so that significant postsurgical deteriorations can no longer be demonstrated) are reported when applicable

ns no significant difference

Discussion

In this study, we investigated the role of hippocampal integrity—as determined by hippocampal cell counts—for postoperative memory outcome in the up to now largest sample of 104 patients with solely mTLE.

When considering the total sample, postoperative memory decline was indicated in all main parameters of the employed memory tests. In line with the literature [2, 4], group and individual level analyses showed a differential negative effect of left-sided surgery on verbal memory. Changes in figural memory appeared to be independent from the side of surgery. This may be partly due to floor effects since nearly half of the patients with right mTLE already displayed severe presurgical impairments that could not become significantly worse.

Table 3 Correlations between neuronal cell densities of the ipsilateral hippocampus and metric pre- to postsurgical memory change (postsurgical minus presurgical test performance) after left ($N = 53$) versus right ($N = 51$) temporal lobe surgery

Memory change	Neuronal cell densities within left hippocampus						
	HCI	CA1	CA2	CA3	CA4	DGint	DGext
Verbal memory							
Learning	**−0.32***	**−0.30***	−0.22	−0.22	**−0.32***	**−0.39***	−0.20
Delayed free recall	**−0.30***	**−0.33***	−0.25	−0.16	**−0.30***	**−0.35***	−0.18
Recognition	**−0.30***	**−0.29***	**−0.27***	−0.27	**−0.31***	−0.22	−0.17
Figural memory							
Learning	−0.03	−0.09	−0.03	−0.08	−0.13	0.01	0.20
Recognition	−0.17	−0.19	−0.05	−0.26	**−0.31***	−0.08	0.03
Memory change	Neuronal cell densities within right hippocampus						
	HCI	CA1	CA2	CA3	CA4	DGint	DGext
Verbal memory							
Learning	−0.06	0.12	−0.07	−0.06	−0.13	−0.04	−0.15
Delayed free recall	−0.08	0.03	0.00	−0.18	−0.20	0.01	−0.07
Recognition	−0.04	0.13	−0.18	−0.04	−0.13	0.08	−0.01
Figural memory							
Learning	0.22	0.08	0.26	−0.02	0.15	0.25	0.27
Recognition	−0.08	0.04	0.04	**−0.31***	−0.24	−0.01	0.07

Significant correlations are highlighted by bold font. Negative correlation coefficients indicate an inverse relationship, i.e. higher cell densities are associated with greater declines in memory function. In case of positive correlation coefficients, higher cell densities would be associated with greater improvements of memory functions

mTLE mesial temporal lobe epilepsy, *HCI* hippocampal integrity index, *CA* cornu ammonis, *DG* dentate gyrus, *int* internus, *ext* externus

* $p < 0.05$

Table 4 Correlations between neuronal cell densities of the left hippocampus and pre- to postsurgical memory performance (postsurgical minus presurgical test performance) in patients without evidence of atypical hemispheric dominance who had undergone left temporal lobe surgery ($N = 37$)

Memory change	Neuronal cell densities within left hippocampus						
	HCI	CA1	CA2	CA3	CA4	DGint	DGext
Verbal memory							
Learning	**−0.54****	**−0.50****	**−0.39***	**−0.44****	**−0.49****	**−0.58****	**−0.45****
Delayed free recall	**−0.58****	**−0.60****	**−0.43****	**−0.39***	**−0.57****	**−0.57****	**−0.50****
Recognition	**−0.39***	**−0.42****	−0.30	−0.29	**−0.40***	**−0.34***	−0.26
Figural memory							
Learning	−0.14	−0.16	−0.14	−0.23	−0.26	−0.02	0.13
Recognition	−0.25	−0.28	−0.12	−0.28	−0.32	−0.22	−0.07

Significant correlations are highlighted by bold font. Negative correlation coefficients indicate an inverse relationship, i.e. higher cell densities are associated with greater declines in memory function. In case of positive correlation coefficients, higher cell densities would be associated with greater improvements of memory functions

mTLE mesial temporal lobe epilepsy, *HCI* hippocampal integrity index, *CA* cornu ammonis, *DG* dentate gyrus, *int* internus, *ext* externus

* $p < 0.05$, ** $p < 0.01$

Analyses revealed no impact of postsurgical seizure freedom (achieved in 65 % of the patients) on memory changes.

The number of patients with significant intraindividual memory decline was within the range of the already cited meta-analysis [2] and in line with our monocentric outcomes in more than 700 patients [43]: verbal memory declined in 42–62 % versus 9–13 % of the patients who had undergone left versus right temporal lobe surgery. Deteriorations in figural memory were observed in 9–11 % versus 10–20 % of the patients after surgical treatment of left versus right mTLE.

In accordance with the functional adequacy theory, greater declines in memory functions were associated with higher neuronal densities within the resected hippocampus. However, this was primarily the case for verbal memory changes after left temporal lobe surgery, and especially when left hemisphere dominance for language and memory was suggested [22, 23].

As for figural memory, the present analysis showed that only the cell densities of one subfield (CA3) of the right hippocampus correlated with the postoperative change, and this was solely observed for figural recognition memory. Again a higher cell density was associated with greater postsurgical declines. However, this single correlation should not be overinterpreted, since all other subfields were unrelated to memory change. Restricted variance due to floor effects in figural memory in patients with right mTLE could have contributed to the lack of a systematic relationship. Presurgical memory profiles, however, were consistent with the material-specific memory model (Fig. 2), i.e. worse figural and better verbal memory performance in patients with right compared to left mTLE [22]. The finding that only verbal memory decline could be predicted by hippocampal cell counts confirms the findings by Baxendale et al. [18].

In summary, the current study emphasizes the role of the structural and functional integrity of the left hippocampus not only for preoperative functioning but also for the degree of verbal memory decline after temporal lobe surgery. Thus, from a diagnostic point of view, presurgical verbal memory performance may be taken as a marker of left hippocampal integrity in left mTLE (in case of typical hemispheric dominance for material-specific memory functions) [22]. Since hippocampal cell counts cannot be determined before epilepsy surgery, presurgical biomarkers of the structural and functional integrity of the hippocampus would be appreciated that would advance individual risk–benefit evaluations before elective epilepsy surgery (e.g. high-field MRI [44, 45], volumetric and FLAIR analysis [46], spectroscopy [47], relaxometry [48], diffusion tensor imaging [49], memory fMRI [50], and EEG-analyses [51, 52]).

The findings of the current study also underscore that there is still the need to find a more precise neuropsychological marker of right hippocampal integrity [53–56].

Future studies would be appreciated which address the question whether a more thorough presurgical determination of the structural and functional integrity of both hippocampi could be provided by a multimethodological approach with additional use of structural and functional imaging techniques and physiological measures.

Acknowledgments Supported by Deutsche Forschungsgemeinschaft (DFG; SFB/TR3 A1 and A10) and to AJB by EuroEpinomics and DFG (SFB 1089, KFO 177), the Else Kröner-Fresenius and German Israeli Foundations and BonFor.

Compliance with ethical standards

Conflicts of interest C. H, I. B, C. E. E, A. J. B, J. S, R. C, and J. A. W have no conflicts of interest.

Ethical standard The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Bonn Medical Center.

References

1. Squire LR, Zola-Morgan S (1991) The medial temporal lobe memory system. Science 253(5026):1380–1386
2. Sherman EM, Wiebe S, Fay-McClymont TB, Tellez-Zenteno J, Metcalfe A, Hernandez-Ronquillo L, Hader WJ, Jette N (2011) Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. Epilepsia 52(5):857–869. doi:10.1111/j.1528-1167.2011.03022.x
3. Helmstaedter C, Kurthen M, Lux S, Reuber M, Elger CE (2003) Chronic epilepsy and cognition: a longitudinal study in temporal lobe epilepsy. Ann Neurol 54(4):425–432. doi:10.1002/ana.10692
4. Helmstaedter C (2004) Neuropsychological aspects of epilepsy surgery. Epilepsy Behav 5(S1):S45–S55 **S1525505003003196**
5. Helmstaedter C, Schramm J, Elger CE (2007) 15 years epilepsy surgery in Bonn: cognitive and seizure outcome. Epilepsia 48:14
6. Hermann B, Seidenberg M (1995) Executive system dysfunction in temporal lobe epilepsy: effects of nociferous cortex versus hippocampal pathology. J Clin Exp Neuropsychol 17(6):809–819. doi:10.1080/01688639508402430
7. Shulman M (2000) The frontal lobes, epilepsy, and behavior. Epilepsy Behav 1(6):384–395. doi:10.1006/ebeh.2000.0127
8. Helmstaedter C (1999) Prediction of memory reserve capacity. Adv Neurol 81:271–279
9. Gleissner U, Sassen R, Schramm J, Elger CE, Helmstaedter C (2005) Greater functional recovery after temporal lobe epilepsy surgery in children. Brain 128(12):2822–2829. doi:10.1093/brain/awh597
10. Helmstaedter C, Elger CE (1998) Functional plasticity after left anterior temporal lobectomy: reconstitution and compensation of verbal memory functions. Epilepsia 39(4):399–406
11. Helmstaedter C, Brosch T, Kurthen M, Elger CE (2004) The impact of sex and language dominance on material-specific memory before and after left temporal lobe surgery. Brain 127(7):1518–1525. doi:10.1093/brain/awh174
12. Chelune GJ (1995) Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. Arch Clin Neuropsychol 10(5):413–432. doi:10.1016/0887-6177(95)00015-V
13. Helmstaedter C, Petzold I, Bien CG (2011) The cognitive consequence of resecting nonlesional tissues in epilepsy surgery—Results from MRI- and histopathology-negative patients with temporal lobe epilepsy. Epilepsia 52(8):1402–1408. doi:10.1111/j.1528-1167.2011.03157.x
14. Hermann BP, Wyler AR, Somes G, Berry AD 3rd, Dohan FC Jr (1992) Pathological status of the mesial temporal lobe predicts memory outcome from left anterior temporal lobectomy. Neurosurgery 31(4):652–657
15. Hermann BP, Wyler AR, Somes G, Dohan FC Jr, Berry AD 3rd, Clement L (1994) Declarative memory following anterior temporal lobectomy in humans. Behav Neurosci 108(1):3–10

16. Rausch R, Babb TL (1993) Hippocampal neuron loss and memory scores before and after temporal lobe surgery for epilepsy. Arch Neurol 50(8):812–817
17. Sass KJ, Westerveld M, Buchanan CP, Spencer SS, Kim JH, Spencer DD (1994) Degree of hippocampal neuron loss determines severity of verbal memory decrease after left anteromesiotemporal lobectomy. Epilepsia 35(6):1179–1186
18. Baxendale SA, Van Paesschen W, Thompson PJ, Duncan JS, Harkness WF, Shorvon SD (1998) Hippocampal cell loss and gliosis: relationship to preoperative and postoperative memory function. Neuropsychiatry Neuropsychol Behav Neurol 11(1):12–21
19. Zaidel DW, Esiri MM, Beardsworth ED (1998) Observations on the relationship between verbal explicit and implicit memory and density of neurons in the hippocampus. Neuropsychologia 36(10):1049–1062 **S0028-3932(98)00058-X**
20. Loring DW, Strauss E, Hermann BP, Barr WB, Perrine K, Trenerry MR, Chelune G, Westerveld M, Lee GP, Meador KJ, Bowden SC (2008) Differential neuropsychological test sensitivity to left temporal lobe epilepsy. J Int Neuropsychol Soc 14(3):394–400. doi:10.1017/S1355617708080582
21. Helmstaedter C, Wietzke J, Lutz MT (2009) Unique and shared validity of the "Wechsler logical memory test", the "California verbal learning test", and the "verbal learning and memory test" in patients with epilepsy. Epilepsy Res 87(2–3):203–212. doi:10.1016/j.eplepsyres.2009.09.002
22. Witt J-A, Coras R, Schramm J, Becker AJ, Elger CE, Blümcke I, Helmstaedter C (2014) The overall pathological status of the left hippocampus determines preoperative verbal memory performance in left mesial temporal lobe epilepsy. Hippocampus 24(4):446–454. doi:10.1002/hipo.22238
23. Sass KJ, Silberfein CM, Platis I, Westerveld M, Buchanan CP, Delaney RC, Kim JH, Spencer DD (1995) Right hemisphere mediation of verbal learning and memory in acquired right hemisphere speech dominant patients. J Int Neuropsychol Soc 1(6):554–560
24. Kral T, Clusmann H, Urbach J, Schramm J, Elger CE, Kurthen M, Grunwald T (2002) Preoperative evaluation for epilepsy surgery (Bonn Algorithm). Zentralbl Neurochir 63(3):106–110. doi:10.1055/s-2002-35826
25. Isaacs KL, Barr WB, Nelson PK, Devinsky O (2006) Degree of handedness and cerebral dominance. Neurology 66(12):1855–1858. doi:10.1212/01.wnl.0000219623.28769.74
26. Loring DW, Strauss E, Hermann BP, Perrine K, Trenerry MR, Barr WB, Westerveld M, Chelune GJ, Lee GP, Meador KJ (1999) Effects of anomalous language representation on neuropsychological performance in temporal lobe epilepsy. Neurology 53(2):260–264
27. Strauss E, Satz P, Wada J (1990) An examination of the crowding hypothesis in epileptic patients who have undergone the carotid amytal test. Neuropsychologia 28(11):1221–1227 **10.1016/0028-3932(90)90057-U**
28. Gleissner U, Helmstaedter C, Elger CE (2002) Memory reorganization in adult brain: observations in three patients with temporal lobe epilepsy. Epilepsy Res 48(3):229–234 **S0920121101003333**
29. Wood AG, Saling MM, O'Shea MF, Jackson GD, Berkovic SF (1999) Reorganization of verbal memory and language: a case of dissociation. J Int Neuropsychol Soc 5(1):69–74
30. Helmstaedter C, Lendt M, Lux S (2001) VLMT Verbaler Lern- und Merkfähigkeitstest. Beltz Test GmbH, Göttingen
31. Rey A (1964) L'examen clinique en psychologie. Presses Universitaires de France, Paris
32. Witt JA, Helmstaedter C (2009) Neuropsychologie bei Epilepsie. Teil II: Gibt es eine gemeinsame Basis zur Etablierung diagnostischer Leitlinien? Fortschritte der Neurologie–Psychiatrie 77(12):691–698. doi:10.1055/s-0028-1109799
33. Gleissner U, Helmstaedter C, Schramm J, Elger CE (2004) Memory outcome after selective amygdalohippocampectomy in patients with temporal lobe epilepsy: one-year follow-up. Epilepsia 45(8):960–962. doi:10.1111/j.0013-9580.2004.42203.x
34. Helmstaedter C, Elger CE (1996) Cognitive consequences of two-thirds anterior temporal lobectomy on verbal memory in 144 patients: a three-month follow-up study. Epilepsia 37(2):171–180
35. Helmstaedter C, Grunwald T, Lehnertz K, Gleissner U, Elger CE (1997) Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: evidence from temporal lobe epilepsy. Brain Cogn 35(1):110–131. doi:10.1006/brcg.1997.0930
36. Zentner J, Wolf HK, Helmstaedter C, Grunwald T, Aliashkevich AF, Wiestler OD, Elger CE, Schramm J (1999) Clinical relevance of amygdala sclerosis in temporal lobe epilepsy. J Neurosurg 91(1):59–67
37. Helmstaedter C, Pohl C, Hufnagel A, Elger CE (1991) Visual learning deficits in nonresected patients with right temporal lobe epilepsy. Cortex 27(4):547–555
38. Gleissner U, Helmstaedter C, Elger CE (1998) Right hippocampal contribution to visual memory: a presurgical and postsurgical study in patients with temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 65(5):665–669. doi:10.1136/jnnp.65.5.665
39. Helmstaedter C, Richter S, Röske S, Oltmanns F, Schramm J, Lehmann T-N (2008) Differential effects of temporal pole resection with amygdalohippocampectomy versus selective amygdalohippocampectomy on material-specific memory in patients with mesial temporal lobe epilepsy. Epilepsia 49(1):88–97. doi:10.1111/j.1528-1167.2007.01386.x
40. Blümcke I, Kistner I, Clusmann H, Schramm J, Becker AJ, Elger CE, Bien CG, Merschhemke M, Meencke H-J, Lehmann T, Buchfelder M, Weigel D, Buslei R, Stefan H, Pauli E, Hildebrandt M (2009) Towards a clinico-pathological classification of granule cell dispersion in human mesial temporal lobe epilepsies. Acta Neuropathol (Berl) 117(5):535–544. doi:10.1007/s00401-009-0512-5
41. Blümcke I, Pauli E, Clusmann H, Schramm J, Becker A, Elger C, Merschhemke M, Meencke H-J, Lehmann T, Deimling A, Scheiwe C, Zentner J, Volk B, Romstöck J, Stefan H, Hildebrandt M (2007) A new clinico-pathological classification system for mesial temporal sclerosis. Acta Neuropathol (Berl) 113(3):235–244. doi:10.1007/s00401-006-0187-0
42. Blümcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, Bernasconi N, Bien CG, Cendes F, Coras R, Cross JH, Jacques TS, Kahane P, Mathern GW, Miyata H, Moshe SL, Oz B, Ozkara C, Perucca E, Sisodiya S, Wiebe S, Spreafico R (2013) International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. Epilepsia 54(7):1315–1329. doi:10.1111/epi.12220
43. Helmstaedter C (2013) Cognitive outcomes of different surgical approaches in temporal lobe epilepsy. Epileptic Disord 15(3):221–239. doi:10.1684/epd.2013.0587
44. Goubran M, Rudko DA, Santyr B, Gati J, Szekeres T, Peters TM, Khan AR (2014) In vivo normative atlas of the hippocampal subfields using multi-echo susceptibility imaging at 7 Tesla. Hum Brain Mapp 35(8):3588–3601. doi:10.1002/hbm.22423
45. Eriksson SH, Thom M, Bartlett PA, Symms MR, McEvoy AW, Sisodiya SM, Duncan JS (2008) PROPELLER MRI visualizes detailed pathology of hippocampal sclerosis. Epilepsia 49(1):33–39. doi:10.1111/j.1528-1167.2007.01277.x
46. Urbach H, Huppertz HJ, Schwarzwald R, Becker AJ, Wagner J, Bahri MD, Tschampa HJ (2014) Is the type and extent of

hippocampal sclerosis measurable on high-resolution MRI? Neuroradiology 56(9):731–735. doi:10.1007/s00234-014-1397-0
47. Hammen T, Hildebrandt M, Stadlbauer A, Doelken M, Engelhorn T, Kerling F, Kasper B, Romstoeck J, Ganslandt O, Nimsky C, Blumcke I, Doerfler A, Stefan H (2008) Non-invasive detection of hippocampal sclerosis: correlation between metabolite alterations detected by (1)H-MRS and neuropathology. NMR Biomed 21(6):545–552. doi:10.1002/nbm.1222
48. von Oertzen J, Urbach H, Blumcke I, Reuber M, Traber F, Peveling T, Menzel C, Elger CE (2002) Time-efficient T2 relaxometry of the entire hippocampus is feasible in temporal lobe epilepsy. Neurology 58(2):257–264
49. McDonald CR, Leyden KM, Hagler DJ, Kucukboyaci NE, Kemmotsu N, Tecoma ES, Iragui VJ (2014) White matter microstructure complements morphometry for predicting verbal memory in epilepsy. Cortex 58:139–150. doi:10.1016/j.cortex.2014.05.014
50. Dupont S (2015) Imaging memory and predicting postoperative memory decline in temporal lobe epilepsy: insights from functional imaging. Rev Neurol (Paris) 171(3):307–314. doi:10.1016/j.neurol.2014.12.001
51. Kuhnert M-T, Bialonski S, Noennig N, Mai H, Hinrichs H, Helmstaedter C, Lehnertz K (2013) Incidental and intentional learning of verbal episodic material differentially modifies functional brain networks. PLoS One 8(11):e80273. doi:10.1371/journal.pone.0080273
52. Grunwald T, Lehnertz K, Helmstaedter C, Kutas M, Pezer N, Kurthen M, Van Roost D, Elger CE (1998) Limbic ERPs predict verbal memory after left-sided hippocampectomy. NeuroReport 9(15):3375–3378
53. Wisniewski I, Wendling A-S, Manning L, Steinhoff BJ (2012) Visuo-spatial memory tests in right temporal lobe epilepsy foci: clinical validity. Epilepsy Behav 23(3):254–260. doi:10.1016/j.yebeh.2011.12.006
54. Frisch C, Helmstaedter C (2014) Object location performance: detection of functional impairment in right temporal lobe epilepsy. Epilepsy Behav 35:28–33. doi:10.1016/j.yebeh.2014.03.027
55. McDermid Vaz SA (2004) Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. Seizure 13(7):446–452. doi:10.1016/j.seizure.2003.12.004
56. Helmstaedter C, Pohl C, Elger CE (1995) Relations between verbal and nonverbal memory performance: evidence of confounding effects particularly in patients with right temporal lobe epilepsy. Cortex 31(2):345–355