Received: 21 June 2019 | Revised: 18 February 2020 | Accepted: 18 February 2020
DOI: 10.1111/epi.16473

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Effects of hippocampus-sparing resections in the temporal lobe: Hippocampal atrophy is associated with a decline in memory performance

Kathrin Wagner[1,2] | Karin Gau[1,2] | Birgitta Metternich[1,2] | Maximilian J. Geiger[1,2] | Anne-Sophie Wendling[3] | Navah E. Kadish[4,5] | Gitta Reuner[6,7] | Hans Mayer[3] | Irina Mader[2,8] | Jürgen Beck[9] | Josef Zentner[9] | Horst Urbach[2,8] | Andreas Schulze-Bonhage[1,2] | Christoph P. Kaller[2,8] | Niels A. Foit[2,9]

[1]Epilepsy Centre, Medical Center - University of Freiburg, Freiburg, Germany
[2]Freiburg Brain Imaging, Medical Center - University of Freiburg, Freiburg, Germany
[3]Epilepsy Centre Kork, Kehl-Kork, Germany
[4]Department of Neuropediatrics, University Medical Centre Schleswig-Holstein, Kiel, Germany
[5]Department of Medical Psychology and Medical Sociology, University Medical Centre Schleswig-Holstein, Kiel, Germany
[6]Institute for Education Studies, Heidelberg University, Heidelberg, Germany
[7]Division of Neuropediatrics and Metabolic Medicine, Clinic I, Centre for Pediatric and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany
[8]Department of Neuroradiology, Medical Center - University of Freiburg, Freiburg, Germany
[9]Department of Neurosurgery, Medical Center - University of Freiburg, Freiburg, Germany

Correspondence
Kathrin Wagner, Epilepsy Centre, Medical Center - University of Freiburg, Breisacher Str. 64, 79106 Freiburg, Germany.
Email: Kathrin.Wagner@uniklinik-freiburg.de

Abstract

Objective: In patients with temporal lobe epilepsy (TLE) with a nonlesional and nonepileptogenic hippocampus (HC), in order to preserve functionally intact brain tissue, the HC is not resected. However, some patients experience postoperative memory decline, possibly due to disruption of the extrahippocampal memory network and secondary hippocampal volume (HV) loss. The purpose of this study was to determine the extent of hippocampal atrophy ipsilateral and contralateral to the side of the surgery and its relation to memory outcomes.
Methods: Hippocampal volume and verbal as well as visual memory performance were retrospectively examined in 55 patients (mean age ± standard deviation [SD] 30 ± 15 years, 25 female, 31 left) before and 5 months after surgery within the temporal lobe that spared the entire HC. HV was extracted based on prespecified templates, and resection volumes were also determined.
Results: HV loss was found both ipsilateral and contralateral to the side of surgery ($P < .001$). Postoperative left HV loss was a significant predictor of postoperative verbal memory deterioration after left-sided surgery ($P < .01$). Together with the preoperative verbal memory performance, postoperative left HV explained almost 60% of the variance ($P < .0001$). However, right HV was not a clear predictor of visual memory performance. Larger resection volumes were associated with smaller postoperative HV, irrespective of side of surgery (left: $P < .05$, right: $P < .01$).
Significance: A disruption of the memory network by any resection within the TL, especially within the language-dominant hemisphere, may lead to HC atrophy and memory decline. These findings may further improve the counseling of patients concerning their postoperative memory outcome before TL resections sparing the entire HC.

Dr. Foit receives research support from the German Research Foundation, DFG, FO996/1-1.

KEYWORDS
epilepsy surgery, hippocampal shrinkage, neuropsychology, postoperative cognitive outcome, tailored resection, volume loss

1 | INTRODUCTION

Epilepsy surgery within the temporal lobe (TL), especially within the language-dominant hemisphere, is known to bear the risk of memory decline. To preserve functionally intact brain tissue, surgical procedures have become more tailored, and memory-associated structures, such as the hippocampus (HC), are preserved whenever possible. However, in a previous study in TL-resected patients with and without hippocampectomy,[1] we found significant memory deterioration after surgery in both groups, although a stronger decrease was observed after HC resection.[1] In the present study, we therefore wished to further elucidate the potential causes behind memory decline in patients with HC-sparing resections. More specifically, we reasoned that postoperative memory loss may be associated with secondary postoperative atrophy of the HC and/or the resection of memory-relevant extrahippocampal sites.

To our knowledge, postoperative hippocampal volume (HV) loss has been analyzed predominantly in patient groups undergoing incomplete HC resections.[2–7] For instance, in a cohort of 17 patients after a standard Spencer-type TL resection, posterior hippocampal remnants revealed atrophy during the immediate postoperative course, which was associated with memory decline.[4] Memory loss was further found to be associated with postoperative hippocampal shrinkage in patients after left-sided resections.[5] Regarding HV changes within the contralateral TL, long-term (8 years) follow-up of patients after selective amygdalohippocampectomy or anterior temporal lobe resections *including* HC, the amygdala and parahippocampal gyrus (ATL) revealed a small but significant reduction in contralateral HV.[7] However, contralateral HC atrophy was *not* found to be associated with memory performance.[6,8]

The main objective of the present study was to investigate postoperative HV changes in patients undergoing TL resections *completely sparing the HC* and their relation to postoperative memory performance. The following questions were addressed:

1. Is there ipsilateral and/or contralateral HV loss after TL surgery sparing the entire HC?
2. Are larger resection volumes associated with smaller postoperative HV?
3. What changes in verbal and visual memory performance can be observed according to the side of surgery?
4. Is HV predictive of postoperative memory performance?

Key Points

- Hippocampal atrophy occurs after hippocampus-sparing resections within the temporal lobe
- Postoperative left hippocampal volume predicted verbal memory performance after left-sided surgery
- Right hippocampal volume was not a clear predictor of visual memory performance after right-sided surgery
- Larger resection volumes were associated with more postoperative hippocampal atrophy, irrespective of side of surgery

2 | PATIENTS AND METHODS

2.1 | Patients

We retrospectively analyzed data from patients who underwent TL resections sparing the HC at the Department of Neurosurgery, University Medical Center Freiburg. The presurgical workup and postoperative assessments were carried out either at the epilepsy center of the University Medical Center Freiburg, the Epilepsy Center Kork, the Department of Paediatric Neurology at the University of Heidelberg, or the Department of Paediatric Neurology at the University of Kiel.

Patients were selected from our database if they met the following criteria: refractory unilateral TLE, resection within the TL with sparing of the HC between 1998 and 2015, no previous neurosurgical resection, preoperative and postoperative neuropsychological raw data on at least one verbal and/or visual memory test, as well as the availability of high-resolution volumetric magnetic resonance imaging (MRI) scans. Postoperative MRI scans and neuropsychological test data were taken retrospectively from the first postoperative follow-up approximately ~3 months after surgery. If data from this early follow-up were not available for a patient, the next possible follow-up was evaluated (in most cases ~12 months after surgery). For the range of durations between surgery and postoperative MRI scan and neuropsychological assessment, see Table 1. No significant correlation between the duration from surgery to postoperative scan and postoperative ipsilateral or contralateral HV loss was found (Pearson; ipsilateral one-sided $P = .17$ and contralateral $P = .13$).

TABLE 1 Demographic and clinical data of the 55 patients with resections sparing the entire hippocampus

Demographic and clinical data	Hippocampus-spared patients Mean (SD)/N
Age at surgery (in y)	29.8 (14.5), range 6-60
Age at epilepsy onset (in y)	21.9 (12.5)
Epilepsy duration (in y)	7.9 (10.5)
Gender (female/male)	25/30
Handedness (right/left/ambidextrous)	51/4/0
Side of surgery (left/right)	31/24
Mean follow-up interval until neuropsychological assessment (in mo)	5.8 (4.3), range 2-19
Mean follow-up interval until MRI examination (in mo)	5.0 (4.0), range 2-17
Seizure free (Engel class 1a in %)	69.1
Main histopathology	
Tumor	19
Malformation of cortical development	14
Vascular lesion	11
Encephalocele	1
Nonspecific alterations	9
No histopathology available	1

Abbreviations: N, number; SD, standard deviation; y, years.

Left-handed and ambidextrous patients were included only if left-lateralized language dominance was verified by functional MRI (fMRI), intracarotid amobarbital procedure, or electroclinical data. For an overview of patient selection, see Figure S1. The study was approved by the local ethics committee.

Fifty-five patients were enrolled in the present analyses; for an overview of demographic and clinical data see Table 1 and supplemental Table S1. An overview of the locations and extent of resections is provided in Figure 1. Prior to and approximately 5 months after surgery, all patients underwent a neuropsychological examination as well as an MRI scan.

2.2 | Neuropsychological evaluation

Because TL-associated memory functions are known to be functionally lateralized based on the material that has to be memorized,[9,10] verbal as well as visual memory functions were assessed. The Verbal Learning and Memory Test (VLMT[11]) was used to investigate changes in verbal memory: Patients were asked to learn a list of 15 words (list A) that was read to them five times. After each trial, they were asked to reproduce as many words as possible. After the fifth trial, a distractor list (also 15 concrete words, list B) was read to them, and they were asked to name all remembered items of list B. Immediately after that, they were asked to recall the words of list A. After a delay of approximately 30 minutes (in which they performed the visual memory test), they were again asked to freely recall as many words of list A as possible. Free recall was followed by a recognition trial. The absolute recall performance after the delay (VLMT trial 7, preoperative and postoperative data available in 53 patients) served as a parameter of *verbal memory performance*, which has been shown previously to serve as a marker of functional integrity of the language-dominant hippocampus.[10]

Visual learning and memory were assessed with a revised version of a figural learning test (Diagnosticum fuer Cerebralschaedigung, DCS-R[12]): Patients were consecutively shown nine cards with geometric figures made of five lines and asked to reproduce as many as possible after the presentation. This was carried out for five learning trials, and the number of correctly remembered figures in the last trial served as a parameter of *visual memory performance* (DCS-R correctly remembered figures in the last trial, preoperative and postoperative data available in 51 patients). The DCS-R has been shown to assess right TL functions in epilepsy patients.[13]

At follow-up after surgery, patients completed parallel versions of the VLMT and DCS-R. The raw test scores were transformed into standardized z-scores according to the age-matched normative data provided by the individual psychometric test manuals.

2.3 | MRI analysis

2.3.1 | Imaging acquisition

High-resolution, T1-weighted volumetric MRI data sets were obtained during routine preoperative and postoperative (5.0 ± 4.0 months) imaging on either a 1.5T (Siemens Magnetom Vision, 30 patients, 2001-2007) or a 3T full-body MRI scanner (Siemens Magnetom TRIO, 18 patients, 2007-2015) with a standard eight-channel head coil. Magnetization-prepared, rapid-acquisition gradient-echo (MPRAGE) sequences were used on both scanners (repetition time (TR)/echo time (TE): 9.7/4 ms and TR/TE: 2200/1100 ms, respectively; flip angle = 12°; matrix = 256×256; isotropic voxel size = 1 mm^3; 160-180 sagittal slices).

2.3.2 | Preprocessing

All volumetric T1 images were processed with the VBM8 toolbox (release r435; dbm.neuro.uni-jena.de) integrated into Statistical Parametric Mapping (SPM8, fil.ion.ucl.ac.uk/spm/software/spm8/). Preprocessing using default

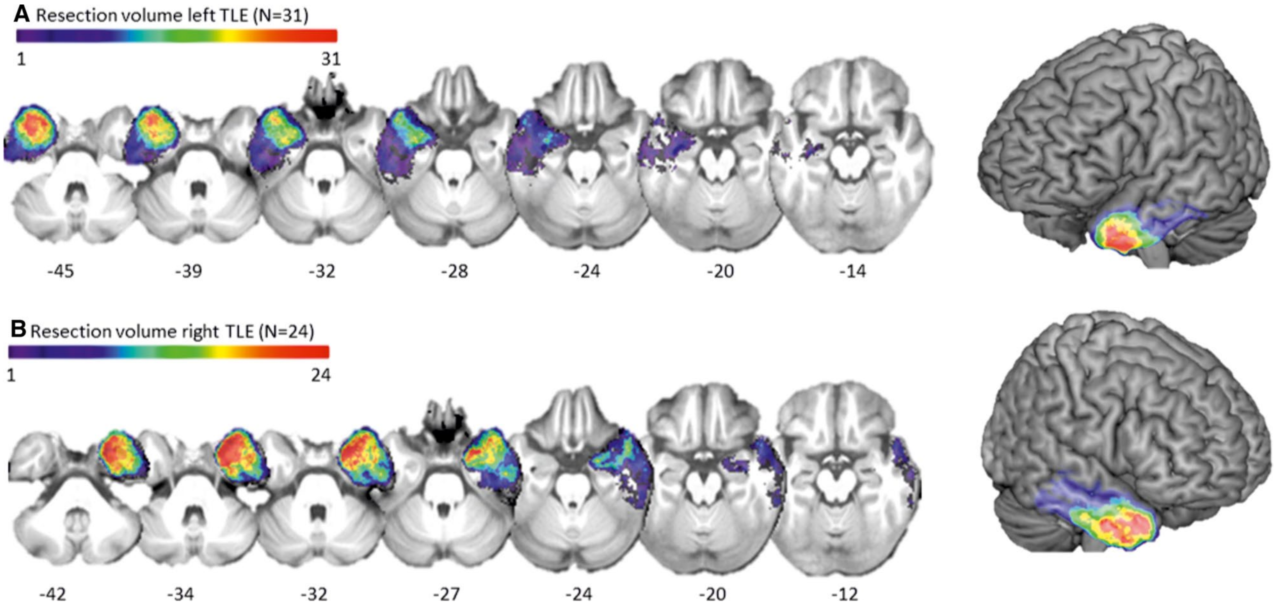

FIGURE 1 Overlap of individual resection volume maps after left (A) and right (B) hippocampus-sparing temporal lobe resections, superimposed on an averaged group-specific template. Color bars indicate the degree of overlap, ranging from a resection volume in a single patient (purple) to overlap in all patients (red). The figure orientation follows the neurological convention (left side of the image is the left side of the brain)

parameters consisted of the following steps: (a) segmentation of tissue classes based on voxel intensities; (b) linear (ie, affine) registration to the ICBM (International Consortium for Brain Mapping) European template, (c) spatial normalization using the DARTEL approach[14] into Montreal Neurological Institute (MNI) standard space; (d) nonlinear but not affine modulation of the normalized probability maps, resulting in a multiplicative data correction to account for interindividual differences in brain size; and (e) smoothing of the individual gray matter probability maps with a 9 mm^3 Gaussian kernel.

2.3.3 | Hippocampus volumetry and resection volume

Hippocampal regions of interest (ROIs) were derived from the Juelich Anatomy Atlas,[15] including the ipsilateral cornu ammonis, dentate gyrus, alveus, fimbria, and subiculum. Left and right HVs were calculated by multiplying the sum of the voxel intensities of the individual preoperative and postoperative gray matter probability maps within each ROI with the maps' spatial resolution, resulting in absolute HV in cubic mm. In addition, a group-specific, preoperative HC mask was hand drawn onto a group-averaged T1-weighted template in common space by an experienced neuroradiologist (IM), using a standardized HC segmentation protocol for TLE.[16]

Resection volume was assessed at the first routine follow-up after surgery. User-guided active contour segmentation as implemented in the ITK-Snap toolbox version 3.4 was used to delineate resection volumes on volumetric T1-weighted scans in native space.[17] All individual resection maps were then normalized to MNI space using the deformation fields obtained during preprocessing of the preoperative T1 scan. The absolute resection volume was calculated by summing all voxels within each resection mask multiplied by the spatial resolution of the underlying T1-image. HV was scaled for total intracranial volume (TIV) as follows: (absolute individual HV/ total individual TIV)*group mean TIV.

2.4 | Statistical analyses

Preoperatively, volumes of the HC ipsilateral and contralateral to the side of surgery were compared (paired *T* test) in order to look for already preoperatively existing volume differences.

Changes in HV were computed using a repeated-measures analysis of variance (rmANOVA) in a 2 x 2 x 2 design (preoperative vs postoperative, ipsilateral vs contralateral, and left-sided vs right-sided surgery as independent variables) and with HV as the dependent variable (see introduction question 1).

The assumption that larger resection volumes were associated with smaller postoperative left and right HV (see introduction question 2) was analyzed via correlation analyses (Pearson, one-sided) and corrected for multiple comparisons (Bonferroni).

In a 2 x 2 design (preoperative vs postoperative, left-sided vs right-sided surgery), an rmANOVA was conducted to evaluate changes in memory performance separately for verbal and visual memory performance as dependent variables. Because some patients performed either VLMT or DCS-R, we performed two separate rmANOVAs for these tests to analyze a larger number of patients (see introduction question 3).

To predict postoperative memory performance (see introduction question 4) with information about postoperative HV, preoperative memory performance, and side of surgery (and their interactions), we conducted two multiple regression analyses with interaction effects (A: prediction of postoperative verbal memory performance; B: prediction of postoperative visual memory performance). For these analyses we used the PROCESS 3.3 macro for SPSS 23.[18] Model type 3 was used, and postoperative memory performance served as outcome variable Y, postoperative HV as continuous predictor (X), and preoperative performance (W) as well as side of surgery (Z) as continuous and dichotomous moderating variables, respectively (all two- and three-way interactions were evaluated as well; predictors were mean centered). In the analysis of verbal memory performance, left-sided postoperative HV served as a moderator, and in the analyses of visual memory performance, right-sided postoperative HV was included as a moderating variable.

Although it is common usage to assess nonadditive effects (interactions) in factorial designs, this approach is only rarely applied in the context of multiple regression analyses. In multiple regression, nonadditive effects are accounted for by extending the additive (or "main effects") model with product terms reflecting the nonadditive components. In the context of the present analyses, it was proposed that better preoperative performance and larger postoperative HV would be related to better postoperative performance. This relationship was assumed to be moderated by the side of surgery (language dominant vs not language dominant TL) because left-sided surgery was expected to have a detrimental effect on verbal memory performance, whereas right-sided surgery was expected to have a negative effect on visual memory performance.

Statistical analyses were performed with SPSS 23.0. Either SPSS 23.0 or RStudio Version 1.1.463 were used for graphical display of the results.

3 | RESULTS

3.1 | Postoperative changes in hippocampal volume

Prior to surgery, preoperative volume did not differ significantly between HC ipsilateral (mean volume 2.67, SD 0.35 cm^3) and contralateral (mean volume 2.63, SD 0.33 cm^3) to the side of surgery ($t(54) = 0.55$, $P = .59$). Of interest, larger resection volumes were associated with smaller left ($r = -.33$, $P < .05$) and also right postoperative HV ($r = -.37$, $P < .01$).

A comparison of preoperative to postoperative HV derived from the Juelich Anatomy Atlas revealed significant postoperative atrophy ($F = 115.48$, $P < .001$, see Figure 2). Furthermore, significantly smaller ipsilateral than contralateral HV was observed after surgery ($F = 19.47$, $P < .001$, see Figure 2, also illustrated in Figures 4 and 5). The side of surgery (left or right TL) did not have an influence (interaction time point*side of surgery: $F = 1.96$, $P = .168$), but ipsilateral compared to contralateral HV decreased significantly more after surgery (interaction ipsilateral/contralateral HV*time point: $F = 76.55$, $P < .001$, see Figure 2). In addition, the interaction between the factors ipsilateral/contralateral HV, left-sided or right-sided surgery, and preoperative and postoperative time points reached significance ($F = 4.11$, $P < .05$, see Figure 2).

Analyses using the hand-drawn hippocampal mask showed comparable results (main effect of time: $F = 160.83$, $P < .001$; main effect of ipsilateral vs contralateral HV: $F = 26.80$, $P < .001$; interaction time point*ipsilateral/contralateral HV: $F = 128.14$, $P < .001$; interaction left-sided/right-sided surgery*ipsilateral/contralateral HV: $F = 5.87$, $P < .05$). However, the interaction between the factors ipsilateral/contralateral HV, left-sided or right-sided surgery, and preoperative and postoperative time point did not reach significance but showed a trend ($F = 2.84$, $P = .098$).

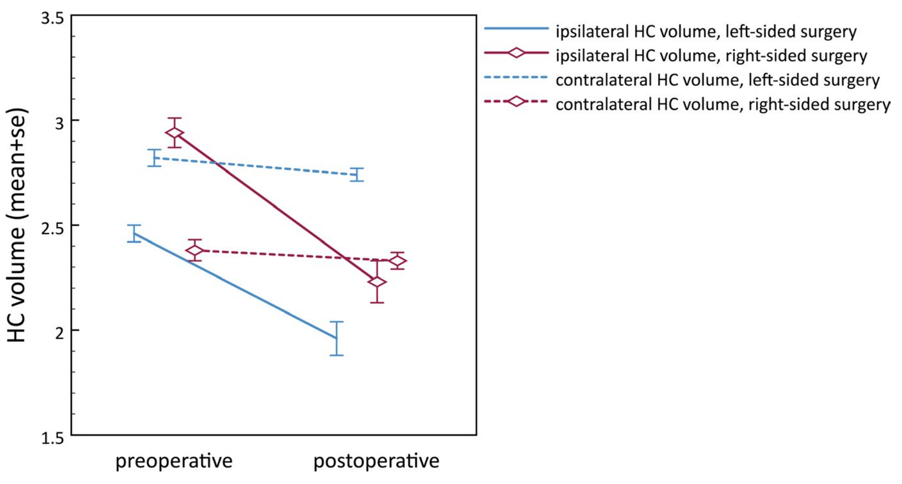

FIGURE 2 Hippocampal volume ipsilateral and contralateral to side of surgery before and ~5 months after resection (derived from Juelich Anatomy Atlas in mm^3, weighted for mean total intracranial volume, displayed as the mean ± 1 standard error [SE])

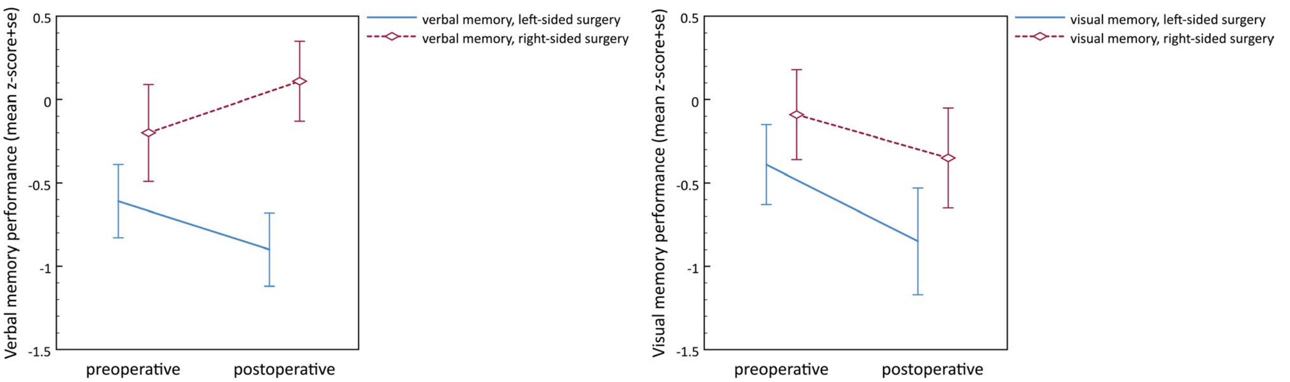

FIGURE 3 Performance in verbal and visual memory before and ~5 months after surgery displayed in mean z-scores (+SE) according to side of surgery

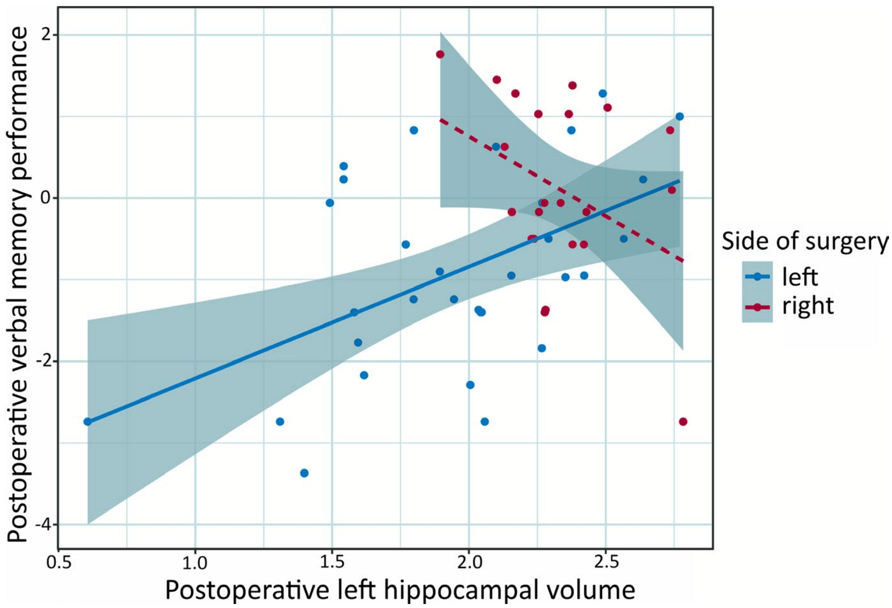

FIGURE 4 Regression of postoperative verbal memory performance (shown on the Y-axis in z-scores) in patients with left- and right-sided surgery (regressor side of surgery) onto the focal variable postoperative left hippocampal volume (depicted on the X-axis in mm^3). Regression lines illustrate how the relationship between postoperative left hippocampal volume and postoperative verbal memory performance changes dependent on the side of surgery (significant interaction effect of postoperative left HV and side of surgery, $P < .01$). Green-gray areas show the 95% confidence interval. Furthermore, the figure illustrates significantly smaller ipsilateral than contralateral HV after surgery: left HV is smaller after left-sided (in blue) than after right-sided surgery (in red)

3.2 | Cognitive Outcomes

3.2.1 | Verbal memory

Left-sided surgery had a negative impact on verbal memory performance, but after right-sided surgery, patients exhibited increased verbal memory performance compared to left-operated patients (rmANOVA: significant effect of side of surgery; $F = 5.91$, $P < .05$). However, the interaction between side of surgery and time point did not reach significance ($F = 2.59$, $P = .11$). For an overview, see Figure 3 (left).

The overall fit of the regression model with interaction effects for prediction of postoperative verbal memory performance with information on side of surgery, postoperative left HV, and preoperative verbal memory performance was highly significant ($P > .0001$, $R^2 = .5921$). Postoperative verbal memory performance was influenced positively by preoperative performance ($P < .01$) and negatively by left-sided surgery ($P < .01$). The association between postoperative left HV and postoperative verbal memory performance was moderated by side of surgery (significant interaction effect $P < .005$, see Figure 4). After left-sided surgery, patients with smaller postoperative left HV performed lower in verbal memory than those with larger left HV, irrespective of preoperative verbal memory performance (see Figure 4, significant interaction effect

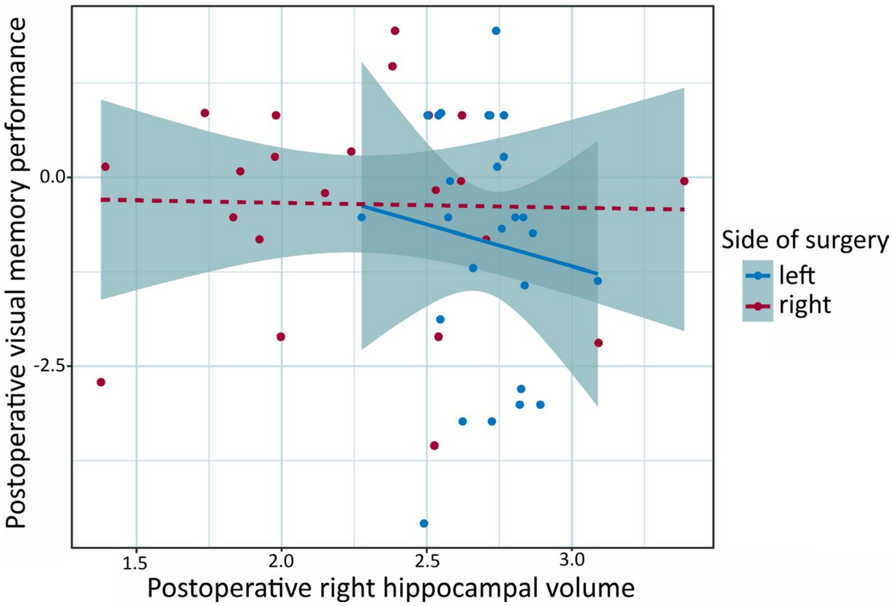

FIGURE 5 Regression of postoperative visual memory performance (shown on the Y-axis in z-scores) in patients with left-sided and right-sided surgery (regressor side of surgery) onto the focal variable postoperative right hippocampal volume (depicted on the X-axis in mm^3). Regression lines illustrate how the relationship between postoperative right hippocampal volume and postoperative visual memory performance changes dependent on the side of surgery (significant interaction effect of postoperative right HV and side of surgery, $P < .05$). Green-gray areas show the 95% confidence interval. Furthermore, the figure illustrates significantly smaller ipsilateral than contralateral HV after surgery: right HV is smaller after right-sided (in red) than after left-sided surgery (in blue)

of side of surgery). No other main or interaction effect reached significance ($P > .1$).

3.2.2 | Visual memory

Visual memory performance showed a tendency toward loss over time ($F = 3.51$, $P = .07$; see Figure 3, right). Neither an effect of side of surgery nor significant interactions were found ($P > .1$).

The overall fit of the regression model to predict postoperative visual memory performance with interaction effects was highly significant ($P < .001$, $R^2 = .4496$). Better preoperative visual memory performance significantly predicted higher postoperative performance ($P < .0001$). Postoperative right HV and side of surgery showed a significant interaction effect ($P < .05$, see Figure 5): After right-sided surgery, right HV was slightly positively associated with better postoperative visual memory performance, which was not seen after left-sided surgery (see Figure 5).

3.3 | Seizure outcomes

At follow-up, 69.1% patients (N = 38) were completely seizure free (Engel class 1a). The distribution of patients according to Engel outcome classes were as follows: Engel class 1 (free of disabling seizures), 42 patients; Engel class 2 (rare disabling seizures), 8 patients; Engel class 3 (worthwhile improvement), 2 patients; and Engel class 4 (no worthwhile improvement), 3 patients.

Postoperative HV loss did not significantly differ ($P > 0.1$, corrected for multiple comparisons) between patients with ongoing seizures (17 patients: ipsilateral -0.42 ± 0.35 mm^3; contralateral -0.06 ± 0.11 mm^3) and completely seizure-free patients (38 patients: ipsilateral, -0.67 ± 0.47 mm^3; contralateral, -0.07 ± 0.12 mm^3).

4 | DISCUSSION

In our retrospective analysis of HV changes in patients with resections sparing the entire HC, we found significant postoperative hippocampal atrophy, especially ipsilateral to the side of surgery. Independent of lateralization of surgery and memory parameters, a better preoperative performance level predicted favorable postoperative memory outcomes. However, HV was also a significant predictor of postoperative memory performance depending on the side of surgery. After left-sided surgery, left HV was a significant predictor of verbal memory performance. In contrast, after right-sided TL resection, right HV was no clear marker for postoperative visual memory performance. Furthermore, ipsilateral HC atrophy was associated with larger resection volumes, which was also related to verbal memory decreases after left-sided surgery. The majority of patients (69%) were completely seizure-free at follow-up (Engel class 1a).

To our knowledge, no study to date has investigated secondary hippocampal atrophy and its association with memory performance in patients with TL resections that spared the *entire* HC. Postoperative hippocampal shrinkage associated with memory decline has been described previously in patients receiving partial HC resections.[2–7] HV and memory loss were also observed in our patient group, even though the HC was completely spared to preserve functional tissue. Because the HC is an integral part of a distributed memory network comprising different structures within and beyond the TL (eg[19–22]), it can be assumed that disruption of this network by *any* resection within the TL might lead to secondary hippocampal atrophy and subsequent memory disturbances. In particular, resections of temporal structures that are directly connected to the HC, for example, the parahippocampal gyrus (PHG), which serves as its major afferent projection, can thus cause secondary HC atrophy.[1] In addition, secondary HV loss disrupts the memory network functionally and therefore—as a major hub for memory functions—results in decreased memory performance. Stoub et al[23] related volumetry of the HC and entorhinal cortex and white matter of the PHG to memory performance in 50 nonoperated TL epilepsy patients. They found that not only HC but also PHG volumes were the best predictors of immediate and delayed memory performance. Therefore, the authors concluded that reduced white matter connections into the hippocampus could disrupt the mesial temporal lobe memory network.[23] Another study[21] showed that parahippocampal connections measured by diffusion MRI were reduced in patients with left TLE and were also associated with impaired memory performance. In our previous study, we were able to show that in a sample of patients without hippocampectomy, resection of the PHG was associated with lower memory performance compared to patients whose PHG was preserved.[1]

The majority of the analyzed patients in our study received temporopolar plus temporomesial resections. This type of resection may have played a major role in the risk for postoperative hippocampal volume loss and therefore memory decrement, and may not necessarily be seen with other hippocampus-sparing resections, for example, temporolateral lesionectomies. Further evaluation of differential influence of extrahippocampal resection site is needed.

In the present study, more extensive postoperative left-sided hippocampal atrophy significantly predicted postoperative lower verbal memory performance (see Figure 4). Thus, postoperative left HV serves as a good marker for verbal memory outcomes after extrahippocampal TL resections. Hippocampal volume has already been shown to be positively associated with memory performance in healthy controls.[24] Furthermore, in patients with left TLE, postoperative remnant HC volume has been shown to be positively associated with postoperative memory outcome in patients whose HC was partly resected.[4]

On the other hand, right HV was not a clear predictor of visual memory performance. Of interest, several studies have observed a difference in material specificity between patients with left and right TLE, in such a manner that the patients with left TLE showed associations with verbal memory impairments, whereas in right TLE, the association with visual memory impairments was not clear.[4,21,25,26] It has been discussed that nonverbal visual memory tests might not be sufficiently specific to assess the integrity of the nondominant (mostly right) temporal lobe.[26–29] We used the visual learning and memory test DCS-R, which requires learning and free recall of nine geometric designs. These designs may elicit associations with already familiar symbols and thereby lead to recall and association of semantic memories. Furthermore, verbal description and naming of the designs may also be used as an implicit strategy when solving the task, which further integrates verbal aspects in the originally nonverbal memory task. Routine assessment of the strategy used to solve material-specific memory tasks might help to further elucidate this aspect. In this context, the results that all patients decreased in visual memory performance irrespective of the side of the surgery may also be discussed. If the chosen visual memory task was solved using verbal strategies, a performance decline after resection within the language-dominant temporal lobe might be possible. Other studies have also shown that in patients with left hippocampal sclerosis or after anterior TL resection nonverbal memory can be impaired.[30,31]

In our sample, even though volume alterations contralateral to the side of surgery were observed, there were no correlations with cognitive performance changes. This is in line with previous studies that also detected no postoperative memory decrement attributable to HC atrophy contralateral to the side of the surgery.[6,8] It is notable that they found more contralateral atrophy in patients with postoperatively ongoing seizures (not seizure free patients, NSF). In our patients, the majority (69.1% patients) were completely seizure free (SF) at follow-up. Postoperative HV loss did not differ significantly between the NSF and SF patients, which indeed might be due to the small number and uneven distribution (NSF, N = 17; SF, N = 38). Moreover, we used a relatively short follow-up interval. However, a study with 8 years of follow- up on HC volumetrics did not reveal any association of contralateral volume and memory changes.[7] Longer follow-up intervals are needed to evaluate whether HV loss has a negative effect on long-term seizure outcomes after HC-sparing surgeries.

Better preoperative performance level and left-sided (mesial) TL surgery have been shown to be associated with worse verbal memory outcomes in numerous studies; for example, Law et al[32] compared 23 children who underwent TL surgery while sparing the mesial structures (TL) to 40 patients with temporal lobectomies that included resection of mesial structures (TL + M) regarding their memory and seizure outcomes. They found that greater declines were evident in children after TL + M resections within the language-dominant hemisphere. Furthermore, the memory abilities of left-operated children with normal preoperative memory performance declined significantly compared to those with preoperative impaired memory, especially after TL + M surgeries. In contrast, they found that children with preoperatively impaired verbal memory improved their performance after TL surgeries. Of interest, in our patient group, verbal memory performance seemed to increase slightly after right-sided surgery (see Figure 3). This improvement trend may have been a sign of a releasing effect induced by seizure freedom in the majority of our patients. Gleissner et al[9] described performance gains after right temporal resections (with and without hippocampectomy) in nonverbal functions, which were not associated with the resected region. Because all of their patients were seizure free, they discussed a release effect of right hemispheric functions beyond the resection site. The improvements did not reach significance in our sample, which might be due to the older age range in our patients. Helmstaedter[33] also found stronger long-term improvements in younger patients and a positive effect of seizure freedom on memory functions. The authors found that after left temporal resections and ongoing seizures, patients were more likely to show significant decreases in verbal memory in the first year after surgery and that they fail to recover from this impairment at long-term follow-up after at least 5 years.

The limitations of our study concern the retrospective design: clinical aspects, such as involvement of the HC in epileptogenesis and/or preserved memory performance, led to HC-sparing resections that influenced patient selection. Furthermore, the MRI analysis was limited to a short-term follow-up interval. Longer follow-up intervals would be helpful in evaluating whether observed HV loss remains stable and if it negatively affects long-term seizure and memory outcomes.

For future studies, the influence of the resection of different extrahippocampal TL structures on HV and memory change should be evaluated to better understand which patients are at risk of ipsilateral HV atrophy and associated memory loss. It is possible that the resection site may have more influence than the resection volume. Larger patient samples are needed to confirm the presented results.

5 | CONCLUSION

Despite sparing the entire HC, patients demonstrated postoperative HV loss, especially ipsilateral to the side of surgery. In patients after left-sided surgery, ipsilateral HC atrophy was a significant predictor of postoperative verbal memory loss. These findings may further improve our understanding of memory functions after tailored TL resections and provide additional information for patient counselling prior to surgery.

CONFLICT OF INTERESTS

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Kathrin Wagner https://orcid.org/0000-0003-2232-1684
Navah E. Kadish https://orcid.org/0000-0003-1548-8216
Niels A. Foit https://orcid.org/0000-0003-3248-1665

REFERENCES

1. Wagner K, Uherek M, Horstmann S, Kadish NE, Wisniewski I, Mayer H, et al. Memory outcome after hippocampus sparing resections in the temporal lobe. J Neurol Neurosurg Psychiatry. 2013;84:630–6.
2. Joo EY, Han HJ, Lee EK, Choi S, Jin JH, Kim JH, et al. Resection extent versus postoperative outcomes of seizure and memory in mesial temporal lobe epilepsy. Seizure. 2005;14:541–51.
3. Helmstaedter C, Roeske S, Kaaden S, Elger CE, Schramm J. Hippocampal resection length and memory outcome in selective epilepsy surgery. J Neurol Neurosurg Psychiatry. 2011;82:1375–81.
4. Baxendale SA, Thompson PJ, Kitchen ND. Postoperative hippocampal remnant shrinkage and memory decline: a dynamic process. Neurology. 2000;55:243–9.
5. Mueller C-A, Kaaden S, Scorzin J, Urbach H, Fimmers R, Helmstaedter C, et al. Shrinkage of the hippocampal remnant after surgery for temporal lobe epilepsy: impact on seizure and neuropsychological outcomes. Epilepsy Behav. 2009;14:379–86.
6. Fernandes DA, Yasuda CL, Lopes TM, Enrico G, Alessio A, Tedeschi H, et al. Long-term postoperative atrophy of contralateral hippocampus and cognitive function in unilateral refractory MTLE with unilateral hippocampal sclerosis. Epilepsy Behav. 2014;36:108–14.
7. Trenerry MR, Jack CR, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA, et al. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology. 1993;43:1800–5.
8. Elliott CA, Gross DW, Wheatley BM, Beaulieu C, Sankar T. Progressive contralateral hippocampal atrophy following surgery for medically refractory temporal lobe epilepsy. Epilepsy Res. 2016;125:62–71.
9. Gleissner U, Helmstaedter C, Elger CE. Right hippocampal contribution to visual memory: a presurgical and postsurgical study in patients with temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 1998;65:665–9.
10. Helmstaedter C, Grunwald T, Lehnertz K, Gleißner U, Elger CE. Differential involvement of left temporolateral and temporomesial structures in verbal declarative learning and memory: evidence from temporal lobe epilepsy. Brain Cogn. 1997;35:110–31.
11. Helmstaedter C, Lendt M, Lux S. VLMT, Verbaler Lern- und Merkfähigkeitstest. Goettingen, Germany: Beltz; 2001.

12. Helmstaedter C, Pohl C, Elger CE. Eine modifizierte Version des Diagnostikums für Cerebralschäden (DCS) zur Diagnostik räumlich-visueller Gedächtnisdefizite bei Patienten mit Temporallappenepilepsie. Epilepsie 90. Reinbeck, Germany: Einhorn-Presse Verlag. 1991;272–9.
13. Helmstaedter C, Grunwald T, Lehnertz K, Gleißner U, Elger CE. Visual learning deficits in nonresected patients with right temporal lobe epilepsy. Cortex. 1991;27:547–55.
14. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage. 2007;38:95–113.
15. Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, et al. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage. 2005;25:1325–35.
16. Jack CR Jr. MRI-based hippocampal volume measurements in epilepsy. Epilepsia. 1994;35(Suppl 6):S21–S29.
17. Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage. 2006;31:1116–28.
18. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis - A Regression-Based Approach, 2nd edn. New York, NY: Guilford Press; 2017.
19. Sidhu MK, Stretton J, Winston GP, Bonelli S, Centeno M, Vollmar C, et al. A functional magnetic resonance imaging study mapping the episodic memory encoding network in temporal lobe epilepsy. Brain. 2013;136:1868–88.
20. Henson RN, Greve A, Cooper E, Gregori M, Simons JS, Geerligs L, et al. The effects of hippocampal lesions on MRI measures of structural and functional connectivity. Hippocampus. 2016;26:1447–63.
21. Yogarajah M, Powell HW, Parker GJ, Alexander DC, Thompson PJ, Symms MR, et al. Tractography of the parahippocampal gyrus and material specific memory impairment in unilateral temporal lobe epilepsy. Neuroimage. 2008;40:1755–64.
22. Adnan A, Barnett A, Moayedi M, McCormick C, Cohn M, McAndrews MP. Distinct hippocampal functional networks revealed by tractography-based parcellation. Brain Struct Funct. 2016;221:2999–3012.
23. Stoub TR, Chicharro AV, Grote CL, Kanner AM. Disconnection of hippocampal networks contributes to memory dysfunction in individuals with temporal lobe epilepsy. Hippocampus. 2019;29:451–457. https://doi.org/10.1002/hipo.22800
24. Pohlack ST, Meyer P, Cacciaglia R, Liebscher C, Ridder S, Flor H. Bigger is better! Hippocampal volume and declarative memory performance in healthy young men. Brain Struct Funct. 2014;219:255–67.
25. Jeyaraj MK, Menon RN, Justus S, Alexander A, Sarma PS, Radhakrishnan K. A critical evaluation of the lateralizing significance of material-specific memory deficits in patients with mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsy Behav. 2013;28:460–6.
26. Alessio A, Damasceno BP, Camargo CHP, Kobayashi E, Guerreiro CAM, Cendes F. Differences in memory performance and other clinical characteristics in patients with mesial temporal lobe epilepsy with and without hippocampal atrophy. Epilepsy Behav. 2004;5:22–7.
27. Wisniewski I, Wendling AS, Manning L, Steinhoff BJ. Visuo-spatial memory tests in right temporal lobe epilepsy foci: clinical validity. Epilepsy Behav. 2012;23:254–60.
28. Vingerhoets G, Miatton M, Vonck K, Seurinck R, Boon P. Memory performance during the intracarotid amobarbital procedure and neuropsychological assessment in medial temporal lobe epilepsy: the limits of material specificity. Epilepsy Behav. 2006;8:422–8.
29. Vaz SA. Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. Seizure. 2004;13:446–52.
30. Glikmann-Johnston Y, Saling MM, Chen J, Cooper KA, Beare RJ, Reutens DC. Structural and functional correlates of unilateral mesial temporal lobe spatial memory impairment. Brain. 2008;131:3006–18.
31. McConley R, Martin R, Palmer CA, Kuzniecky R, Knowlton R, Faught E. Rey Osterrieth complex figure test spatial and figural scoring: relations to seizure focus and hippocampal pathology in patients with temporal lobe epilepsy. Epilepsy Behav. 2008;13:174–7.
32. Law N, Benifla M, Rutka J, Smith ML. Verbal memory after temporal lobe epilepsy surgery in children: Do only mesial structures matter? Epilepsia. 2017;58:291–9.
33. Helmstaedter C, Elger CE, Vogt VL. Cognitive outcomes more than 5 years after temporal lobe epilepsy surgery: Remarkable functional recovery when seizures are controlled. Seizure. 2018;62:116–23.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Wagner K, Gau K, Metternich B, et al. Effects of hippocampus-sparing resections in the temporal lobe: Hippocampal atrophy is associated with a decline in memory performance. *Epilepsia*. 2020;61:725–734. https://doi.org/10.1111/epi.16473