

Long-term postoperative atrophy of contralateral hippocampus and cognitive function in unilateral refractory MTLE with unilateral hippocampal sclerosis

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ABSTRACT

Objective: This study aimed to evaluate long-term atrophy in contralateral hippocampal volume after surgery for unilateral MTLE, as well as the cognitive outcome for patients submitted to either selective transylvian amygdalohippocampectomy (*SelAH*) or anterior temporal lobe resection (*ATL*).

Methods: We performed a longitudinal study of 47 patients with MRI signs of unilateral hippocampal sclerosis (23 patients with right-sided hippocampal sclerosis) who underwent surgical treatment for MTLE. They underwent preoperative/postoperative high-resolution MRI as well as neuropsychological assessment for memory and estimated IQ. To investigate possible changes in the contralateral hippocampus of patients, we included 28 controls who underwent two MRIs at long-term intervals.

Results: The volumetry using preoperative MRI showed significant hippocampal atrophy ipsilateral to the side of surgery when compared with controls ($p < 0.0001$) but no differences in contralateral hippocampal volumes. The mean postoperative follow-up was 8.7 years (± 2.5 SD; median = 8.0). Our patients were classified as Engel I (80%), Engel II (18.2%), and Engel III (1.8%). We observed a small but significant reduction in the contralateral hippocampus of patients but no volume changes in controls. Most of the patients presented small declines in both estimated IQ and memory, which were more pronounced in patients with left TLE and in those with persistent seizures. Different surgical approaches did not impose differences in seizure control or in cognitive outcome.

Conclusions: We observed small declines in cognitive scores with most of these patients, which were worse in patients with left-sided resection and in those who continued to suffer from postoperative seizures. We also demonstrated that manual volumetry can reveal a reduction in volume in the contralateral hippocampus, although this change was mild and could not be detected by visual analysis. These new findings suggest that dynamic processes continue to act after the removal of the hippocampus, and further studies with larger groups may help in understanding the underlying mechanisms.

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1. Introduction

Mesial temporal lobe epilepsy (MTLE) is one of the most frequent types of focal and AED refractory epilepsy in adults [1]. The resection of mesial structures has been indicated for the treatment of AED refractory MTLE, yielding a rate of 65–80% with seizure freedom or almost complete seizure control in short-term follow-up [2,3]. In addition to seizure control, an essential aspect of epilepsy surgery is related to the postoperative cognitive outcome [4].

Postoperative cognitive outcome in MTLE has raised debates regarding decline and recovery [5–7], as well as the impact of the side of resection [8,9], seizure control [6,10], and the surgical approach [11,12]. Some of these studies associated a better cognitive outcome with right-sided hippocampal sclerosis, selective resection of mesial structures, and postoperative seizure freedom. In addition, there is also the question whether postoperative cognitive outcome is a stable [6] or a dynamic process [9,13], meaning that early evaluations could mislead the interpretation of eventual cognitive function. So far, most studies have evaluated patients shortly after surgery [5,14], and few have performed long-term evaluation (over 5 years) [8,9,13].

Therefore, in this study, we aimed to investigate postoperative cognitive changes in patients with clear MRI signs of unilateral hippocampal sclerosis evaluated at long-term after surgery with both cognitive

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tests and high-resolution MRI analysis. The following questions were raised in our study:

- 1) What is the long-term postoperative cognitive outcome in our group of patients?
- 2) Does the volume of the contralateral hippocampus change after surgery?
- 3) Can we correlate changes in contralateral hippocampal volume with postoperative cognitive outcome?

2. Materials and methods

2.1. Subjects

The cohort consisted of 47 patients (17 males, 44.7 ± 8.7 years of age) out of 106 patients with MRI evidence of unilateral hippocampal sclerosis (HS), without evidence of any other lesion on MRI, who underwent surgical treatment for MTLE between 1998 and 2007 in our service. All had two MRI exams and about the same protocol for neuropsychological assessment and seizure frequency calendars before and after surgery [15].

We included 28 controls (9 males, 40.9 ± 8.2 years of age) to compare the volumes of manually segmented hippocampi.

All patients underwent our routine outpatient investigation, which includes comprehensive neurological examination, a series of electroencephalograms, MRIs, and neuropsychological assessments. In patients with bilateral interictal EEG findings, we complemented the investigation with prolonged video-EEG monitoring for ictal recordings [2]. The diagnosis of unilateral signs of HS was carried out by visual analysis and manual volumetry of the hippocampi in our MRI diagnostic protocol for epilepsy that consists of T1- and T2-weighted MRIs in three orthogonal planes, axial fluid-attenuated inversion recovery, as well as thin coronal (3 mm) T1-weighted inversion recovery (IR) and T2 images as described below. One of the investigators (F.C.) with experience in neuroimaging in epilepsy (F.C.) performed visual analyses of the routine MRI protocol to detect unilateral signs of HS (hippocampal atrophy, abnormal shape, and loss of internal structure with or without hyperintense T2/FLAIR signal). In addition, we certified that there were no visual abnormalities in the contralateral hippocampus or other suspected MRI abnormalities, thus excluding patients with MTLE with bilateral HS or dual pathology. In this particular study, we only included patients who underwent both preoperative and postoperative MRIs in the same 2 T scanner; therefore, it is important to note that this is not a consecutive group of patients as we had to exclude those who did not have postoperative MRI available for analysis or had postoperative MRI in another scanner, as well as patients with bilateral signs of HS on MRI [16]. However, these 47 patients represent our series of 106 patients with unilateral MTS who underwent surgery between 1998 and 2007.

All individuals were required to sign a consent form approved by the Ethics Committee of the UNICAMP Medical School.

2.2. Surgical procedure

Patients underwent either selective transylvian amygdalohippocampectomy (*SeIAH*, 24 subjects) or anterior temporal lobe resection (*ATL*, 23 subjects), with successful removal of their mesial temporal lobe structures (hippocampus, amygdala, and parahippocampal gyrus). Each surgical procedure was performed according to the surgeon's considerations.

Seizure outcome was classified according to Engel's classification. Patients were then separated into two groups: *seizure-free* (21 patients classified as Engel IA – completely seizure-free since surgery) and *seizure-recurrent* (26 patients classified as Engel IB–IIIA).

2.3. MRI scanning

Patients and controls underwent two MRIs in the same 2 T scanner (Elscent Prestige, Haifa, Israel) with intervals of 4 ± 2.5 (range: 0.5–9.6 years) and 5.5 ± 3.2 (range: 0.3–11.6 years), respectively. Patients were scanned 6 months or longer after surgery. As part of our MRI diagnostic protocol, they also underwent a high-resolution T1-weighted 3D gradient echo with 1-mm isotropic voxels (1 mm thick; flip angle = 35° , TR = 22 ms, TE = 9 ms, matrix = 256×220 , and FOV = 25×22 cm). Patients underwent a second MRI after surgery as part of a clinical research protocol.

2.3.1. MRI volumetric analysis

The DICOM 3D T1-weighted images were converted to MNC format to be used in manual segmentation as previously described [17]. We used DISPLAY software (<http://www.bic.mni.mcgill.ca/software>) developed at the Brain Imaging Center of the Montreal Neurological Institute to manually determine the volumes of the hippocampi (patients and controls) and surgical lacunae (patients) [17]. We then obtained the volumes of both hippocampi from the preoperative scan and the volume of surgical lacuna and the contralateral hippocampus on the postoperative scan.

2.4. Neuropsychological test

Patients underwent both preoperative and postoperative neuropsychological assessments with a mean postoperative interval of 8.7 ± 2.5 years. To evaluate verbal memory and nonverbal memory, we used the Wechsler Memory Scale – Revised (WMS-R) and Rey Auditory Verbal Learning Test (RAVLT) [18,19]. We also obtained the estimated intelligence coefficient (IQ) using block design and vocabulary subtests from the Wechsler Adult Intelligence Scale – Revised (WAIS-R). To evaluate changes between preoperative and postoperative evaluations, we calculated the ratio between postoperative and preoperative scores, which allowed us to determine the percentage of change.

2.5. Statistical analysis

The results of neuropsychological tests were transformed into Z-scores (the number of standard deviations away from the mean of the respective control group), using normative data adapted for our population.

We used SPSS21® for statistical analysis, selecting multivariate analysis with repeated measures on General Linear Models (GLM) for longitudinal analysis of the nonaffected hippocampus, comparing groups of patients and controls. We also applied multivariate analysis to evaluate the cognitive performance of patients before and after surgery. For subgroup analysis of ratios between postoperative and preoperative scores, we applied multivariate analysis of variance for the 4 memory tests (with Bonferroni adjustment for multiple comparisons), and univariate analysis for estimated IQ test. To evaluate differences in proportions between groups, we used Chi-square test.

For correlations between variables (volumetric and memory performance), we used Pearson's correlation analysis.

3. Results

3.1. Descriptive data

Patients and controls were balanced for gender ($p = 0.881$) and age ($p = 0.063$). However, there was a difference in MRI interval between groups (patients' mean = 4.0 years, SD = 2.5; controls' mean = 5.5 years, SD = 3.2) ($p = 0.021$). Twenty-three had right-sided HS and 24 had left-sided HS.

3.2. Surgical outcome

The postoperative seizure control 8.7 ± 2.5 years after surgery according to Engel's classification was: Engel IA—40%, Engel IB—9.1%, Engel IC—21.9%, Engel ID—9.1%, Engel IIA—3.6%, Engel IIB—9.1%, Engel IID—5.5%, and Engel IIIA—1.8%.

Therefore, approximately 80% of the patients were classified as Engel class I. Seizure control was similar for both surgical approaches (p = 0.56).

3.3. Volumetric analysis

As expected, the manual volumetry confirmed the atrophy of the resected hippocampus on preoperative MRIs (Table 1) (p = 0.0001). We also confirmed larger lacuna for the *ATL* group (mean = 18,755.09 mm³, SD = 7885.98 mm³) compared with the *SelAH* group (mean = 10,452.42 mm³, SD = 4798.32 mm³) (t = 4.382, p = 0.0001). The size of the surgical resection was not associated with better postoperative seizure control (*seizure-free* group: 15,267.48 ± 7513.99 mm³; *seizure-recurrent* group: 14,187.65 ± 7894.17 mm³) (t = 0.476, p = 0.636).

The volumetric analysis of the contralateral hippocampus obtained from the preoperative MRI scan was not statistically different when compared with controls, p = 0.768 (Supplemental Fig. 1 and Table 1). However, the longitudinal analysis between preoperative and postoperative contralateral hippocampus volumes (covaried for the time interval between the 2 MRI scans) revealed a significant interaction between groups (patients/controls) and time (MRI1/MRI2) [Wilk's Lambda = 0.897, F(1,72) = 8.252, p = 0.005, partial η² = 0.103], revealing a reduction of volume in patients (preoperative = 5437.53 ± 404.65 mm³, postoperative = 5225.26 ± 475.25 mm³) (p < 0.005) but not in controls (image I = 5398.79 ± 627.02 mm³, image II = 5442.04 ± 551.84 mm³) (p = 0.485) (Fig. 1).

We investigated whether this reduction in contralateral hippocampus volume after surgery could be associated with lateralization, surgical approach, or seizure control. The ratio between the postoperative and preoperative volumes of the contralateral hippocampus did not differ significantly when we compared it between left-sided and right-sided resections (p = 0.735), surgical techniques (*SelAH* versus *ATL*, p = 0.619), or postoperative seizure control (*seizure-free* versus *seizure-recurrent*, p = 0.182).

The reductions in volume in the contralateral hippocampi could not be detected by visual analysis.

3.4. Cognitive analysis

With long-term follow-up (mean = 8.7 years), we observed a decline in neuropsychological test scores for the preoperative/postoperative group analyses (Table 2) and for most patients individually (Supplemental Figs. 2 and 3). Most patients scored below - 1 SD after surgery, although the worst postoperative scores were from those with low preoperative scores, patients with left-sided surgery, and those who

Table 1

Volumes of the hippocampi and surgical lacuna (in mm³). For patients, we have preoperative and postoperative MRIs (1 and 2, respectively), and we show the results from the first and the second scan for controls.

Structures	Volumetric measurements	
	Patients	Controls
Affected hippocampus (MRI: - 1)	3908.2 ± 634.7	-
Contralateral hippocampus (MRI: - 1)	5437.5 ± 494.9	5398.8 ± 627.0
Contralateral hippocampus (MRI: - 2)	5225.3 ± 475.3	5442.0 ± 551.8
Lacunae (MRI: - 2)	14,515.4 ± 7671.1	-

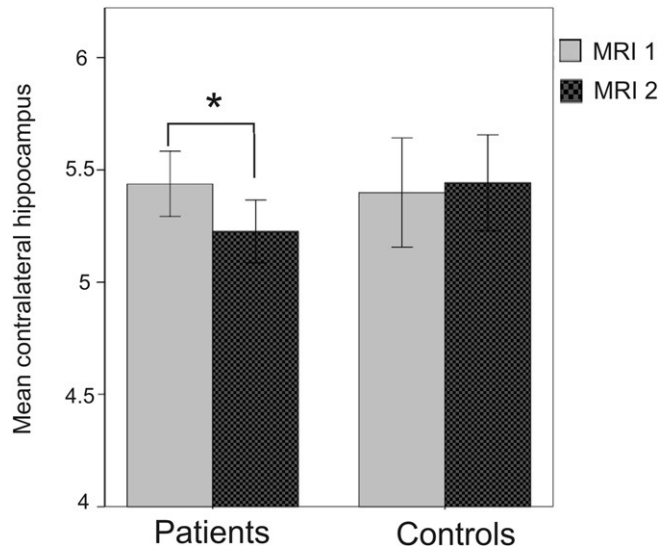


Fig. 1. Progression of atrophy in the contralateral hippocampus of patients with MTL after surgery. Legend: volumes in cubic centimeters. * indicates a significant reduction in contralateral hippocampal volume in patients.

continued to suffer from postoperative seizures (Figs. 2 and 3). From the 47 patients analyzed, we observed a drop in scores in 38 patients (mean reduction ± SD, 6.9 ± 9%) for estimated IQ, in 44 patients (27% ± 16%) for general memory, in 45 patients (19.2% ± 12.2%) for verbal memory, in 42 patients (19.5% ± 16.5%) for visual memory, and in 40 patients (17.4% ± 17.5%) for delayed recall. The repeated measure analysis of memory scores within GLM showed a significant interaction between time (preoperative and postoperative) and the testing (4 memory tests), [Wilk's Lambda = 0.507, F(3,43) = 14.283, p < 0.001, partial η² = 0.493]. The *post hoc* analysis of paired comparisons between preoperative and postoperative scores on all 4 tests (general memory, verbal memory, visual memory, and delayed recall) was significant with p < 0.001, adjusted with Bonferroni for multiple comparisons. We then investigated whether the decline could be associated with the side of resection, seizure control, or surgical approach.

Considering the side of resection, we observed that patients with left-sided resection presented lower memory ratios (except for visual memory) compared with patients with right-sided resection; nevertheless, the multivariate analysis did not show significant differences between right-sided and left-sided resections [Wilk's Lambda = 0.821, F(4,42) 2.292, p = 0.075, partial η² = 0.179] (Fig. 2).

Seizure freedom was not significantly associated with higher postoperative/preoperative ratios on memory tests [Wilk's Lambda = 0.821, F(4,42) 2.292, p = 0.075, partial η² = 0.179] (Fig. 3).

Table 2

Preoperative and postoperative cognitive performances of patients with mesial temporal lobe epilepsy.

Cognitive test	Preop Mean ± SD	Postop Mean ± SD	Statistical test	p
IQ estimated	89.8 ± 9.6	83.5 ± 11.6	t = 5.41	0.0001*
WMS-R general mem.	92.1 ± 19.7	67.7 ± 21.7	t = 12.11	0.0001*
WMS-R verbal mem.	94.9 ± 18.7	76.33 ± 17.2	z = - 5.70	0.0001*
WMS-R visual mem.	90.6 ± 14.6	72.7 ± 17.6	t = 8.35	0.0001*
WMS-R delayed recall	90.3 ± 20.4	73.26 ± 18.7	t = 7.25	0.0001*

IQ: estimate intelligence coefficient, WMS-R: Wechsler Memory Scale - Revised, mem.: memory, preop = preoperative scores, postop = postoperative scores.

* Significant at p < 0.05.

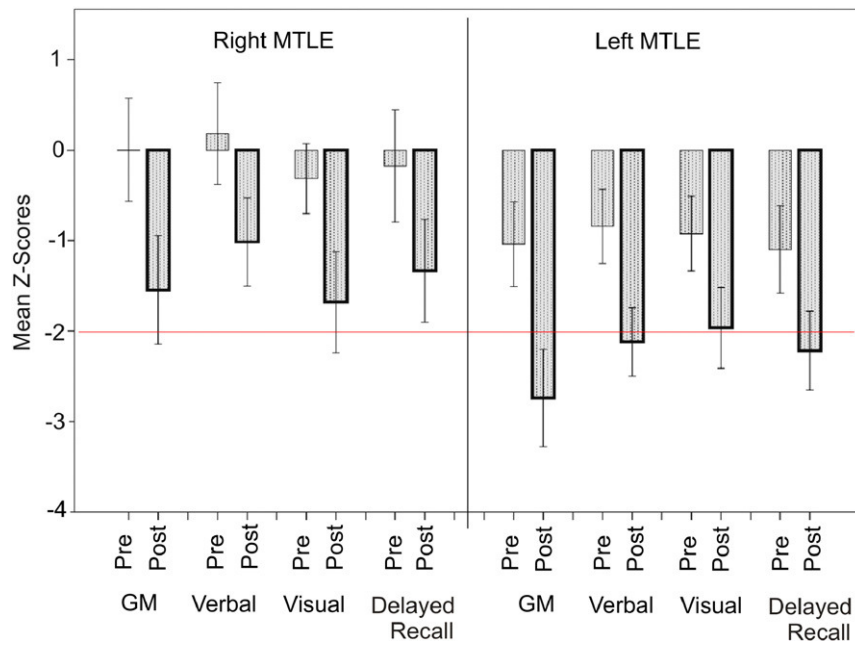


Fig. 2. Memory performance before and after surgery in patients with left-sided and right-sided hippocampal resections. Legend: RTLE = right-sided hippocampal resection, LTLE = left-sided hippocampal resection, GM = general memory, verbal = verbal memory, visual = visual memory, pre = preoperative scores, post = postoperative scores. The red line shows the threshold below 2 standard deviations (SDs) from the mean of normative data.

Different surgical approaches (SeLAH versus LTA) did not produce significant differences in memory ratios [Wilk's Lambda = 0.927, $F(4,42) 0.833$, $p = 0.512$, partial $\eta^2 = 0.073$].

The paired analysis of estimated IQ scores preoperative (89.77 ± 9.59) and postoperative (83.53 ± 11.57) revealed a significant decrease ($T = 5.41$, $p < 0.001$). Subsequent investigation of differences in the estimated IQ ratio (postoperative/preoperative) between subgroups

revealed better postoperative performance by patients who became seizure-free (0.96 ± 0.094) compared with those with persistent seizures (0.91 ± 0.083), ($T = 2.04$, $p = 0.047$). In addition, patients with right-sided resection also presented better postoperative performance (0.96 ± 0.09) compared with those with left hemisphere resection (0.90 ± 0.08), ($T = 2.188$, $p = 0.034$) (Supplemental Table, Fig. 4). The surgical approach did not influence the estimated IQ

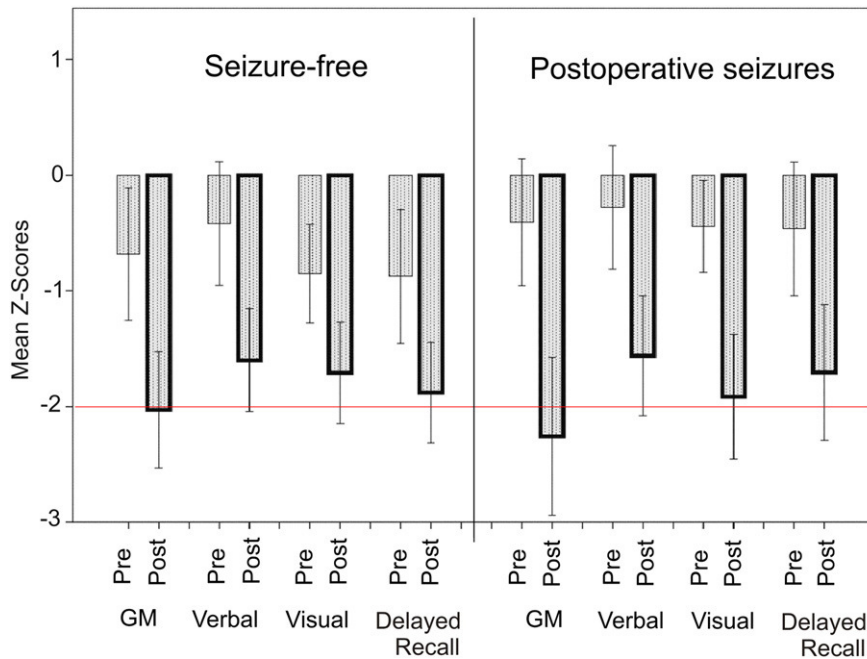


Fig. 3. Memory performance before and after surgery according to postoperative seizure control. Legend: seizure-free = patients who were seizure-free after surgery (Engel IA), postoperative seizures = patients who continued to suffer from seizures after surgery (Engel IB–III), GM = general memory, verbal = verbal memory, visual = visual memory, pre = preoperative scores, post = postoperative scores. The red line shows the threshold below 2 standard deviations (SDs) from the mean of normative data.

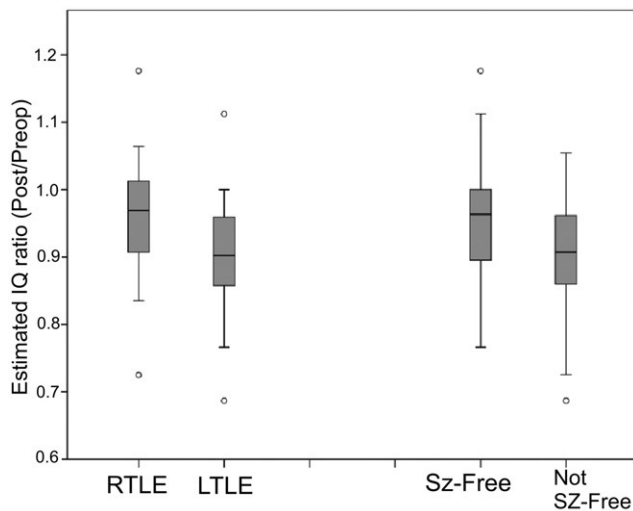


Fig. 4. Comparison of estimated IQ ratio (postoperative/preoperative scores) between patients with LTLE and patients with RTLE and between patients who became seizure-free and those who continued to suffer from seizures after surgery. The box plots show that patients with LTLE and those with recurrent seizures presented greater reductions in estimated IQ score after surgery. Legends: RTLE = right-sided hippocampal resection, LTLE = left-sided hippocampal resection, SZ-free = patients who were seizure-free after surgery, not SZ-free = patients who continued to suffer from seizures after surgery (Engel IB–III).

ratio ($T = 0.938$, $p = 0.353$). Although we observed significant reductions in estimated IQ scores with most of our subjects, we noticed some degree of improvement in a few patients, [1 with left TLE (seizure-free) and 6 with right TLE (4 with seizure freedom and 2 with persistent seizures)].

3.5. Correlations

We searched for correlations between the postoperative contralateral hippocampus volume and cognitive tests but did not identify significant results.

4. Discussion

We evaluated seizure control, contralateral hippocampus volume, and memory performance in patients with unilateral MTLE who underwent epilepsy surgery.

At long-term follow-up, we observed that approximately 80% presented significant improvement in seizure control (classified as Engel class I). Combining those patients identified as Engel classes IA and IB, we obtained 49.1%, which is quite consistent with a recent large study that estimated that 51% of patients remained seizure-free (other than simple partial seizures) 10 years after surgery [20].

One interesting finding in our study was the small (and visually undetected) but significant reduction in the contralateral hippocampus long-term after surgery revealed by manual volumetry, which was not observed in controls.

Most of our patients presented small declines in both estimated IQ and memory, which were more pronounced in patients with left MTLE and in those with persistent seizures. Fig. 2 shows clearly that the group with right-sided MTLE had a significant, but small, drop of verbal memory and a more intense drop of nonverbal memory after surgery. On the other hand, patients with left-sided MTLE had an important drop on verbal memory and nonverbal memory after surgery. Although there was a clear predominance on material specific memory decline depending on the side of surgery, our data also showed evidence of postoperative dysfunction of the contralateral hippocampus, which parallels the volume loss of the nonoperated hippocampus.

We have identified a single longitudinal study [21] with manual volumetry, which did not detect a reduction in the contralateral hippocampus after surgery (24 patients versus 16 controls); however, the postoperative MRI was performed within a short period of time after surgery (6 months), while, in our study, the minimum interval between the two scans was longer both for patients (mean = 4 years) and controls (mean = 5.5 years). We then tried to identify clinical factors that could be related to this finding; however, neither the side of resection nor the persistence of seizures influenced the volume of the reduction in the contralateral hippocampus. Different surgical approaches also resulted in similar degrees of volume reduction. A possible speculative explanation for the mechanisms responsible for this volumetric reduction could be an association with the deafferentation process triggered after severing the connections between both hippocampi via surgical intervention. Bonilha et al. [22] showed some significant correlations between reductions in hippocampal connections (as analyzed with tractography) and gray matter atrophy in extrahippocampal areas of nonoperated subjects with MTLE, suggesting that hippocampal deafferentation could play a role in extrahippocampal abnormalities in MTLE. Following this idea, it could be possible that the disconnection of the contralateral hippocampus could result in an active process of atrophy. In support of this speculative idea, we identified a recent elegant experimental study in mice designed to evaluate the responses of the contralateral hemisphere after stereotactically induced lesions in the entorhinal cortex, provoking a partial unilateral deafferentation of the hippocampus [23]. By studying mice deficient in glial fibrillary acidic protein (GFAP) and vimentin, the authors were able to conclude that, even after a limited focal lesion, there is a response in the contralateral hippocampus that depends on astrocyte activation and reactive gliosis [23]. So far, it is not possible to explain the pathophysiology of this volumetric reduction, neither can we associate this finding with any clinical variable. This finding warrants further study, as this phenomenon may have some implications for postoperative cognition.

Although many studies have investigated the cognitive outcome of epilepsy surgery [5], few of them have actually focused on long-term outcome [24]. These studies present some controversies, as some identify a degree of recovery (for memory and nonmemory functions) [6,8] while others observed declines in both verbal and visual memory scores for all investigated patients [25]. Our results showed a small decline in memory scores and estimated IQ for most of our subjects at a long-term evaluation. Some longitudinal studies with different time points of evaluation showed a progressive decline after the first year [13,25], while others demonstrated a stable course, with no significant changes after 2 years, 6 years [26], or 10 years [6]. We did not have intermediate time point evaluation to confirm the dynamic aspect of the cognitive decline; however, we present an additional and interesting finding that could possibly be associated with the progression of decline, which is a reduction of the contralateral hippocampus detected by volumetry. Our relatively small sample size poses a limitation on investigating the association between the volume of the contralateral hippocampus and cognitive scores.

It is also possible that the small sample size may have limited the power of our analysis to detect significant differences in cognitive scores when we analyzed factors such as the side of resection and postoperative seizure control. Although patients with left TLE presented lower postoperative memory scores (most of the patients scored below -1 SD), they also presented lower scores before surgery, and, consequently, the ratios (post/pre) were not so small (Fig. 4). If we consider the postoperative scores in isolation, patients with left TLE clearly presented more deficits than those with right TLE. This is in accordance with a recent long-term study [6] that observed a decrease in performance on memory tests by patients in the dominant temporal lobe group at a 2-year evaluation that was stable at 10-year follow-up. Our patients with left TLE also presented significant reductions in estimated IQ scores, but, on average, the change was less than 10% compared with the preoperative score. Most previous studies have focused on memory

function, and few of them have actually evaluated a long-term estimated IQ test [5]. Contrary to our results, most previous studies showed some degree of improvement in estimated IQ [5], mainly for patients with right TLE [6], while others showed more stable results over time [13]. In a retrospective analysis of 25 patients, Tanriverdi et al. [11] described a decrease in estimated IQ in patients submitted to left *SeIAH*, a finding that is at least partially concordant with our results. Estimated IQ is possibly less stable than full-scale IQ [27] because it is based only on block design and vocabulary subtests from the WAIS-R, and vocabulary subtests may be affected by memory and language changes related to surgical resections or ongoing seizures.

Our results showed a trend for better memory outcomes and significant postoperative estimated IQ for patients who became seizure-free in accordance with previous studies [8,13,28]. It is also worth noting that other studies have reported cognitive results that were independent of seizure outcome at long-term follow-up [6,9]. We believe that cessation of seizures may somehow help improve the performance of some subjects; It may also be that for those patients who continue to experience seizures and progressive memory decline, a common underlying epileptogenic process persists even after resection of mesial structures [13].

The impact of different surgical approaches on cognitive outcome has also been open to debate and under investigation by other authors [10–12,29]. We did not identify significant differences on memory tests (or estimated IQ) regarding different surgical approaches in accordance with others [29,30]. However, some studies have pointed to particular deficits associated with the type of resection. Helmstaedter et al. [31] observed significant loss in verbal learning and recognition in patients submitted to left *SeIAH*, while patients who underwent a right-sided procedure presented some improvement in language functions; in addition, right *ATL* resulted in significant loss in figural learning. Sagher and colleagues [32] showed that seizure outcome and neuropsychiatric sequelae are similar in both *SeIAH* and *ALT*. In a more recent study of a large group of patients, the authors described verbal memory impairment after left-sided resections, especially in patients who underwent *SeIAH*, while a decrease in nonverbal memory occurred after right-sided surgeries, especially corticoamygdalohippocampectomy [11]. In a controlled comparison between subtemporal versus transylvian selective amygdalohippocampectomy, the authors observed that both approaches caused similar degrees of verbal memory decline; however, subtle differences could also be identified, as the transylvian approach affected verbal recognition memory more, while verbal fluency and figural memory were more affected by the subtemporal approach [12].

In this study, we did not evaluate the impact of antiepileptic drugs or other possible genetic aspects that could eventually be associated with cognitive impairment and/or hippocampal abnormalities.

Despite the limited size of our patient group, we present an interesting finding of changes in contralateral hippocampal volume compared with healthy controls. This new information points to the importance of continuous evaluation of these patients after surgery, as we also observed that cognitive changes may occur even for patients with good seizure control. The dynamic processes underlying both cognitive decline and reductions in the contralateral hippocampus are not clear and deserve future studies with multimodal approaches combining both functional and structural analyses.

5. Conclusions

Our study provides support to the concept that surgical treatment is an effective therapy for seizure control in patients with refractory MTLE. Our data suggest that patients with better seizure control and right-sided HS may present less long-term cognitive impairment compared with those with persistent seizures and left-sided HS. Further larger longitudinal studies combining cognitive tests with both structural and functional imaging analyses may provide additional explanation for the dynamic changes in cognition and the contralateral hippocampus.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.yebeh.2014.04.028>.

Conflict of interest

The authors have no conflict of interest.

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