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Mesial temporal lobe epilepsy: Revisiting the relation of hippocampal volumetry with memory deficits

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Objective: Neuropsychological tests can infer the lateralization of the epileptogenic focus, associating verbal memory to mesial structures in the left temporal lobe and visual or nonverbal memory to the right side. High-field magnetic resonance imaging (MRI) with high-resolution protocols allows acquisitions suitable for advanced postprocessing with precise volumetry of brain structures, and functional MRI demonstrates evidence that epilepsy should be seen as a network pathology, involving several structures in the brain. Since the literature showing associations between the volumetry of brain structures in left and right mesial temporal lobe epilepsy (MTLE) and verbal and visual memory performance on neuropsychological tests is conflicting, we revisited these relationships, considering the hippocampal volumetry of patients with unilateral MTLE.

Methods: Automatized hippocampal volumes were obtained using FreeSurfer software from MRI exams of 35 patients with unilateral MTLE and hippocampal atrophy and homolateral ictal onset zone defined by video electroencephalography concordant to the side of hippocampal volume reduction (15 on the left side). Verbal memory was assessed using the Rey Auditory-Verbal Learning Test (RAVLT), and visual memory tests employed the Rey–Osterrieth Complex Figure Test (ROCFT). The statistical analysis explored relationships between hippocampal volumetry, lateralization, and performance on memory tests.

Results: In general, we observed deficits in both verbal and visual memory for patients with left and right hippocampal volume reduction. Patients with left hippocampal volume reduction had poorer performance on verbal memory tests compared with those with right hippocampal atrophy ($t = -3.813$, $p < 0.001$). Visual memory deficits were seen on both left and right MTLE without a statistically significant difference ($t = 0.074$, $p = 0.942$). The correlation between the Hippocampal Asymmetry Index (HAI) and visual and verbal Z-scores was significant only for visual Z-score in right MTLE ($R = -0.45$, $p = 0.048$).

Conclusions: Verbal memory deficit seems to be more consistent in patients with left hippocampal volume reduction. Although it had only a moderate correlation to HAI, visual memory deficit is suggested as a poorer indicator for right MTLE. Considering that verbal and visual memory deficits are seen on both right and left MTLE, MTLE should not be regarded as a unilateral, focal, or local insult but as a multifactorial and network pathology, possibly involving several brain structures.

1. Introduction

The International League Against Epilepsy defined epilepsy conceptually as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [1]. A practical clinical definition of epilepsy was established by this healthcare association in 2014 [2]. According to the World Health Organization, "approximately 50 million people worldwide have epilepsy, making it one of the most common neurological diseases globally." The incidence of epilepsy is generally accepted to be lower in high-income countries compared with low- and lower-middle-income countries whereas studies of estimated prevalence rates show large variations [3,4]. Temporal lobe epilepsy is the most frequently studied epilepsy syndrome in adults, and hippocampal sclerosis hippocampal sclerosis (HS) is one of the most common pathological findings [5–8]. Approximately one-third of individuals with epilepsy will have drug-resistant seizures refractory to adequate drug therapy [9] and are potential candidates for surgery.

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Among the presurgical evaluation of patients with epilepsy, magnetic resonance imaging (MRI) [9] and neuropsychological assessments [10] have an important role in surgical planning. However, contributions of quantitative MRI data derived from postprocessing techniques for the detection of hippocampal pathology are not clear [11], giving rise to a wide range of research [11–15]. Several studies have investigated the relationship between brain morphometry and epilepsy [8, 16–19], especially regarding surgical outcome, but the literature comparing hippocampal volumetry and verbal and visual memory is conflicting, maybe because of the different methodologies used to measure hippocampal volumetry and test memory.

Kilpatrick et al. [20] assessed 25 patients (17 left mesial temporal lobe epilepsy (MTLE) with hippocampal atrophy) using the Rey Auditory-Verbal Learning Test (RAVLT) and Rey–Osterrieth Complex Figure Test to test verbal and nonverbal memory, reporting a moderate to strong association between the degree of left hippocampal atrophy and severity of verbal memory deficits and no association between right hippocampal atrophy and tests of nonverbal memory. Baxendale et al. [21] studied 67 patients with MRI evidence of HS and reported that the right hippocampal volume was correlated with the delayed recall of a complex figure, but none of the verbal memory test scores were significantly correlated with hippocampal volumes. Sawrie et al. [22] evaluated the verbal memory of 22 patients (16 left MTLE determined by video electroencephalography and clinical features) using the Wechsler Memory Scale (WMS) and did not find a statistically significant correlation between verbal memory and either left or right hippocampal volumes. Orozco-Giménez et al. [23] evaluated 36 patients (19 left MTLE) using an equivalent version of the California Verbal Learning Test and the Rey Complex Figure Test, indicating that structural damage in the right hippocampus implies worse performance in visual memory, but did not find a correlation between left hippocampus integrity and verbal memory. Alessio et al. [24] studied 39 patients with MTLE and found a positive correlation between the degree of left hippocampal atrophy and the degree of verbal memory deficit but no association between right hippocampal atrophy and visual memory deficit.

Considering the inconsistent results presented previously, we revisited this issue, analyzing patients with MTLE with hippocampal atrophy. We used an automated technique (FreeSurfer) to determine hippocampal volumes, used an asymmetry index to identify and lateralize hippocampal atrophy, paired the RAVLT and the Rey–Osterrieth Complex Figure Test (ROCFT) to assess memory performance, and explored relationships between hippocampal volumetry and the memory tests, discussing and comparing our results with the previous studies in light of current volumetry protocols.

2. Material and methods

2.1. Subjects

We analyzed 35 patients with unilateral hippocampal atrophy evaluated during presurgical planning between September 2013 and August 2018, 15 left MTLE (6 males) and 20 right MTLE (7 males), with homolateral ictal onset zone defined by video electroencephalography concordant to the side of hippocampal volume reduction, without any other pathology evident in the MRI reading. Age at MRI examination ranged from 18 to 63 years (mean age, 39.7 years), and the mean education level was 9 years (range, 3–20 years). The median age of onset of seizures was 7 years, and the mean duration of epilepsy was 29.1 years. Morphometric hippocampal references were extracted from a set of 59 healthy controls recruited at the imaging site and the university campus. This study is registered in the Brazilian platform (Plataforma Brasil) for researches involving human subjects, and the Ethics Committee of the Universidade Federal do Paraná approved the study. All subjects agreed with the informed consent.

2.2. Neuropsychological evaluation

Patients were evaluated for verbal and visual memory, ranging from 1 week to 15 months before the MRI scan (median, 42 days). We used the RAVLT and the ROCFT, deriving Z-scores compared with healthy controls.

2.3. Acquisition protocol and MRI interpretation

All MRI scans of patients and controls were acquired on a 3T MRI scanner (Siemens MAGNETOM Skyra) using a 16-channel head coil. The morphometry protocol consisted of a three-dimensional (3D) magnetization prepared rapid acquisition Gradient Echo (GRE) sequence using recommended parameters optimized for FreeSurfer postprocessing, acquired in the sagittal plane (176 slices, field of view 256 mm, slice thickness 1 mm, voxel volume 1 mm^3, echo time 3.36 ms, repetition time 2530 ms, inversion time 1100 ms, pixel bandwidth 200 Hz/px, flip angle 7°). Additional sequences consisted of coronal T2-weighted fast spin echo perpendicular to the hippocampi, 3D T2 fluid-attenuated inversion recovery, susceptibility weighted imaging, and diffusion tensor imaging. Two neuroradiologists (SEO and GRS) read the scans, and unilateral alterations in one of the hippocampus and affected side were established by consensus, considering visual and qualitative parameters: hippocampus height, morphology, and altered signal.

2.4. MRI volumetry

The T1-weighted MRI scans were processed using the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu/), stable version 6.0 (January 2017), documented in detail in several articles [25–33, 47–50]. We ran the recon-all script, a fully automated pipeline, and extracted hippocampal volumes. During the visual inspection of the segmentation, some minor errors were observed in the hippocampal volumes and were not considered for editing as bias due to over- or undercorrection along the process could occur. We used a database of 59 healthy controls (19 to 62 years of age, mean of 38 years, 32 females) to obtain hippocampal reference volumes. The analysis considered the Hippocampal Asymmetry Index (HAI), highly accurate in the diagnosis

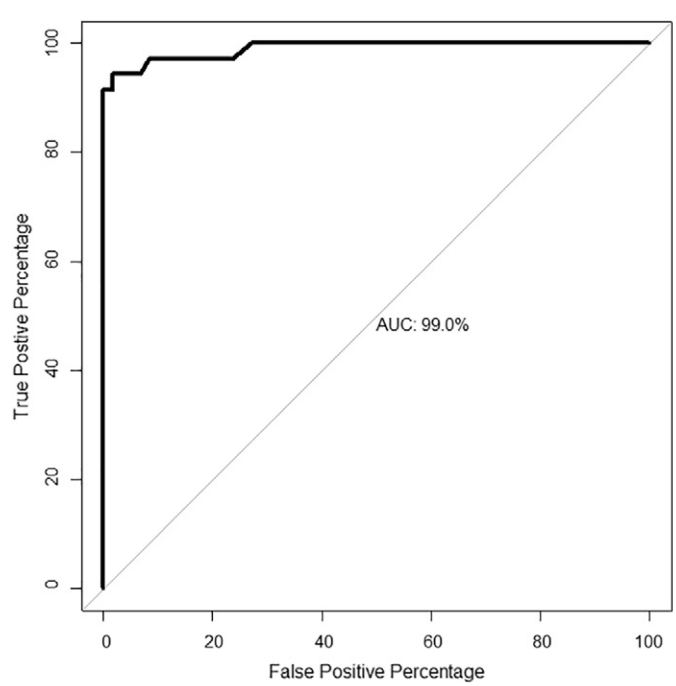

Fig. 1. Plot of the AUC-ROC curve of the HAI classification of left and right hippocampal atrophy.

Table 1
Demographic, clinical, neuropsychological, and the side of hippocampal volume reduction on MRI reading and ictal onset zone.

Laterality on MRI reading and VEEG	Gender	Age (years)	Age at onset (years)	Disease duration (years)	Education (years)	Left hippocampal volume in SD	Right hippocampal volume in SD	HAI	RAVLT Z-score	ROCFT Z-score
Left	Female	26.7	6.0	20.7	10	−2.78	−0.24	−0.185	−1.19	−1.62
		29.7	16.0	13.7	11	−3.17	0.00	−0.216	−2.35	−0.01
		38.9	7.0	31.9	10	−2.74	−0.27	−0.163	−1.58	−1.19
		41.3	0.8	40.5	5	−3.54	−0.80	−0.189	−1.96	−1.43
		41.9	25.0	16.9	8	−2.32	−0.66	−0.119	−1.96	−1.56
		42.6	8.0	34.6	11	−1.72	0.10	−0.123	−3.50	−1.62
		53.0	9.0	44.0	5	−2.57	0.59	−0.207	−2.73	−1.62
		53.6	8.0	45.6	8	−2.76	1.68	−0.258	−3.12	−1.00
		63.1	13.0	50.1	4	−3.21	−0.49	−0.176	−3.50	−1.00
	Male	26.2	1.2	25.0	12	−1.51	−0.41	−0.078	−1.96	1.78
		31.8	0.9	30.9	11	−3.12	−0.02	−0.182	−0.81	−1.25
		33.0	27.0	6.0	11	−0.99	−0.30	−0.056	−1.96	−0.94
		34.1	0.3	33.8	11	−4.49	0.39	−0.299	−3.50	−2.05
		37.4	7.0	30.4	11	−2.33	0.79	−0.177	−0.04	−0.38
		45.8	18.0	27.8	6	−1.89	1.97	−0.204	−1.96	−0.20
Right	Female	24.7	3.0	21.7	7	−0.69	−3.63	0.176	−0.81	−1.06
		28.3	0.8	27.6	3	0.09	−2.60	0.146	−1.19	−1.74
		33.7	1.4	32.3	11	0.30	−3.22	0.193	−0.81	−1.37
		34.5	30.0	4.5	16	−0.62	−1.74	0.041	−1.58	0.17
		40.7	29.0	11.7	11	0.08	−2.31	0.117	−2.35	−0.88
		41.6	17.0	24.6	3	0.24	−2.47	0.161	−3.12	−1.80
		45.4	3.0	42.4	4	−1.37	−3.24	0.110	0.35	−1.37
		45.9	7.0	38.9	7	0.04	−3.44	0.228	−1.58	−1.25
		46.5	14.0	32.5	8	0.57	−2.00	0.132	0.35	−0.81
		47.1	34.0	13.1	15	−0.31	−1.91	0.070	0.35	−0.14
		48.2	20.0	28.2	11	0.17	−3.32	0.200	−0.04	−0.63
		48.9	28.0	20.9	3	−1.34	−3.94	0.192	1.12	−0.44
		49.7	12.0	37.7	11	0.40	−2.09	0.142	−0.42	−1.49
	Male	17.8	4.0	13.8	11	1.81	−1.82	0.144	1.12	−0.81
		27.2	4.0	23.2	11	3.43	−0.13	0.117	−1.19	−1.19
		33.7	4.0	29.7	11	−0.47	−3.99	0.173	−1.19	−1.06
		38.5	3.0	35.5	5	0.32	−3.93	0.253	−0.81	−1.43
		41.9	1.5	40.4	4	1.94	−3.24	0.237	−0.81	−0.69
		46.7	6.0	40.7	10	−1.21	−3.06	0.093	−1.19	−0.38
		50.5	5.0	45.5	20	0.17	−2.46	0.124	−1.58	−0.75

MRI, magnetic resonance imaging; VEEG, video electroencephalography; HAI, Hippocampal Asymmetry Index; SD, standard deviation; RAVLT, Rey Auditory-Verbal Learning Test; ROCFT, Rey–Osterrieth Complex Figure Test.

of unilateral MTLE [12], defined as the ratio between the difference of volumes of the left (HVL) and right (HVR) hippocampus and the sum of both volumes (HAI = [HVL − HVR] / [HVR + HVL]).

Hippocampal volumes were normalized using the covariance method, described by Jack et al. [34], and we considered the cranial volume in the correction [35].

2.5. Statistical analysis

Data analysis was carried out using R software [36], version 3.5.3, R Foundation for Statistical Computing, Vienna, Austria (URL http://www.R-project.org/) and packages pROC [37], car [38] e ggpubr [39]. We used the Shapiro–Wilk test to test the normalities of the samples,

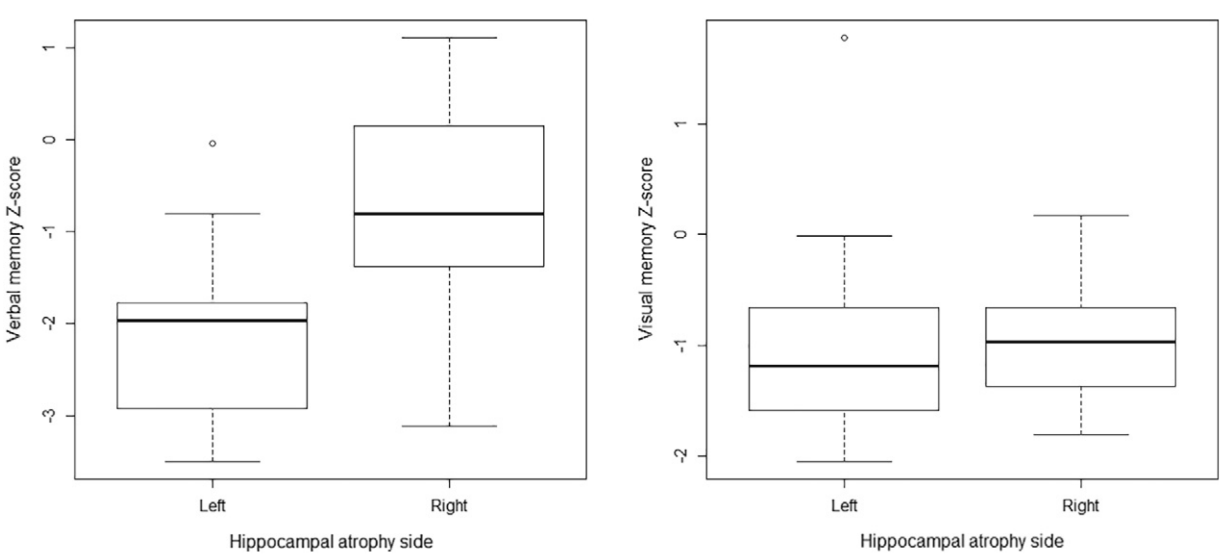

Fig. 2. Boxplots of verbal ($t = -3.813$, $p < 0.001$) and visual ($t = 0.074$, $p = 0.942$) memory Z-scores.

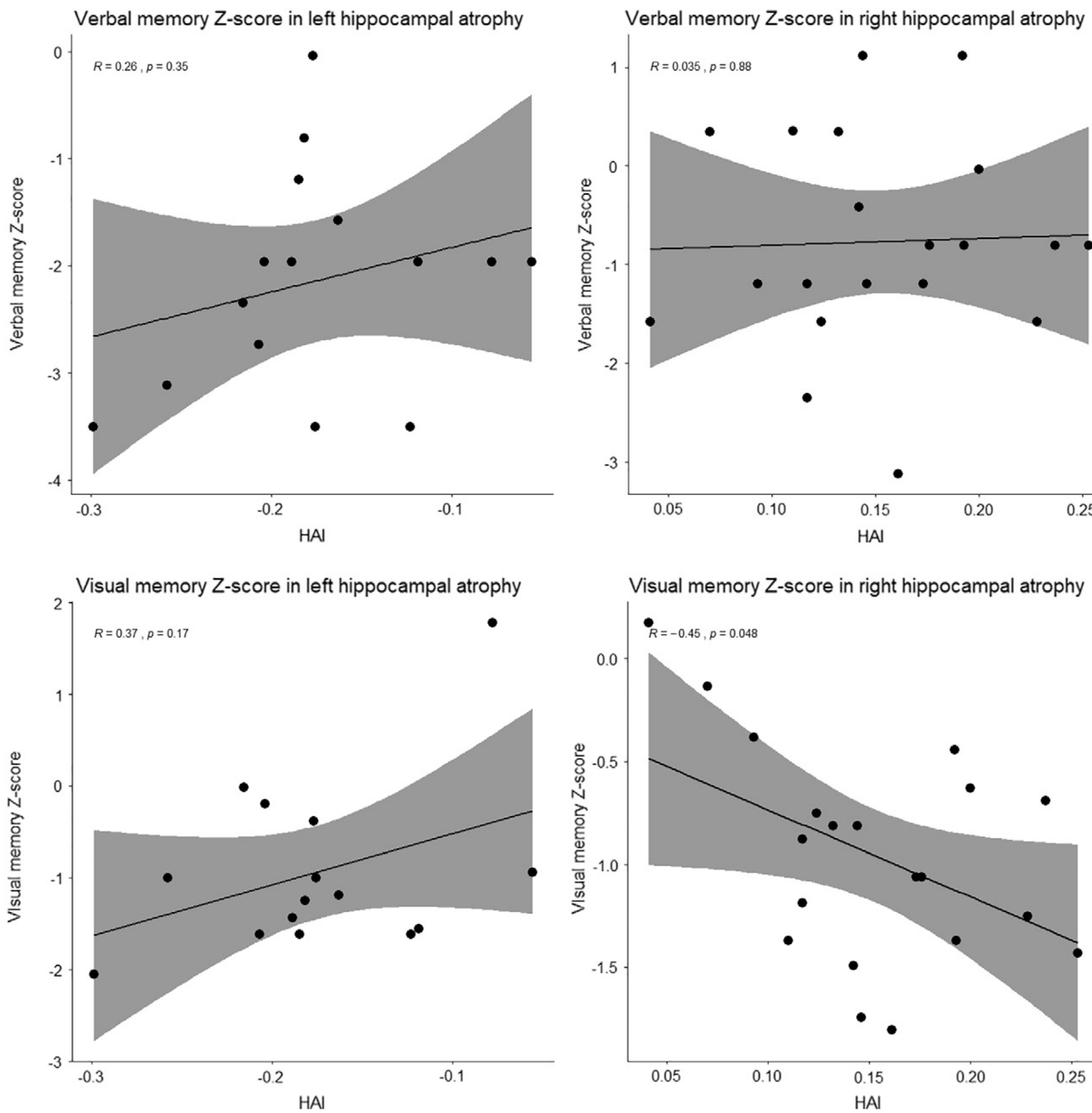

Fig. 3. Correlation plots of verbal (top) and visual (bottom) memory Z-scores for left (left) and right (right) hippocampal atrophy according to HAI. Only visual memory Z-score in the right hippocampal atrophy showed significant ($p = 0.048$) moderate ($R = -0.45$) correlation.

the Levene test to analyze variances, and the Student *t* test as a parametric statistic. We considered a significance level of $p < 0.05$.

3. Results

The HAI was accurate and classified the side of the hippocampal atrophies correctly, and the area under the receiver-operating characteristic curve (AUC-ROC) provided an AUC of 99.0% (Fig. 1). In our sample, a cutoff value for HAI of 0.064, equivalent to a unilateral volume loss of 12%, provided a sensitivity of 94% and specificity of 95%.

Table 1 summarizes demographic data, clinical features, results of neuropsychological verbal and visual memory tests, MRI reading (laterality), and postprocessed results. Statistical tests showed that the right and left MTLE did not differ in terms of sex ($\chi^2 = 0.092$, $p = 0.762$), absolute value of HAI ($t = 1.148$, $p = 0.259$), age ($t = 0.110$, $p = 0.913$), age at onset ($t = -0.443$, $p = 0.660$), disease duration ($t = 0.465$, $p = 0.645$), and education ($t = -0.123$, $p = 0.903$).

Considering that lower (positive or negative) values of HAI may indicate near-normal bilateral volumes or bilateral atrophy, we analyzed the hippocampal volumes considering the standard deviations, with a threshold of <-1.65 standard deviations to consider a significant volume reduction, as adopted by Pardoe et al. [40]. We did not detect bilateral atrophies in our set of patients.

We found a moderate correlation between disease duration and the absolute value of HAI ($R = 0.460$, $p = 0.005$).

We used the Bonferroni method to correct for multiple comparisons in the post hoc analysis and considered a significance level of corrected $p < 0.025$. Verbal memory Z-scores for left and right hippocampal atrophy are statistically significant ($t = -3.813$, $p < 0.001$), but visual memory Z-scores did not show a statistically significant difference ($t = 0.074$, $p = 0.942$) (Fig. 2).

When analyzing the relation between HAI and verbal and visual Z-scores, we found a moderate correlation only for visual Z-score for the right MTLE ($R = -0.45$, $p = 0.048$) (Fig. 3).

4. Discussion

Qualitative MRI readings may not detect minor volume differences in hippocampal volumes, and quantitative volumetry could help in these cases. The accuracy in the determination of hippocampal volumes by experts can be superior to automated methods [40], but in the era of robots, automation, and artificial intelligence, much of our work relies on robust automated algorithms. In our database of healthy controls, the hippocampal volumes (right = 4179 mm^3, left = 3999 mm^3) are similar to values obtained in a previous study using a similar methodology, with mean values of right hippocampi of 4280 mm^3 and left hippocampi of 4210 mm^3 [11], suggesting reproducibility of the automated segmentation. Considering that small differences between right and left hippocampal volumes are observed in healthy controls [35], this could pose a certain degree of difficulty in the detection of minor volume reductions. However, in our study, based on automated segmentation (FreeSurfer), all hippocampal volume reduction sides were correctly classified with HAI, and the ROC curve showed a good performance for classification, indicating the reliability and the usefulness of these tools.

Considering the effects of the disease on hippocampal volume reduction, we observed a moderate ($R = 0.460$) correlation between disease duration and HAI. We believe that individual differences in response and adherence to treatment, among other causes, could interfere in this association and explain the moderate correlation.

Neuropsychological data have been shown to correlate with focal areas of brain dysfunction in patients with epilepsy [10,41], and MTLE provides one of the better prototypes for the study of hippocampal pathology and memory function [22,23]. However, current literature reveals that connectivity plays an important role in brain functioning, reinforcing that cerebral functioning does not rely on single structures but on a complex interconnected network. This recent consensus that epilepsy is a network disease [42] may help explain some of the contradictory results observed when studying apparent focal lesions.

The choice of a memory task may influence the identification of a memory deficit [21]. The ideal memory battery test is one that maximizes the lateralization, using tasks highly verbal or highly nonverbal [10]. We paired the RAVLT and the ROCFT because we consider that the drawing task of the ROCFT minimizes the use of verbal elements compared with the WMS visual test, in other words, minimizes that the patient encodes a figure to remember in a verbal manner. In our study, we identified a greater dependency of left hippocampal integrity on the verbal memory test, and we found a moderate correlation between right hippocampal volume and visual memory test performance.

Some inconsistency is seen in previous results comparing hippocampal volumetric data and visual and verbal memory tests. Our results related to verbal memory are concordant with what was observed in the papers of Kilpatrick et al. [20] and Alessio et al. [24], which used RAVLT and WMS-R tests, respectively (i.e., an association between verbal memory deficits and left hippocampal atrophy). Regarding nonverbal memory performance, our results are in line with the findings of Baxendale et al. [41] and Orozco-Giménez et al. [23], which used the Rey Figure Test and found an association between visual memory tests and right hippocampal volumes. We believe that the choice of the battery of memory tests may play a role in the outcomes. We observed that the methodologies to determine hippocampal volumes varied along the years, with operator-dependent issues in the first studies, and also that there is a variation in the battery of memory tests applied. We agree with Orozco-Giménez et al. [23] that these factors may influence the outcomes of the studies. Another possible explanation to the discrepancies is that a considerable proportion of patients with temporal lobe epilepsy have atypical memory profiles and atypical neuropsychological examinations [43].

Hippocampal volumetry has been recognized as a reliable surrogate marker of HS [44,45], and the correlation between MRI and histopathology should improve with higher resolution and dedicated protocols, and postprocessing advances, like improved segmentation of hippocampal subfields. Correlation and histopathology differentiation between gliosis only and HS on MRI have also been studied [46]. We determined MTLE on clinical grounds, and the only alteration on MRI was hippocampal atrophy. We do not have histopathological confirmation for possible HS or gliosis only in this set of patients, but as they are submitted to surgery, data will become available to study the relationships between volumetry, neuropsychological tests, histopathology, and outcomes.

One important limitation of our study is the small sample size, which may have an impact on the statistical analysis. However, we opted to study a homogeneous group of patients with MTLE and hippocampal atrophy, mitigating different effects if we had included other pathologies found in MTLE. Another potential limitation is that we did not edit minor corrections on the automated segmentation of the hippocampus, intending to reduce eventual operator-dependent bias, with excessive or insufficient corrections, thus relying on the robust algorithm of the FreeSurfer software. Another factor to consider is the intrinsic limitation of the memory battery tests, in the sense that the ideal situation of tasks purely verbal or purely nonverbal is difficult to achieve, besides the fact that other cognitive functions can interfere in the neuropsychological assessment [10].

5. Conclusions

Our results suggest that tests of verbal memory are statistically significantly worse for the left MTLE-HS, and visual memory performance has a moderate correlation with HAI in the right MTLE-HS. These observations lead us to believe that unilateral MTLE has an asymmetric impact on these material-specific tests, which is probably explained by alterations in the architecture of the connections involving these structures. Several factors may influence the conflicting results seen in the literature, and we list three to consider: the methodology employed to obtain the volumes, the battery tests chosen, and the fact that a large proportion of patients with MTLE have atypical neuropsychological profiles.

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Declaration of competing interest

None.

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