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Automated evaluation of hippocampal subfields volumes in mesial temporal lobe epilepsy and its relationship to the surgical outcome

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ABSTRACT

The International League Against Epilepsy (ILAE) classification system for hippocampal sclerosis (HS) is based on location and extent of hippocampal neuron loss.

Specific subgroups have a better surgical prognosis. Automated hippocampal subfields segmentation and volume measure could be obtained from high field MRI and used to pre-operatively classify the patients in ILAE subgroups to define best candidates for surgery.

This prospective study included 86 MTLE patients, candidates to surgical treatment and ten healthy volunteers. Volumetric analysis of the hippocampal sublayers was performed through the Freesurfer software, using 3 Teslas volumetric T1 weighted MRI. We correlated the hippocampal subfields measures with the seizure control after one year from surgery.

Volume loss in Cornu Amonis (CA) 1 and 4 were related to better surgical outcome after one year. Atrophy in CA 2 and CA 3 did not improve the prognosis. These results are in agreement with the ILAE classification of hippocampal subfields sclerosis.

1. Introduction

Epilepsy is a serious health problem that involves people regardless of age, race, and socioeconomic backgrounds. Epilepsy has a prevalence of 5–10 per 1000 population in North America. (Wiebe et al., 2001) In underdeveloped countries, epilepsy is more prevalent reaching 12–20 per 1000. (Gomes et al., 2002; Sander, 2003)

Mesial temporal lobe epilepsy (MTLE) secondary to hippocampal sclerosis (HS) is the most common focal, drug-resistant epilepsy syndrome. The hippocampus is a highly complex structure, including *cornu Ammonis* (CA) CA1–CA4 subfields, dentate gyrus (DG), fimbria, subiculum (SUB), parasubiculum, and entorhinal cortex (ERC) (Na et al., 2015).

A recent pathological classification identifies three HS subtypes according to patterns of neural loss in CA1, CA2, CA3, and CA4. (Cendes et al., 2014; Kwan et al., 2010) Three types of HS were classified. HS ILAE (International League Against Epilepsy) type 1 refers to severe neuronal cell loss and gliosis predominantly in the CA1 and CA4 regions; HS ILAE type 2 shows predominant neuronal cell loss and gliosis in the CA1 region, and HS ILAE type 3 presents predominant neuronal cell loss and gliosis in the CA4 region. HS subtypes have different clinical courses and surgical outcomes with better results in type 1 (Na et al., 2015; Thom, 2014).

Surgical techniques have improved the treatment of epilepsy to such an extent that some experts now suggest that physicians should offer surgery early to patients with surgically remediable epileptic syndromes instead of waiting for years until multiple anticonvulsant drugs have failed (Lee, 2014). Among the patients with refractory MTLE-HS, only 8% are cured with the best clinical treatment while 60% become free of seizures with surgery (Wiebe et al., 2001) Thus, research efforts to uncover predictors to seizure freedom are required to help define which patients will benefit the most from surgery of MTLE-HS. Ultimately, we sought to use variations of hippocampal subfield volume as a predictor for MTLE resolution through surgery. To this end, we used the Freesurfer, a suite of applications for cortical parcellation and automatized volumetric measure of brain structures. Freesurfer's fully automatic algorithm allows for multi-atlas-based labeling of hippocampal subfields and adjacent cortical subregions also using high-resolution weighted images.

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2. Methods

2.1. Ethical statement

All patients signed n informed consent, and the study was conducted following the Declaration of Helsinki. The national ethics board approved the study (CAAE number 01364012.9.0000.5149).

2.2. Participants

The study was conducted between June 2013 and June 2016. We prospectively recruited 103 patients with TLE secondary to HS at the epilepsy surgery unit in Santa Casa Hospital and ten volunteers without any signal of neurological illness or epilepsy. All patients were seen by an epilepsy specialist for medical therapy adjustments and met the criteria for refractory epilepsy established by ILAE (Kwan et al., 2010). Before surgery, patients performed a Video-EEG, neuropsychological tests for temporal lobe function and at least one 3 Teslas MRI with sagittal 1 mm volumetric acquisition. The control group composed of ten healthy volunteers performed a 3 Teslas MRI to estimate the average volumes of hippocampal structures. The inclusion criteria were:

1 Refractory temporal lobe epilepsy
2 Unilateral hippocampal sclerosis on MRI
3 Volumetric 1 mm slice tickness T1 MRI
4 Video EEG with ictal onset on the same side as MRI
5 Absence of dual lesions

Patients with inadequate MRI protocol (n = 8) and with dual lesions (n = 5) were excluded from the study. Three patients refused surgery after being selected as good candidates for it and one deceased before one year of follow up (pulmonary embolus). This study presents the results of the remaining 86 patients. All of them had unilateral hippocampal sclerosis in MRI, video-EEG with ictal discharges starting in the sclerotic side and refractory focal epilepsy with impaired awareness.

We also investigated clinical data including gender, age, years of seizures and schooling as seen in Table 1.

2.3. MRI acquisition and analysis

All patients performed a 3 Teslas high field (Philips (Achieve Dual 3.0 T, Philips Medical Systems, Netherlands) or GE (Signa 3.0 T, GE Healthcare, United Kingdom). The protocol included a volumetric T1 weighted sequence with 1 mm cuts in a 256/256 matrix. During the study the exchange of MRI scanner was performed. We maintained the same study protocol with the same sequences. The literature shows that the Freesurfer has good reproducibility on different MRI scanners (Chiappiniello et al., 2018).

The FreeSurfer software ver.6.0 (Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital, Boston USA) (Fischl, 2012; Iglesias et al., 2015; Van Leemput et al., 2009) was used to evaluate the volumes of hippocampal subregions (Iglesias et al., 2015). We used the longitudinal pipeline of Freesurfer v6.0 with the

Table 1
Demographic data of patients and controls.

	Patients	Controls
n	86	10
Sex (Females/Males)	F 45/M 41	F 5/M 5
Age (Mean/SD)	36.5 (11.08)	29.6 (8.38)
Years of Schooling (Mean/SD)	9.42 (3.62)	19.3 (3.86)
Years of epilepsy (Mean/SD)	24.24 (12.68)	–
Side of HS (Right/Left)	41/45	

SD: Standard Deviation, HS: Hippocampal sclerosis.

"hipposubfields" flag. No manual adjustments were applied. This validated method is widely used in clinical research (Marizzoni et al., 2015). We measured the volumes of CA1, CA2–CA3, CA4, granular cell field of the dentate gyrus, and whole hippocampus.

Fig. 1 shows the hippocampal subfields labeling in one of the study patients using Freesurfer. Video 1 shows comlete labeling in sagittal view. We compared the results obtained for the affected and normal hippocampus and those obtained for both hippocampi of 10 healthy controls.

2.4. Surgery

All patients were operated by the same surgeon following the following protocol:

Left hippocampal sclerosis: Access through the middle temporal gyrus as described by Niemeyer (1958) with selective resection of the amygdala and hippocampus.

Right hippocampal sclerosis: anterior temporal lobectomy with at least 4.5 cm associated with resection of the amygdala and hippocampus according to technique published by Spencer et al. (1984).

2.5. Surgical outcome

The surgical results were evaluated one year after the surgery using the Engel classification of epilepsy surgery outcome (Engel, 1993).

2.6. Data analysis

SPSS 24 software (IBM Corporation) was used for data analysis. We compared the HS and non-HS (sclerotic and normal sides) subfields in MTLE-HS patients and control individuals using the Student t-test. We also performed an analysis of variance (ANOVA) using the side of HS, age at surgery, schooling, years of epilepsy, and surgical outcome. Before doing the ANOVA, we checked that all variables had homogeneous variances using the Levine test. The level of statistical significance was set at 0.05.

3. Results

Eighty-six HS cases (45 female) were included. Patients age varied from 15 to 57 years (36.5 ± 11.08), with a mean epilepsy duration of 24 years. Complete seizure freedom (Engel 1A) was achieved by 47 (54.65%) with good outcome in 63 (82.56%) patients one year after surgery. These results, specifically the patients totally free of convulsions or auras, are somewhat worse than the recent literature data (Deleo et al., 2015). One explanation for this result is the difficulty in maintaining high-cost medications, especially Lamotrigine and Topiramate in low-income patients. The state provides the medications but, from 2014 we have had long periods of lack of availability causing early withdrawal after surgery.

In most of the studies the patients free of disabling seizures (Engel 1 and 2) are classified as good results. Wiebe et al. (2001), in a prospective study, found 59% of patients Engel 1 and 2 in one-year. Engel et al. (2003), in a systematic review of 24 studies totaling 1952 patients operated found 1285 patients (67%) free of disabling seizures(Engel 1 and 2) and 49.5% completely seizure free.

3.1. Volumetric analyses of hippocampal subfields for MTLE-HS patients

Table 2 presents the hippocampal subfield volumes calculated with the FreeSurfer ver.6.0. In all subfields volumes, a significant difference was found between the HS side and non-HS side. In addition, all MTLE subfields volumes, HS and non-HS sides, were significantly smaller than the control group. Fig. 2 presents hippocampal subfields means graphics with a 95% confidence interval.

Table 3 presents the analysis of variance (ANOVA) for the surgical

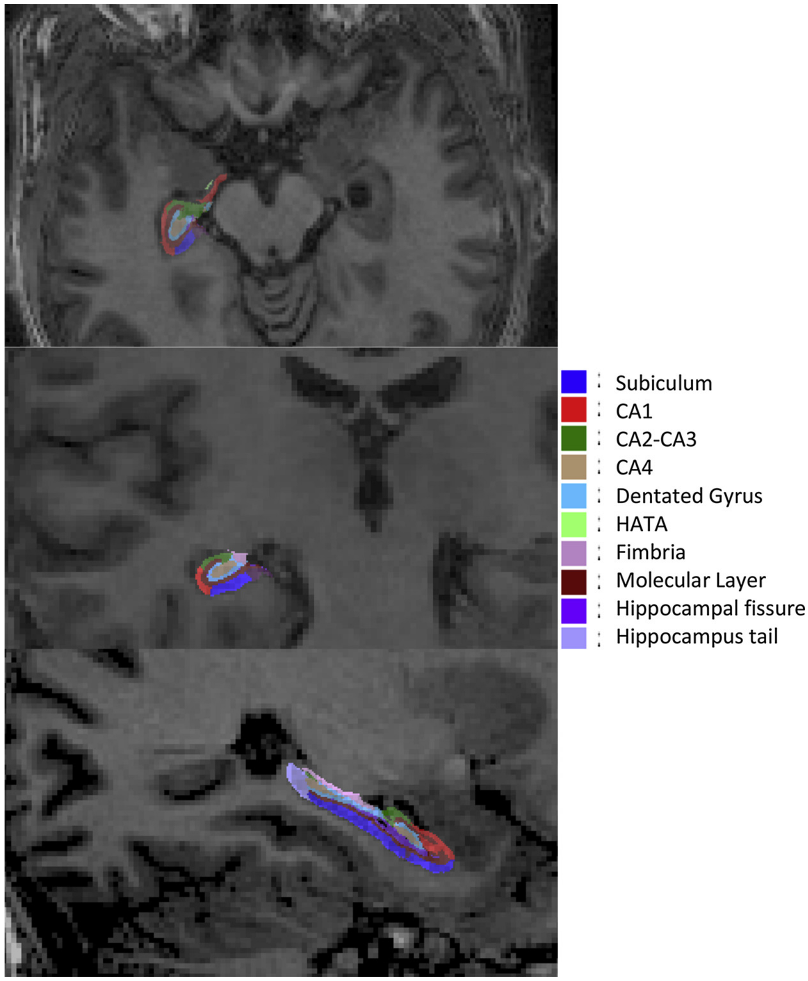

Fig. 1. Automated labeling of hippocampal subfields with Freesurfer in the same patient in axial, coronal and sagittal planes.
HATA: hippocampal-amygdaloid transition region.

outcome. We considered two groups in the surgical outcome: completely free of seizures (Engel class 1A) and not free of seizures during the follow-up period of one year after surgery. We used CA1, CA2-CA3, CA4, DG, and whole hippocampus volumes in the HS and non-HS sides, age, years of epilepsy, and schooling as dependent variables and freedom of seizures as a factor. The ANOVA results showed that only the HS side subfields CA1, CA4, DG, and whole hippocampus were associated with the surgical outcome. The epidemiological variables age, years of epilepsy, HS side, and schooling did not affect the outcome in this series.

4. Discussion

Surgery for MTLE-HS can lead to significant complications in 4% of surgeries (Mathon et al., 2017b), although mortality is rare (Georgiadis et al., 2013). After surgery, 20–40% of patients do not become seizure free (Wiebe et al., 2001) and are therefore exposed to operation risks without rearing the aimed results. Further understanding the reasons underlying these adverse outcomes may avoid subjecting the patients to unnecessary surgical stress and the associated costs. Moreover, research on this topic may contribute to improving surgical results on these refractory patients.

We found that age, years of epilepsy, side of sclerosis and education do not correlate with prognosis. However, the reduction in CA1, CA4,

Table 2
Hippocampus and hippocampal subfields mean volume and standard deviation in HS side, non-HS side and controls. *t*-test between HS side and non-HS side and controls and non-HS side.

	HS side Mean (SD)	Non-HS side Mean (SD)	Controls Mean (SD)	T test HS/ non-HS p	T test Controls/ non-HS p
CA1	540.85 (114.80)	623.29 (113.46)	688.27 (75.70)	< **0.001**	< **0.001**
CA2- CA3	168.58 (43.47)	202.06 (43.82)	256.64 (45.40)	< **0.001**	< **0.001**
C4	198.41 (51.09)	244.05 (48.03)	291.04 (37.65)	< **0.001**	< **0.001**
DG	233.40 (59.51)	284.82 (56.06)	291.00 (36.70)	< **0.001**	< **0.001**
Hippocampus	2849.54 (565.55)	3321.50 (575.46)	3740.41 (404.25)	< **0.001**	< **0.001**

Measurements were done by FreeSurfer version.6.0. All values in mm3.
CA: *cornus ammonis*; HS: hippocampal sclerosis, DG: Dentated gyrus, Hippocampus: whole hippocampus volume; SD:Standard deviation.
Statistical analysis was performed using the Student -t test and considered significant if $p < 0.05$.

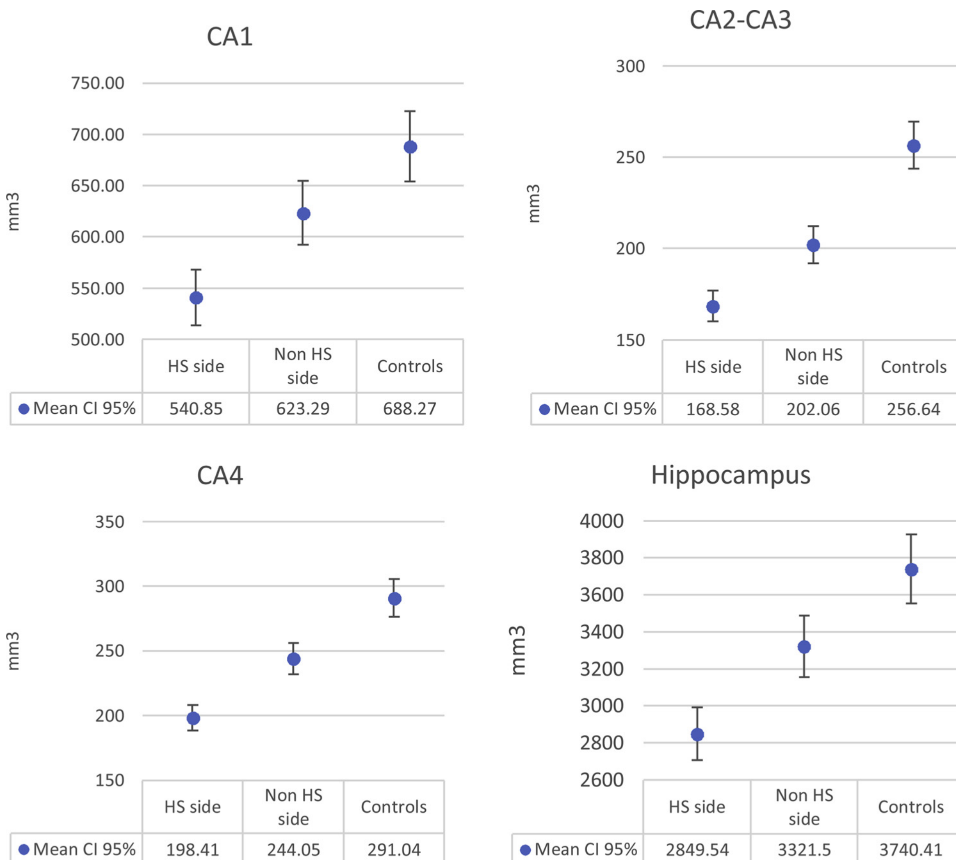

Fig. 2. Comparison of means of the hippocampus and subfields volumes between the Hippocampal sclerosis side, non-sclerotic side and the control group. CI 95%: Error bar with 95% confidence interval. HS: Hippocampal sclerosis; CA: *Cornu amonnis*.

Table 3
Analysis of variance (ANOVA) for surgery outcome comparing demographic variables.

Variables	Seizure free patients Mean in years (SD)	Non seizure free patients Mean in years (SD)	F	P value
Age	36.34(10.98)	36.59 (11.64)	0.008	.925
Years of epilepsy	24.25 (12.74)	24.67(12.65)	.149	.701
Schooling	9.46(3.38	9.43 (3.62)	.018	.894

SD: Standard deviation.

and DG volumes strongly predict a good outcome.

Another relevant finding is that the HS and non-HS sides present significantly lower volumes than controls, suggesting that the disease also affects the non-HS side. Also, our volumetric analysis confirmed that the HS side is significantly smaller than the non-HS side. However, the volume of non-HS subfields did not affect surgical outcomes. This pattern of asymptomatic bilateral atrophy was seen in other studies, but we could not link it to surgical results. (Keller et al., 2007; Keller and Roberts, 2008)

Even though epilepsy surgery is performed in multiple centers around the world, outcome data are scarce. Some authors issues in reasons of failed MTLE surgeries (Salanova et al., 2002; Siegel et al., 2004). Previous studies have suggested that predictors of poor outcome in MTLE-HS include bilateral discharges on EEG, incomplete resection, early seizures recurrence (Holmes et al., 1999; Wyler et al., 1989; Wyllie et al., 1998). However, these studies have statistical shortcomings due to the small series analyzed.

The international league against epilepsy (ILAE) defined a hippocampal subfields classifications and its relationship to the surgical outcome with the classical pattern (CA1 and CA4 predominant atrophy) associated with better prognosis (Blümcke et al., 2007; Jardim et al., 2016; Kwan et al., 2010). Many studies confirmed that the most frequent form of HE is the type 1 (CA1 and CA4 predominant) (Blümcke et al., 2007; Calderon-Garcidueñas et al., 2018; Deleo et al., 2015; Mathon et al., 2017a).

In our series, we found that CA1, CA4, and DG but not CA2-CA3 vol reduction is associated with better prognosis. This finding corroborates pathological studies in hippocampal subfields atrophy (Jardim et al., 2016; Kwan et al., 2010). Although neuronal loss and volume reduction are not the same, the reduction of volume is due to the neuronal loss, but we do not have studies that correlate the depopulation of neurons with the volumetric reduction. Our work shows that the preoperative evaluation of the hippocampal volumes can help to predict which patients will have a better surgical outcome. Although the results are similar to those found in pathological studies, we can not confirm that the volume reduction demonstrates pathological anatomic sclerosis because no surgical specimen studies have been performed.

5. Conclusion

Automated evaluation of the hippocampus performed by freesurfer software is an effective way to evaluate the hippocampal sclerosis patterns to define the surgical outcome. The association of CA1 and CA4 sclerosis and better surgical outcome is consistent with pathological studies. (Blümcke et al., 2007) Further studies are needed to try to define the cut-off points for hippocampal sublayer atrophy and to attempt to define HS subtypes preoperatively, but we have a new field to work in predictors for best outcomes in epilepsy surgery using MRI automated volumetric measure software.

Disclosure

None of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.05.011.

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