Memory impairment is not necessarily related to seizure frequency in mesial temporal lobe epilepsy with hippocampal sclerosis


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**Summary**

**Objective:** To investigate the effect of seizure frequency on memory, we performed a cross sectional study comparing mesial temporal lobe epilepsy (MTLE) patients with frequent and infrequent seizures.

**Methods:** We performed magnetic resonance imaging (MRI) hippocampal volume (HV) measurements and neuropsychological assessment in 22 patients with frequent seizures (at least one dis-cognitive seizure [DS] per month) that were refractory to antiepileptic drugs and 20 patients with infrequent seizures (three or less DS per year and no event evolving to a bilateral convulsive seizure), all with MRI signs of hippocampal sclerosis (HS) on visual analysis. We also included 29 controls for comparison of volumetric data.

**Results:** There was no difference in memory performance between patients with frequent seizures and infrequent seizures. We observed a significant bilateral reduction of HV in patients with MTLE when compared to controls \( (p < 0.001) \). The degree of hippocampal atrophy (HA) between patients with frequent and infrequent seizures was not different. There was a negative correlation between seizure frequency and HV, with \( r = -0.3 \) for the HV ipsilateral to the HS and \( r = -0.55 \) for the contralateral side, thus, explaining only 9% and 30% of the HV loss. There was a positive correlation between age of onset and degree of HA \( (r = 0.37) \).

**Significance:** Our data suggest that seizure frequency does not explain most of the HV loss or memory impairment in MTLE. Memory impairment appears to be more influenced by hippocampal damage than by seizure frequency. Further studies are necessary to identify the factors that influence memory decline in patients with MTLE.

**KEY WORDS:** Mesial temporal lobe epilepsy, Memory impairment, Hippocampal atrophy, Seizure frequency, Neuropsychological assessment.

Mesial temporal lobe epilepsy (MTLE) associated with hippocampal sclerosis (HS) is a syndrome that is highly refractory to clinical treatment, with up to 60% of patients not achieving optimal seizure control despite adequate antiepileptic drugs (AEDs).\(^1\) However, a subgroup of MTLE patients with excellent response to AEDs has been described and referred to as “benign MTLE,”\(^2\) although, this term is not recommended by the recent classification and terminology proposed by International League Against Epilepsy (ILAE).\(^3,4\)

In “benign MTLE,” seizures begin typically in adulthood. Patients often have a family history of febrile seizures and epilepsy. Although they have good seizure control, nearly 40% of these patients have magnetic resonance imaging (MRI) signs of hippocampal sclerosis (HS),\(^2,5\) showing that HS is not necessarily associated with poor outcome, as
suggested previously. The real frequency of “benign MTLE” may still be underestimated, probably because most studies of MTLE were performed by tertiary centers that usually follow patients with refractory epilepsies. It is not clear whether “benign MTLE” is a different syndrome or whether it is part of the spectrum of MTLE.

Independently, irrespective of whether these are two different syndromes, the presence of hippocampal atrophy (HA) in both subgroups enables comparisons between MTLE patients with HA with different seizure frequencies, allowing us to investigate the influence of the seizure frequency on several clinical features, especially on cognitive performance, one of the major complaints.

Studies regarding the relationship between seizure frequency and cognitive impairment show contradictory results. Some have demonstrated that seizure frequency could influence cognitive outcome, whereas other studies suggest that seizure frequency does not affect cognition. However, most of these studies did not evaluate the additional influence of HA in the context of memory and seizure frequency, with few exceptions.

Several studies indicate that patients with MTLE have progressive memory deficits due to hippocampal system damage. However, these studies were performed in surgical series and did not include a subgroup of MTLE with good seizure control; therefore, the impact of seizure frequency on neuropsychological performance remains difficult to ascertain. One study analyzed seizure frequency and memory in the presence of HA and did not find differences. However, in this study, no MRI quantitative method was used.

Because the literature describes mainly patients with frequent seizures, the description of patients with good seizure control with HA would help us to better understand the relationship between seizure frequency, HA, and memory impairment. Therefore, considering the hypothesis that higher seizure frequency would result in poorer memory performance, we studied MTLE patient with MRI signs of HS on visual analysis with different seizure frequencies comparing their memory performances with hippocampal volumes (HVs) and other clinical features.

**Methods**

**Participants**

We studied 48 patients with MTLE followed at the outpatient epilepsy clinic of our institution. Inclusion criteria for the present study were diagnosis of MTLE, according to the ILAE criteria and presence of signs of HS on visual analysis. All patients were older than 18 years and signed a written consent approved by the UNICAMP Ethics Committee.

Patients with brain pathology other than HS (e.g., neoplasm, dysplasia, or vascular disease) or with other major neurologic comorbidities (e.g., stroke, autoimmune disorders) were excluded from this study. Patients who underwent epilepsy surgery were also excluded from this analysis. All patients with frequent seizures were either under investigation for possible surgery or were not willing to undergo surgery.

We performed a detailed clinical and neurologic evaluation. Seizure frequency was determined based on seizure calendars and structured interviews during routine visits over the last year before the neuropsychological assessment. We considered the age of onset, the age when recurrent seizures started.

MTLE patients were classified based only on seizure frequency, and they were divided into two groups, considering the monthly seizure frequency:

1. **Infrequent Seizure Group (ISg)**: We included in this group patients with three or fewer dyscognitive seizures per year and/or just typical MTLE auras, and no event evolving to a bilateral convulsive seizure (CS). Isolated auras were not counted in the monthly seizure frequency.

2. **Frequent Seizure Group (FSg)**: We included in this group patients with at least one dyscognitive seizure per month. Dyscognitive seizures and CS were counted together in the monthly seizure frequency.

Seizure frequency cutoff choice was arbitrary, based on a previous study.

Patients were also classified according to electroencephalography (EEG) results. Patients with unilateral epileptiform discharges (EDs) were classified as unilateral EEG; patients with bilateral ED were classified as bilateral ED.

We included 29 healthy individuals from a local University community as a control group for volumetric measurements comparisons. Controls were matched with MTLE patients on age (p = 0.07) and gender (p = 0.17). Neuropsychological evaluation was not performed in the control group.

**MRI acquisition**

MRI was performed in a 3-T scanner (Philips Medical Systems, Best, The Netherlands), with an epilepsy protocol that includes thin coronal T1-inversion recovery, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images, and axial and sagittal T1- and T2-weighted images, for visual analyses.

A T1-weighted gradient-echo volumetric 3D (3-dimensional) sequence acquired in the sagittal plane (thickness = 1 mm, flip angle = 8 degrees, repetition time (TR) = 7.1 msec, echo time (TE) = 3.2 msec, matrix 240 × 240, field of view = 24 × 24 cm, pixel = 1 × 1) was used for hippocampal volumetry.

**MRI volumetric analysis**

A neuroimaging expert reviewed all MRI images independently of clinical and EEG data, with particular attention to asymmetry of hippocampi and abnormal internal structure with increased T2 signal. Patients with MTLE
without clear MRI signs of HS (six patients) were excluded from this analysis. None of the controls had MRI signs of HS.

We used manual segmentation, a validated method, to correlate volumetric findings with neuropsychological data. The hippocampal region was manually delineated according to the segmentation protocol of our group using the Display software (http://www.bic.mni.mcgill.ca/software/Display/Display.html). The HV was obtained by a single observer (D.P.), without prior knowledge of clinical history and subject’s identification.

MRIs originally acquired in the 3-T scanner in Digital Imaging and Communications in Medicine (DICOM) format were converted to medical imaging network common data (MINC) format for compatibility with the software Display. HVs were normalized for brain volumes of each individual. We used the statistical parametric mapping program version 8 (SPM8) (www.fil.ion.ucl.ac.uk/spm/software/spm8/) to extract the individual gray matter, white matter, and CSF maps and to calculate the total intracranial volume (TIV). The individual HV was normalized for TIV as follows: HV × (control group mean TIV/individual TIV).

To compare HVs and to avoid cancellation of atrophy with right or left HA, we classified HV as smaller (the side of MRI signs of HS in MTLE patients and the side of smaller volume in controls) and larger hippocampus. The asymmetry index (AI) was defined as smaller/larger HV.

Neuropsychological assessment

Neuropsychological assessment included the Edinburgh Handedness Inventory; vocabulary and block design subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III) to estimate intelligence quotient (IQ); Rey Auditory Verbal Learning Test (RAVLT); Logical Memory and Verbal Paired Associates (immediate and delayed recall) of the Wechsler Memory Scale - Revised (WMS-R) to investigate verbal memory; and the Figural Memory, Visual Reproduction (immediate and delayed recall), and Visual Paired Associates (immediate and delayed recall) of the WMS-R to investigate visual memory. The neuropsychological data were compared to normative data provided for each test.

We transformed Wechsler’s raw scores using normative data according to age into z-score values to compare ISg and FSg. We also transformed RAVLT’s raw scores according to age and years of education using normative data based on preestablished parameters for Brazilian population. Z-score values below –2 were considered abnormal. To analyze WAIS-III scores we used raw scores.

Statistical analysis

Analyses of data were performed using IBM SPSS Statistics, version 21 (Armonk, New York, U.S.A). Kolmogorov-Smirnov test was used to investigate the distribution of each variable. To compare the distribution of categorical variables between groups, we used the chi-square test and Fisher’s exact test when necessary. The comparisons of clinical features between groups were performed with Student’s t-test or Mann-Whitney test according to the distribution of the sample.

We used the general linear models (GLMs) with multivariate analysis (with Bonferroni adjustment to correct for multiple comparisons) to analyze data from neuropsychological tests and HVs. For the comparisons of neuropsychological tests between FSg and ISg, we included intelligence quotient (IQ) and side of HA as covariates, because the ISg had more left HA patients than the FSg.

A univariate analysis of variance (ANOVA; with Bonferroni for post hoc tests) was performed to compare the AI between controls, ISg and FSg.

Correlations between volumetric data, neuropsychological data, and clinical features were evaluated by Pearson correlation or Spearman correlation, also according to the distribution of the variables. The level of statistical significance was set at \( p < 0.05 \).

RESULTS

Demographic and clinical features

We evaluated 22 patients in the FSg (mean age ± standard deviation 48.36 ± 9.43 years, 13 women), 20 patients in the ISg (mean age 45.85 ± 12.38 years, 15 women), and 29 healthy individuals (mean age 40.83 ± 12.67 years, 14 women).

The demographic and clinical features are shown in Table 1 and Table S1. The mean seizure frequency per month was 8.05 ± 9.8 seizures in the FSg. In the ISg, there were 18 patients (90%) with only isolated auras; one (5%) patient with isolated auras and three dyscognitive seizures per year; and one (5%) patient with isolated auras and one dyscognitive seizure per year. The seizure-free intervals in patients from the ISg ranged from 3 to 128 months; whereas none in the FSg was seizure-free for more than a month. There were 2 left-handed patients (9.1%) in the FSg and 3 left-handed patients (15%) in the ISg (\( p = 0.66 \)).

Regarding the use of AEDs: All patients were taking medication, either monotherapy or polytherapy. There was no difference between the two groups with regard to use of monotherapy versus polytherapy (\( p = 0.08 \)).

On visual analysis there were 18 patients (81.8%) with right HA and 4 patients (18.2%) with left HA in the FSg, and 8 patients (40%) with right HA and 12 patients (60%) with left HA in the ISg; therefore, there was a significant difference in HA laterality between groups (\( p = 0.01 \)).

The lateralization of the epilepsy was defined by the side of HA. However, EEG results were also evaluated. In the FSg, 50% had unilateral ED on EEG, concordant to the side of HA; 45.5% had bilateral ED, and 4.5% had nonlateralized
EEG. In the ISg, 45% had unilateral ED on EEG, concordant to the side of HA; 20% had bilateral ED and 35% had nonlateralized EEG.

Volumetric analysis
Manual volumetric HV values normalized for TIV, as well as the AI and neuropsychological data are presented in Table S2.

There was an agreement with the side of the smaller hippocampus on manual volumetry and the side of HA on visual analyses.

To investigate differences in HVs between controls and MTLE patients (controls × FSg × ISg) we performed a multivariate analysis, with two dependent variables, smaller and larger HVs. We identified significant differences between groups \(F_{4,136} = 24.8, p < 0.001, \text{ Pillai's trace} = 0.84, \text{ partial } \eta^2 = 0.42\). Regarding the smaller hippocampus we observed differences between control × FSg (p < 0.001) and controls × ISg (p < 0.001), but not between FSg × ISg (p = 0.14). By contrast, the larger hippocampus of FSg was significantly smaller than ISg (p = 0.001); in addition, we identified significant differences between controls × FSg (p < 0.001) and controls × ISg (p = 0.02) (Fig. 1).

Regarding the AI, there was a significant asymmetry in FSg and ISg when compared to controls (p < 0.001); however, no difference was found between MTLE patient groups (p = 0.89).

We found a negative correlation between seizure frequency and smaller (ipsilateral) HV \((r = -0.3, p = 0.05)\) and larger (contralateral) HV \((r = -0.56, p < 0.01)\).

We found a positive correlation between the age at onset and smaller HV \((r = 0.37, p = 0.01)\).

Neuropsychological analysis
The frequency of MTLE patients with abnormal memory performance in each neuropsychological test (z-scores below −2) are described in Table S3. The proportion of individuals with abnormal scores was similar in both groups for all neuropsychological tests performed.

There were no significant differences in memory performance in the following comparisons: (1) FSg × ISg (Table 2); (2) ISg with right HA × FSg with right HA (Table 3); and (3) ISg with left HA × FSg with left HA (Table 4).

Table 1. Demographic and clinical features of frequent seizure group (FSg) and infrequent seizure group (ISg)

<table>
<thead>
<tr>
<th></th>
<th>FSg</th>
<th>ISg</th>
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<th>FSg</th>
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<th></th>
<th>FSg</th>
<th>ISg</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Maximum</td>
<td>Minimum</td>
<td>Mean (SD)</td>
<td>Maximum</td>
<td>Minimum</td>
<td>Mean (SD)</td>
<td>Maximum</td>
<td>Minimum</td>
</tr>
<tr>
<td>Age(^a)</td>
<td>48.36 (9.43)</td>
<td>71</td>
<td>36</td>
<td>45.65 (12.38)</td>
<td>74</td>
<td>23</td>
<td>0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first seizure(^a)</td>
<td>14.27 (10.76)</td>
<td>38</td>
<td>2</td>
<td>12.45 (10.26)</td>
<td>36</td>
<td>1</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset(^b)</td>
<td>18.59 (12.16)</td>
<td>51</td>
<td>2</td>
<td>17.25 (11.76)</td>
<td>39</td>
<td>2</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of epilepsy(^a)</td>
<td>29.77 (12.26)</td>
<td>58</td>
<td>11</td>
<td>28.6 (14.02)</td>
<td>54</td>
<td>8</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education(^c)</td>
<td>6.59 (4.26)</td>
<td>15</td>
<td>0</td>
<td>6.44 (4.26)</td>
<td>15</td>
<td>0</td>
<td>0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>70.77 (14.37)</td>
<td>103</td>
<td>57</td>
<td>73.2 (14.99)</td>
<td>100</td>
<td>51</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure frequency(^d)</td>
<td>96.55 (117.60)</td>
<td>360</td>
<td>57</td>
<td>0.2 (0.7)</td>
<td>3 DS</td>
<td>0</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)IQ, intelligence quotient; SD, standard deviation; DS, dyscognitive seizure.
\(^b\)In years.
\(^c\)Years of education.
\(^d\)Per year.
A one-way multivariate analysis of variance between groups was performed to investigate group differences in memory tests (IQ and side of HA as covariates). The first analysis involved four dependent Wechsler’s variables: general memory, verbal memory, visual memory and delayed recall; the independent variable was “groups” (FSg × ISg). There was no statistically significant difference between FSg × ISg on the combined dependent vari-

Table 2. Memory performance comparisons between frequent seizure group (FSg) and infrequent seizure group (ISg)

<table>
<thead>
<tr>
<th></th>
<th>FSg</th>
<th>ISg</th>
</tr>
</thead>
<tbody>
<tr>
<td>General WMS-R</td>
<td>2.06(1.55)</td>
<td>2.27(1.45)</td>
</tr>
<tr>
<td>Verbal WMS-R</td>
<td>1.37(1.19)</td>
<td>1.65(1.12)</td>
</tr>
<tr>
<td>Visual WMS-R</td>
<td>2.27(1.40)</td>
<td>1.95(1.66)</td>
</tr>
<tr>
<td>Delayed Recall WMS-R</td>
<td>2.13(1.15)</td>
<td>1.97(1.46)</td>
</tr>
<tr>
<td>RAVLT A1-A5</td>
<td>0.89(1.10)</td>
<td>0.88(0.94)</td>
</tr>
<tr>
<td>RAVLT B1</td>
<td>0.73(0.57)</td>
<td>0.50(0.66)</td>
</tr>
<tr>
<td>RAVLT A6</td>
<td>1.27(1.41)</td>
<td>1.54(1.04)</td>
</tr>
<tr>
<td>Delayed Recall RAVLT</td>
<td>1.63(1.63)</td>
<td>1.66(0.89)</td>
</tr>
<tr>
<td>Recognition RAVLT</td>
<td>3.25(2.17)</td>
<td>3.64(2.96)</td>
</tr>
</tbody>
</table>

SD, standard deviation. There were no significant differences between groups. Values of Wechsler Memory Scale-Revised (WMS-R) and Rey Auditory Verbal Learning Test (RAVLT) in z-score.

Table 3. Memory performance comparisons between frequent seizure group (FSg) and infrequent seizure group (ISg) with right hippocampal atrophy (HA)

<table>
<thead>
<tr>
<th></th>
<th>FSg</th>
<th>ISg</th>
</tr>
</thead>
<tbody>
<tr>
<td>General WMS-R</td>
<td>1.83(1.53)</td>
<td>2.07(1.57)</td>
</tr>
<tr>
<td>Verbal WMS-R</td>
<td>1.27(1.24)</td>
<td>1.32(1.40)</td>
</tr>
<tr>
<td>Visual WMS-R</td>
<td>2.08(1.42)</td>
<td>2.40(1.76)</td>
</tr>
<tr>
<td>Delayed Recall WMS-R</td>
<td>1.98(1.17)</td>
<td>1.87(1.39)</td>
</tr>
<tr>
<td>RAVLT A1-A5</td>
<td>0.75(1.05)</td>
<td>0.59(0.62)</td>
</tr>
<tr>
<td>RAVLT B1</td>
<td>0.75(0.59)</td>
<td>0.44(0.66)</td>
</tr>
<tr>
<td>RAVLT A6</td>
<td>1.07(1.19)</td>
<td>1.17(0.86)</td>
</tr>
<tr>
<td>Delayed Recall RAVLT</td>
<td>1.41(1.63)</td>
<td>1.27(0.81)</td>
</tr>
<tr>
<td>Recognition RAVLT</td>
<td>3.15(2.16)</td>
<td>3.54(2.45)</td>
</tr>
</tbody>
</table>

SD, standard deviation. There were no significant differences between groups. Values of Wechsler Memory Scale-Revised (WMS-R) and Rey Auditory Verbal Learning Test (RAVLT) in z-score.

Table 4. Memory performance comparisons between frequent seizure group (FSg) and infrequent seizure group (ISg) with left hippocampal atrophy (HA)

<table>
<thead>
<tr>
<th></th>
<th>FSg</th>
<th>ISg</th>
</tr>
</thead>
<tbody>
<tr>
<td>General WMS-R</td>
<td>3.11(1.39)</td>
<td>2.41(1.42)</td>
</tr>
<tr>
<td>Verbal WMS-R</td>
<td>1.81(0.94)</td>
<td>1.86(0.89)</td>
</tr>
<tr>
<td>Visual WMS-R</td>
<td>3.14(1.03)</td>
<td>1.65(1.60)</td>
</tr>
<tr>
<td>Delayed Recall WMS-R</td>
<td>2.82(0.88)</td>
<td>2.04(1.56)</td>
</tr>
<tr>
<td>RAVLT A1-A5</td>
<td>1.52(1.26)</td>
<td>1.07(1.09)</td>
</tr>
<tr>
<td>RAVLT B1</td>
<td>0.63(0.57)</td>
<td>0.54(0.68)</td>
</tr>
<tr>
<td>RAVLT A6</td>
<td>2.15(2.12)</td>
<td>1.79(1.11)</td>
</tr>
<tr>
<td>Delayed Recall RAVLT</td>
<td>2.61(1.43)</td>
<td>1.92(0.87)</td>
</tr>
<tr>
<td>Recognition RAVLT</td>
<td>3.71(2.52)</td>
<td>3.71(3.21)</td>
</tr>
</tbody>
</table>

SD, standard deviation. There were no significant differences between groups. Values of Wechsler Memory Scale-Revised (WMS-R) and Rey Auditory Verbal Learning Test (RAVLT) in z-score.
ables, \([F_{4,35} = 0.4, p = 0.81, \text{ Pillai’s trace} = 0.43, \text{ partial } \eta^2 = 0.04]\). The second analysis with the same independent variable involved five dependent RAVLT’s variables: A1–A5, B1, A6, delayed recall, and recognition. Similarly, we did not identify significant differences between the two groups, \([F_{5,34} = 0.56, p = 0.73, \text{ Pillai’s Trace} = 0.76, \text{ partial } \eta^2 = 0.08]\).

The analysis of Wechsler’s variables (memory performance) on the right-sided HA group (IQ as covariate), comparing FSg × ISg, was not statistically significant \([F_{4,20} = 1.33, p = 0.49, \text{ Pillai’s trace} = 0.15, \text{ partial } \eta^2 = 0.015]\). The analysis of RAVLT’s variables was not significant either \([F_{5,19} = 0.50, p = 0.77, \text{ Pillai’s Trace} = 0.12, \text{ partial } \eta^2 = 0.12]\), indicating that within right-sided HA, higher seizure frequency did not interfere with memory performance.

The analysis of Wechsler’s variables (memory performance) on the left-sided HA group (IQ as covariate), comparing FSg × ISg, was not statistically significant \([F_{4,10} = 0.69, p = 0.61, \text{ Pillai’s trace} = 0.22, \text{ partial } \eta^2 = 0.22]\). The analysis of RAVLT’s variables was not significant either \([F_{5,9} = 0.93, p = 0.50, \text{ Pillai’s trace} = 0.34, \text{ partial } \eta^2 = 0.34]\), indicating that within left-sided HA, higher seizure frequency did not interfere with memory performance.

There were positive correlations between educational level and estimated IQ with neuropsychological data (Table S4). We found no significant correlations between seizure frequency and neuropsychological data.

**Discussion**

To investigate whether higher seizure frequency would result in poorer memory performance, we evaluated MTLE patients who were refractory to AEDs, and MTLE patients with good seizure control, all of whom had signs of HS on MRI.

We observed memory impairment in patients with frequent and infrequent seizures, but no significant difference in neuropsychological performance between them. The literature suggests that there might be different subtypes of MTLE, “benign” MTLE being one of them. Although our patients with infrequent seizures probably represent the previously described benign MTLE, the term “benign” is probably not appropriate, considering that there are other cognitive problems in addition to seizures.

The present study confirms findings of a previous study performed by our group, with a different series of patients that compared memory performance in patients with refractory familial MTLE, patients with familial MTLE with well-controlled seizures, and asymptomatic first-degree relatives. Different from the present study, in that series Alessio et al. included patients with or without MRI signs of HS, and indeed, several had normal HVs. In that study, they found that individuals with HA had more severe memory deficits than those with normal hippocampi, independent of clinical status (asymptomatic, “benign,” or refractory epilepsy). In addition, individuals with HA and who were seizure-free, have had only a few seizures in life, or were asymptomatic, showed significant memory-specific impairment, indicating an independent role of HA in memory dysfunction.

Ozkara et al. performed neuropsychological assessment in MTLE patients with good response to AED and patients with pharmacoresistant seizures, and also did not find differences in memory between the two groups, except that in their study the refractory group showed worse performance in “digit span,” more related to working memory and attention deficit, not performed in our study. Their findings and our results suggest that memory dysfunction is probably more related to hippocampal damage than to seizure frequency.

We found positive correlation between memory performance, educational level, and estimated IQ, in agreement with previous studies with healthy individuals. The estimated IQ is based on vocabulary and block design tests, and vocabulary test is influenced by education. This may justify, at least in part, the low levels of estimated IQ in our series.

The influence of medication and HS on cognitive testing is already known. In our study both groups were using AEDs and had HS; therefore, it is difficult to predict the influence of these variables on our results. However, previous studies with asymptomatic first-degree relatives of patients with MTLE with MRI signs of HS without seizures and not using AEDs showed memory impairment in neuropsychological testing, suggesting that our findings are probably more related to the HA than to the use of AEDs.

Volumetric analysis in our patients showed significant reduction in the hippocampal ipsilateral and contralateral to the MRI signs of HS when compared to controls. This agrees with studies of brain autopsy and other MRI studies, which frequently show bilateral asymmetric hippocampal abnormalities in patients with MTLE, with a severe HA on one side, and different degrees of neuronal loss on the contralateral side.

The literature shows contradictory results, some reporting a relationship between seizure frequency and hippocampal volume, and others not showing a relationship. In the present study, the degree of atrophy between FSg and ISg was not different. This does not represent the universe of patients with MTLE and ISg, because the main selection criterion for the study was the presence of MRI signs of HS in all patients. We found a negative correlation between seizure frequency and HV, meaning that the higher the seizure frequency, the smaller the HV. However, this correlation was weak for the ipsilateral (atrophy) hippocampus, explaining only 9% \((r = -0.3)\) of the change in volume, and stronger in the contralateral hippocampus, explaining 31% \((r = -0.56)\) of the hippocampal volume by seizure fre-

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Memory and Seizure Frequency in MTLE-HS

frequency. This finding is also important and supports the notion that seizure frequency might be related to the presence of MRI signs of HS or to the degree of HA, as suggested in surgical series. However, this relationship is complex because the HA is most likely the result of two main factors: (1) the original “damage,” which is related to the causes of epilepsy and (2) the additional damage, which is produced by ongoing seizures. Therefore, depending on the series of patients analyzed, the cross-sectional correlation between seizure frequency and degree of atrophy may or may not be present. In addition, the seizure frequency and response to AEDs in MTLE are multifactorial and do not depend only on the original hippocampal damage. For example, a given patient may have a small degree of HA originally, and frequent ongoing seizures may induce further atrophy that will result in a less atrophic hippocampus later on than in a patient who had a pronounced HA originally and had similar frequency of seizures over a similar period. By contrast, another patient with similar degree of HA who originally had well-controlled seizures will end up with a smaller degree of HA over a similar duration of epilepsy. In fact, our correlation coefficients between seizure frequency and HV suggested that the contralateral hippocampus may be more influenced by frequent ongoing seizures compared to the ipsilateral hippocampus, and this could explain in part the worsening of memory over time about which patients with MTLE usually complain.

Other studies that investigated the relationship between seizure frequency and reduction in brain volume indicated a more diffuse and significant loss of gray matter in patients with refractory MTLE when compared with patients with benign MTLE. Coan et al. observed a more intense progression of gray and white matter atrophy in patients with left MTLE and correlated it with poor seizure control and longer duration of epilepsy.

There was a significant relationship between seizure frequency and HV, but not between seizure frequency and memory. Based on previous surgical reports showing that there is a relationship between HV and seizure frequency and a relationship between HV and memory, we would expect a relationship between seizure frequency and memory, at least in an indirect way. However, all these studies investigated patients with refractory epilepsy who were surgical candidates and did not include patients with HS and good seizure control. When adding the group of patients with good seizure control and MRI signs of HS, the relationship between memory and seizure frequency changes. This is most likely because the hippocampal damage or atrophy may be caused by an initial precipitating injury (IPI) or genetic predisposition and further seizures may increase the atrophy. This is further supported by the fact that the smaller HV did not differ between FSg and ISg, but the contralateral hippocampus was smaller in the FSg (corroborating the correlation findings discussed earlier). Furthermore, those with good seizure control already having HA due to IPI will likely have memory problems, which will not correlate with seizure frequency, unless they are analyzed together with the entire spectrum of HV (with and without atrophy), which was not done in this article. This is supported by our previous findings of asymptomatic individuals with HA, who presented memory impairment. Because our patients were selected based on the presence of HA, they were more or less “matched” for the presence of hippocampal damage, which in theory would “isolate” the atrophy factor, leaving only, or mainly, the relationship between seizure frequency and neuropsychological tests. The other factor to consider is the possible “floor effect” of HA in the available neuropsychological tests; that is, after a certain degree of atrophy, the memory impairment will change in a much smaller scale, which could not be easily detected by these tests. Longitudinal analyses with more sensitive tests will be necessary to further clarify these findings.

In this study, the age at onset of seizures (age at which recurrent seizures started) was correlated with smaller HVs, showing that the sooner the seizure began, the greater the neuronal damage in the atrophic hippocampus. Seidenberg et al. also reported this correlation, as well as a reduction of ipsilateral white matter when compared to contralateral white matter.

One limitation of our study is the difference of HA laterality between groups and gender distribution. However, considering that our two groups of patients were homogeneous with respect to duration of epilepsy, age at recurrent seizure onset, estimated IQ, memory deficits, and degree of HA, and differing only in frequency of seizures, our findings suggest that in MTLE associated with MRI signs of HS, the memory deficits are more influenced by the degree of damage on both hippocampi than by the frequency of seizures.

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Disclosures

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.

References


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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Summary of demographic data and clinical features.

**Table S2.** Summary of MRI volumetric data and neuropsychological assessment.

**Table S3.** Percentage of patients with abnormal neuropsychological assessment (below 2 standard deviations [SD]) in frequent seizure group (FSg) and infrequent seizure group (Isg).

**Table S4.** Correlations between neuropsychological data and educational level and estimated IQ.