Extrahippocampal temporal lobe atrophy in temporal lobe epilepsy and mesial temporal sclerosis

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Summary

Visual inspection and volumetric analysis of MRIs allow mesial temporal sclerosis (MTS) to be reliably identified in patients with temporal lobe epilepsy. The presence of unilateral MTS ipsilateral to the side of habitual seizure onset is an indicator for the prognosis of good outcome after temporal lobe resection. There is evidence to suggest that widespread temporal lobe pathology, leading to atrophy, may be associated with MTS and such abnormal tissue may play an important role in epileptogenesis. We have analysed quantitatively the volumes of the mesial and lateral temporal lobe substructures in MRIs from 62 patients with intractable mesial temporal lobe epilepsy and in 20 normal controls. We found significant atrophy in these structures, ranging from 8.3 to 18.4% compared with controls. The degree of atrophy in the extrahippocampal structures correlated with the degree of hippocampal atrophy, suggesting that a common process may be responsible. There was no correlation between the degree of atrophy in the extrahippocampal structures and the duration of epilepsy, a history of febrile convulsions or of generalized seizures. These findings suggest that there may be widespread pathological abnormalities in the temporal lobe associated with MTS. The importance of extrahippocampal atrophy to surgical outcome and whether it occurs in temporal lobe epilepsy not associated with MTS remain to be investigated.

Keywords: epilepsy; temporal lobe; volumetry; MRI; hippocampus; mesial temporal sclerosis

Abbreviations: AC = anterior commissure; HA = hippocampal atrophy; HV = hippocampal volume; HVR = hippocampal volume ratio; ICV = intracranial volume; LOT/IT/MTG = the lateral occipitotemporal gyrus plus the inferior temporal gyrus plus the middle temporal gyrus; LTLV = lateral temporal lobe volume; MR = magnetic resonance; mTLE = mesial temporal lobe epilepsy; MTS = mesial temporal sclerosis; PC = posterior commissure; PH/MOTG = parahippocampal gyrus plus the medial occipitotemporal gyrus; STG = superior temporal gyrus; TLE = temporal lobe epilepsy; TLV = temporal lobe volume; TP = temporal pole; $V_n$ = normalized substructure volume

Introduction

In the 1950s, Falconer stressed the importance of mesial temporal sclerosis (MTS) in surgery for mesial temporal lobe epilepsy (mTLE). He showed that patients with intractable epilepsy tended to have a better seizure outcome after standard anterior temporal lobectomy with amygdalohippocampectomy if MTS was found pathologically (Falconer and Serafetinides, 1963). However, it was not possible to detect MTS preoperatively with any confidence. Over the last decade or so, MRI has allowed MTS to be reliably identified by conventional visual inspection aided by measurement of hippocampal volume (HV) (Jack, 1996). In concordance with Falconer’s observations, the presence of MTS on MRI is a prognostic feature for good seizure outcome, and many epilepsy surgery programs now include hippocampal volumetry in the routine preoperative work up (Jack et al., 1992). In addition to hippocampal volumetry, MRI post-processing techniques may be used to identify extratemporal abnormalities that are unapparent on visual inspection. The presence of abnormalities in the proportion of white matter to grey matter in extratemporal regions may be determined and has been found to predict poor seizure outcome after temporal lobectomy (Sisodiya et al., 1997).

The hippocampus is widely regarded as the generator of seizures in patients with MTS on MRI and concordant surface EEG findings and seizure semiology. However, there are several observations which suggest that seizure generation
may depend upon a more anatomically diffuse substrate. The histological abnormalities in MTS are not confined to the hippocampus but extend into the parahippocampal gyrus and entorhinal area. Also, MTS is frequently associated with microdysgenesis in the temporal neocortex (Falconer, 1974; Hardiman et al., 1988). On depth EEG and intraoperative electrocorticography, epileptiform activity is usually detected in several areas of the temporal lobe, both mesially and laterally. Early attempts to tailor temporal lobe resections according to the distribution of electrocorticographic activity produced poor seizure outcome and it was soon recognized that a standard temporal lobe resection was required regardless of the intraoperative EEG findings (Bailey and Gibbs, 1951).

Whilst hippocampal volumetry has become widely used, less attention has been paid to the detection of MRI abnormalities in other temporal lobe structures. There have been a number of non-quantitative or semi-quantitative reports of temporal lobe atrophy in TLE. More recently, fully quantitative measurements have shown extrahippocampal volume deficits in TLE patients in the whole temporal lobe, extratemporal cortical regions and subcortical structures (Marsh et al., 1997; DeCarli et al., 1998; Lee et al., 1998). In psychiatry there has been more interest in the lateral temporal lobe and several volumetric and morphometric studies have reported abnormalities of the superior temporal gyrus and planum temporale in schizophrenia (Dauphinais et al., 1990; DeLisi et al., 1994). Volumetric analysis of the extrahippocampal temporal structures may contribute to the understanding of seizure generation in TLE. In addition, volumetric abnormalities, if present, may be of significance in the assessment of the likelihood of a favourable surgical outcome. It is not known whether it is necessary to resect the lateral temporal lobe structures to ensure good seizure outcome or if amygdalohippocampectomy is sufficient; more selective operations may be less likely to produce neuropsychological deficit and psychiatric disturbance (Moran et al., 1999). It is possible that the need for lateral resection depends upon the presence of pathology in that region. Again, volumetric analysis may prove to be useful in the preoperative identification of subtle, extrahippocampal abnormalities and contribute to the tailoring of operations.

We have sought to examine the hypothesis that there are widespread structural abnormalities in the extrahippocampal, temporal lobe substructures in patients with TLE associated MTS. We also aimed to examine the relationship between the severity of hippocampal and extrahippocampal abnormalities and between three clinical factors (febrile convulsions, generalized seizures and duration of epilepsy) to lend support to the hypothesis that the same process that leads to MTS and intractable epilepsy acts diffusely in the temporal lobe.

Methods

Subjects
Sixty-two consecutive patients with the radiological diagnosis MTS without additional abnormalities were collected from the epilepsy surgery programme at the National Hospital for Neurology and Neurosurgery, London, UK. For all patients, evaluation included MRI, video-EEG and neuropsychometry. The diagnosis of MTS was based on routine inspection of MRI films supplemented by HV measurements and T2 mapping of the hippocampi (Cook, 1994; Van Paesschen et al., 1997). Wada testing was performed where indicated. The radiological diagnoses were made by two senior neuroradiologists and supplemented by routine hippocampal volumetry. At the time of MRI scanning, the mean age was 32 years (range 19–56, median quartiles: 26.2, 31.2, 36.1). There were 26 males and 36 females. In selected cases video-EEG was carried out with anti-epileptic drug reduction and/or sleep deprivation. Seizures were recorded in 56 patients (91%). Seizure focus localization and lateralization were based on the presence of interictal epileptiform abnormalities on EEG and, where possible, ictal semiological observations and ictal EEG. In six patients there was additional interictal epileptiform activity that appeared to originate outside the temporal lobe (unilateral or bilateral frontal regions).

All patients and controls gave informed consent. The study was approved by the Ethics Committee of the National Hospital for Neurology and Neurosurgery.

Controls
There were 20 control volunteers (10 male and 10 female) with no history of serious medical disorders or learning difficulties; the mean age was 34.8 years (range 20–58, median quartiles: 29.4, 32.6, 40.8).

Imaging
MRIs were acquired using a T1-weighted inversion recovery prepared volume acquisition [fast ISPRG: TI/TR/TE (effective)/flip = 450 ms/15 ms/4.2 ms/20°; 1.5-mm thick coronal slices; 256 × 192 matrix, 24 × 18 cm FOV; scan time 6 min 56 s] on a Signa 1.5T imager (GE Medical Systems, Milwaukee, Wis., USA).

Temporal lobe volumetry
Six temporal lobe substructures were measured on both sides of the brain in patients and controls: the hippocampus; the amygdala; the parahippocampal and medial occipitotemporal gyri (combined as one substructure) (PH/MOTG); the lateral occipitotemporal, inferior temporal and middle temporal gyri (combined as one substructure) (LOT/IT/MTG); the superior temporal gyrus (STG); and the temporal pole (TP). The operator was blind to the subject identity and to whether the case was a patient or control. The method for substructure volumetry and its validation have been described in detail previously (Moran et al., 1999). In brief, using locally developed image analysis software MReg (Lemieux et al., 1998), the mid-points of the anterior and posterior commissures (AC and PC) were identified. The volumetric
images were then automatically reformatted such that a line joining these points came to lie perpendicular to the display plane. The substructures other than the amygdala and TP were manually delineated in each slice between, posteriorly, the slice where the columns of the fornices were maximally evident and, anteriorly, the slice where the maximum extent of the AC was identified. Delineation of the amygdala was commenced in the slice in which it could be clearly distinguished from the hippocampal head and continued anteriorly so far as the medial boundary could be clearly identified. The TP was defined as all of the temporal lobe anterior to the frontotemporal articulation. The definitions of the boundaries of each substructure were developed to be reproducible and, as far as possible, to respect anatomical definitions and account for normal variations. To obtain the substructure volumes, the sum of the slice volumes were multiplied by the slice thickness (1.5 mm).

In each case, the temporal lobe volume (TLV) was obtained by summing the volume of all substructures; the lateral temporal lobe volume (LTLV) was obtained by summing the volumes of all the substructures except the amygdala and hippocampus.

Measurement of intracranial volume
Intracranial volume (ICV) was measured by manual delineation of the inner surface of the intracranial cavity in every tenth coronal slice, beginning with slice 10, using a method developed by previous workers (Free et al., 1995). The ICV was obtained by multiplying the sum of the measurements by 15 (the product of the slice thickness in millimetres and the measurement gap).

Normalization for ICV
For all the substructures other than the amygdala and the TL, volume was significantly positively correlated with ICV (see below). Therefore, in order to minimize the effect of differences in ICV on substructure volumes in the patient group, the volumes were adjusted using the linear regression equation derived from the control group. For each substructure, other than the amygdala, a normalized volume \( V_n \) was calculated using the following equation:

\[
V_n = V + \beta_1(\hat{ICV} - ICV)
\]

(1)

where \( V \) is the substructure volume; \( \beta_1 \) is the slope of the regression line for the substructure volume versus ICV; \( \hat{ICV} \) is the mean ICV in the controls.

In the patients, the differences between the actual and normalized hippocampal volume (\( \Delta HV \)), and between the actual and normalized lateral temporal lobe volume (\( \Delta LTLV \)) were estimated for each case in order to examine the relationship between mesial and lateral atrophy.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Correlation</th>
<th>( \beta_1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hipp</td>
<td>0.62</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Amyg</td>
<td>0.08</td>
<td>0.0840</td>
</tr>
<tr>
<td>LOT/IT/MOTG</td>
<td>0.35</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>STG</td>
<td>0.60</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>PH/MOTG</td>
<td>0.38</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>TP</td>
<td>0.41</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>LTLV</td>
<td>0.76</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>

Hipp = hippocampus; Amyg = amygdala; LOT/IT/MOTG = lateral occipitotemporal/inferior temporal/middle temporal gyrus; STG = the superior temporal gyrus; PH/MOTG = parahippocampal and medial occipitotemporal gyrus; TP = temporal pole; TL = temporal lobe; \( r^2 \) = coefficient of determination \((r = Pearson’s correlation coefficient); \( \beta_1 \) = slope of regression (see Equation 1).

Hippocampal volume ratios
For controls, the hippocampal volume ratio (HVR) was calculated by dividing the hippocampal volume on the side where it was the smallest by that on the side where it was largest. In patients, the HVR was calculated by dividing the HV on the side of intended resection to that on the contralateral side.

Statistics
To examine differences between normalized substructure volumes and TLV in patients and controls, the means in the two groups were compared using two-tailed \( t \)-tests. Within the patient group, two-tailed \( t \)-tests were used to test for volume differences related to dichotomous clinical variables (history of febrile convulsions and history of generalized seizures); for the continuous clinical variable (duration of epilepsy), bivariate correlation was used. We chose to use two-tailed tests to ensure that our findings were robust.

Results
Controls
Intracranial volume
For each temporal lobe substructure and TLV, the coefficient of determination \((r^2 \), where \( r \) is Pearson’s correlation coefficient) and the regression coefficient (\( \beta_1 \)), derived from linear regression, for the relationship between volume and ICV are shown in Table 1. The coefficient of determination estimates the proportion of the variation of substructure volume that is accounted for by variation in ICV. The mean ICV in 20 normal controls was 1840 cm\(^3\) (range: 1410–2310, SD 221). The mean ICV in males was 1971 cm\(^3\) (range: 1750–2310, SD 184) and in females was 1713 cm\(^3\) (range:
111-113). The significance of the gender difference in ICV was 0.003 (two-tailed t-test).

The $\beta$ values for the different substructures (excluding the amygdala) varied between 0.35 and 0.76; $\beta$ for the TL was 0.76. There was a close linear relationship between the mean volume and $\beta$; (for the substructures alone: Pearson’s $r = 0.91$, $P = 0.05$; for the substructures and TL: Pearson’s $r = 0.99$, $P = 0.01$).

**Hippocampal volume ratios**

In controls, the mean HVR was 96% (range 87.7–100.4, SD 3.4) and in the patient 63.5% (range 34.4–110.7, SD 17.1). In the patient group, five individuals (8%) had an HVR within 2 SD of the mean HVR in controls.

**Temporal lobe substructures**

TLV and the volumes of all the substructures with the exception of the amygdala were significantly correlated with intracranial volume (Table 1). The value of $\beta$ for each substructure, except for the amygdala, was used to correct for ICV according to Equation 1. Therefore, all volumes reported below are normalized (except for the amygdala). The details of the substructure volumes in controls are shown in Table 2. The TP was significantly larger on the left side (two-tailed t-test $P = 0.020$). For the remaining substructures there were no significant side differences ($P$ range 0.234–0.649).

**Patients: side of intended resection**

**Temporal lobe substructure volumes**

The findings are summarized in the top half of Table 3. The percentage difference between the mean normalized volume of each structure (except amygdala) in patients and controls with the confidence limits and the significance (two-tailed t-test) are shown. The final two columns give the percentage of cases in which the substructure volume was less or greater than twice the standard deviation (of the control volumes) below and above the mean control volume. The mean volumes of all the substructures except the amygdala were significantly smaller than in the controls. Figure 1 illustrates a case of clear temporal lobe atrophy that can be appreciated visually.

**Relationship between mesial and lateral atrophy**

On the MTS side the mean $\Delta HV$ was 38.2% (range –67.6 to 12.2, SD 15.4); the mean $\Delta TLV$ was –12.3% (range –33.9 to 11.3, SD 11.0). The Pearson’s correlation coefficient for the relationship between $\Delta HV$ and $\Delta TLV$ was 0.51 ($P < 0.002$). On the contralateral side, the $\Delta HV$ was –1.2 (range –48.6 to 29.8, SD 14.2); the mean $\Delta TLV$ was –2.8% (range –22.8 to 11.3, SD 16.0). The Pearson’s correlation coefficient for the relationship between $\Delta HV$ and $\Delta TLV$ was 0.34 ($P = 0.007$).

**Patients: contralateral side**

The normalized substructure volumes contralateral to the side of intended resection are shown in the bottom half of Table 3. On this side there were no significant differences compared with controls except for the STG, which was 9.63% less than that in controls with a significance of 0.003 (two-tailed t-test). There was no significant difference in any of the substructure volumes between subjects with or without bilateral interictal epileptiform activity on continuous EEG monitoring.
Table 3 Temporal lobe substructure and total volumes in 62 patients

<table>
<thead>
<tr>
<th>Structure</th>
<th>$V_n$ (cm³)</th>
<th>Mean differences compared with controls</th>
<th>Cases ±2 SD different compared with controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$V_n$ (cm³)</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Ipsilateral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hipp</td>
<td>1.56 1.98 0.43</td>
<td>–38.7</td>
<td>–44.6 to –32.8</td>
</tr>
<tr>
<td>Amyg†</td>
<td>1.33 1.41 0.30</td>
<td>5.5</td>
<td>3.7 to 14.7</td>
</tr>
<tr>
<td>LOT/IT/MTG</td>
<td>17.15 13.32 2.65</td>
<td>–11.7</td>
<td>–16.9 to –6.6</td>
</tr>
<tr>
<td>STG</td>
<td>10.88 7.59 1.81</td>
<td>–10.1</td>
<td>–15.5 to –4.6</td>
</tr>
<tr>
<td>PH/MOTG</td>
<td>8.06 11.11 1.62</td>
<td>–8.3</td>
<td>–14.9 to –1.8</td>
</tr>
<tr>
<td>TP</td>
<td>8.56 10.12 1.95</td>
<td>–18.4</td>
<td>–25.6 to –11.2</td>
</tr>
<tr>
<td>TL</td>
<td>47.52 24.13 5.80</td>
<td>–13.0</td>
<td>–16.7 to –9.3</td>
</tr>
<tr>
<td>Contralateral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hipp</td>
<td>2.50 2.01 0.37</td>
<td>–1.81</td>
<td>–7.01 to 3.40</td>
</tr>
<tr>
<td>Amyg†</td>
<td>1.33 1.30 0.30</td>
<td>5.70</td>
<td>–3.41 to 14.81</td>
</tr>
<tr>
<td>LOT/IT/MTG</td>
<td>19.46 11.97 2.57</td>
<td>0.19</td>
<td>–4.85 to 5.24</td>
</tr>
<tr>
<td>STG</td>
<td>10.94 11.58 2.16</td>
<td>–9.63</td>
<td>–15.86 to –3.41</td>
</tr>
<tr>
<td>PH/MOTG</td>
<td>8.91 7.42 1.09</td>
<td>1.38</td>
<td>–3.54 to 6.31</td>
</tr>
<tr>
<td>TP</td>
<td>9.90 10.62 2.14</td>
<td>–5.57</td>
<td>–13.23 to 2.09</td>
</tr>
<tr>
<td>TL</td>
<td>53.17 20.48 4.96</td>
<td>–2.64</td>
<td>–5.88 to 0.61</td>
</tr>
</tbody>
</table>

Hipp = hippocampus; Amyg = amygdala; LOT/IT/MTG = lateral occipitotemporal/inferior temporal/middle temporal gyri; STG = the superior temporal gyrus; PH/MOTG = parahippocampal and medial occipitotemporal gyri; TP = temporal pole; TL = temporal lobe; $V_n$ = normalized volume; range = maximum – minimum; M = mean (controls); SD = standard deviation (controls); CI = confidence interval; Sig = significance. †Not normalized.

Fig. 1 Coronal slice through temporal lobes in a male patient. Atrophy of the left temporal lobe is clearly visible. The volumetric traces are shown and labelled for the structures visible in this slice. Hipp = hippocampus; LOT/IT/MTG = lateral occipitotemporal/inferior temporal/middle temporal gyri; STG = the superior temporal gyrus; PH/MOTG = parahippocampal and medial occipitotemporal gyri.

Table 4 Relationships between the temporal lobe substructure and total volumes ipsilateral to MTS and the clinical factors

<table>
<thead>
<tr>
<th>Clinical variable</th>
<th>Statistic</th>
<th>Hipp</th>
<th>Amyg</th>
<th>LOT/IT/MTG</th>
<th>STG</th>
<th>PH/MOTG</th>
<th>TP</th>
<th>TL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of epilepsy</td>
<td>$r$</td>
<td>–0.10</td>
<td>0.01</td>
<td>0.01</td>
<td>–0.19</td>
<td>–0.14</td>
<td>–0.19</td>
<td>–0.16</td>
</tr>
<tr>
<td>Sig.</td>
<td></td>
<td>0.48</td>
<td>0.94</td>
<td>0.93</td>
<td>0.18</td>
<td>0.30</td>
<td>0.17</td>
<td>0.26</td>
</tr>
<tr>
<td>FC</td>
<td>Ratio (%)</td>
<td>96.50</td>
<td>97.07</td>
<td>101.41</td>
<td>92.16</td>
<td>100.59</td>
<td>97.49</td>
<td>98.01</td>
</tr>
<tr>
<td>Sig.</td>
<td></td>
<td>0.64</td>
<td>0.64</td>
<td>0.74</td>
<td>0.06</td>
<td>0.92</td>
<td>0.67</td>
<td>0.54</td>
</tr>
<tr>
<td>GS</td>
<td>Ratio (%)</td>
<td>97.65</td>
<td>94.73</td>
<td>91.52</td>
<td>99.89</td>
<td>99.12</td>
<td>101.80</td>
<td>96.61</td>
</tr>
<tr>
<td>Sig.</td>
<td></td>
<td>0.74</td>
<td>0.36</td>
<td>0.03</td>
<td>0.98</td>
<td>0.87</td>
<td>0.76</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Hipp = hippocampus; Amyg = amygdala; LOT/IT/MTG = lateral occipitotemporal/inferior temporal/middle temporal gyri; STG = the superior temporal gyrus; PH/MOTG = parahippocampal and medial occipitotemporal gyri; TP = temporal pole; TL = temporal lobe; FC = febrile convulsions; GS = generalized seizures; $r$ = Pearson’s correlation coefficient; Sig = significance (two-tailed).
Discussion

We have presented quantitative evidence that there is widespread temporal lobe volume loss in patients with intractable mTLE associated with MTS. Volume loss was found in all the substructures examined except the amygdala and ranged from 8.3% in PH/MOTG to 18.4% in the TP. For the whole temporal lobe the mean volume loss was 13%.

The substructure volumes were normalized with respect to ICV to, as far as possible, eliminate variations arising from normal developmental influences. The intracranial rather than the cerebral volume was used for normalization as we conjectured that the latter might be subnormal in individuals with MTS (and this was confirmed by our findings). A priori, intracranial volume is less likely to differ in patients and controls as, even if cerebral growth is the principal determinant of cranial growth, MTS and mTLE are acquired. Based on these observations, it seems likely that any cerebral atrophy which occurs in association with MTS is also acquired and therefore ICV will have at least tended to attain its expected, normal magnitude.

Interestingly, in controls, the values of $\beta_1$ for the substructures had widely different values and correlated very closely with the mean substructure volume. With increasing size, cerebral structures will inevitably have a closer relationship with ICV as the influence of particular local factors wanes. Individual hippocampal volume is influenced by ICV and possibly by gender (Free et al., 1995), but these factors do not account for all of the variability between individuals. Any relationship between the volume of a cerebral structure and parameters reflecting overall cerebral dimensions, such as ICV or cerebral volume, is likely to be complex, with myriad phylogenetic and ontological determinants. For example, food-storing bird species tend to have greater HV : brain volume ratios than bird species that cache food in one larder, or do not cache at all (Clayton, 1998) and, in individuals of some avian species, hippocampal neurogenesis and HV increase in parallel with food-storing or migratory experience (Clayton, 1996; Healy et al., 1996). Additionally, in humans, a recent MRI study found morphological differences in the hippocampi of taxi drivers’ compared with normal control subjects (Maguire et al., 2000).

The absence of volume loss in the amygdala appears inconsistent. This may be due to deficiencies in the measurement technique for this structure. We found it difficult to reliably identify boundaries for the amygdala, particularly anteriorly. The absence of a correlation between amygdala volume and ICV in the controls may also reflect this problem. The literature on MR amygdala volumetry is mixed in terms of the success with which the structure can be reliably and meaningfully measured, and, in reports where satisfactory measurements have been attained, the occurrence of amygdala volume abnormalities in patients with mTLE. Whilst some workers have attained satisfactory amygdala measurements and identified amygdala atrophy in mTLE (e.g. Cendes et al., 1993a), others have not done so. Moriarty and colleagues abandoned amygdala measurements because of poor interrater reliability (Moriarty et al., 1997). Kälviäinen and colleagues found that in patients with chronic temporal lobe epilepsy, the mean amygdaloid volume on the side of the seizure focus did not differ from that in either controls or newly diagnosed patients, or from that on the contralateral side (Kälviäinen et al., 1997). Convit and colleagues have pointed out that most workers have attempted amygdala volumetry using coronal slices, and produced direct evidence that this approach may lead to inadvertent inclusion of parts of the hippocampus in nearly half of the slices examined (Convit et al., 1999). Our failure to identify volumetric abnormalities in the amygdala in mTLE should not be interpreted as evidence against this structure being damaged in the condition, since both MRI $T_2$ relaxometry studies (which appear to be more universally technically successful) and histological studies have clearly demonstrated significant abnormalities in the amygdala in association with mTLE, and in some cases the amygdala may contain the principal epileptic focus (Van Paesschen et al., 1996; Pitkänen et al., 1998).

The pathogenesis and clinical significance of extra-hippocampal temporal volume loss cannot be determined from the results presented here. In MTS, atrophy is due to neuronal death, which, the weight of evidence suggests, is a result of excitotoxicity produced by excessive electrical activity occurring in epileptic discharges, rather than the effect of metabolic derangements associated with clinical seizures (Meldrum, 1990, 1991). Our finding of a correlation between mesial and lateral volume loss is consistent with the suggestion that the epileptogenic process associated with MTS is dependent on a network diffusely distributed within the temporal lobe. Equally, however, the correlation could be the consequence of excitotoxicity arising from invasion by mesially generated activity rather than primary epileptogenic activity. In either case, the degree of mesial and lateral atrophy might be expected to be correlated. Furthermore, any putative epileptogenic capacity of the lateral structures in MTS could arise either secondary to or in conjunction with a mesial focus.

The degree of neither HA nor extrahippocampal atrophy was correlated with either the duration of epilepsy or a history of febrile convulsions. The patients in this study all had severe, intractable epilepsy and it is possible that, pathologically, most had reached an end-stage of HA, thus obscuring any relationship between atrophy and duration of disease that might be evident in less chronic patients. Other authors have reported a relationship between the severity of MTS and a history of prolonged or complicated febrile convulsions (e.g. Cendes et al., 1993b). Unfortunately, we did not feel that we could be completely confident about the details of febrile convulsions as these are remote events and original documentation was often unavailable. Therefore, we did not carry out a subanalysis of patients with complicated or prolonged febrile convulsions. We found no significant correlation between the duration of epilepsy or the number of generalized seizures and the degree of HA. Previous
findings on this question have been mixed. In an MRI study of mTLE, Barr and colleagues found that the degree of HA ipsilateral to the EEG focus was not related to the duration of epilepsy, but was inversely related to seizure frequency (Barr et al., 1997). Cendes and colleagues also found no relationship between HA and seizure duration, but also found none between seizure frequency and HA (Cendes et al., 1993c). The latter study also found no relationship between HA and the occurrence of generalized seizures, whereas Van Paesschen found that the number of generalized seizures did correlate with the degree of HA (Van Paesschen et al., 1997). Histologically, Davies found no correlation between the grade of HS and the duration of mTLE (Davies et al., 1996). The time-course of HA is poorly understood, although it has been observed by serial scanning to occur rapidly in association with status epilepticus and may be advanced in young children with a history of febrile convulsions (Wieshmann et al., 1997; Van Landingham et al., 1998). The resolution of these conflicting findings may help elucidate the pathogenesis of MTS, particularly the question of whether it develops quite rapidly in response to an insult, most commonly a febrile seizure, or whether ongoing damage arising from partial and/or generalized seizures plays an important role.

For the temporal lobe substructures, other than the amygdala, the mean volumes on the side contralateral to the intended resection tended towards subnormality, although, interestingly, this only reached significance for the STG. Additionally, the STG on the ipsilateral side was, in terms of the proportion of patients with a significantly subnormal volume (but not the mean degree of atrophy), the extrahippocampal structure most frequently affected by atrophy on the side ipsilateral to the side of intended resection. Conjecturally, the apparent particular involvement of the STG may lie, based on anatomical studies of non-human primates, in its rich afferent connections from extratemporal unimodal association cortices and higher-order association cortices, as well as other temporal areas, that subserve its function as a supramodal association area (Seltzer and Pandya, 1978; Amaral et al., 1983; Barnes and Pandya, 1992). This might increase the vulnerability of the STG to excitotoxic injury that may arise from epileptic discharges (Meldrum, 1991).

On the contralateral side, the degrees of mesial and lateral atrophy were also significantly positively correlated, although the relationship was weaker than on the side of intended resection. Our findings with regard to the contralateral volumes are consistent with previous findings (e.g. Lee et al., 1998) on the volumetry of the grey matter over the whole temporal lobe. The absence of significant atrophy of mesial temporal structures contralateral to the side of intended resection in our patient group may reflect the characteristics of our normal control group. For example, we have found that by excluding the values for one normal subject whose substructure volumes were consistently the smallest among the 20 controls, the difference between patients and controls reached significance for the hippocampus. We recognize that the control with outlying values raises the question of the definition of normality. The substructure volumes in this case were statistically different from those in the other controls but, on balance, we judged that it was more scientifically acceptable to leave this outlier in the control data set rather than obtain a replacement.

In our control group, the only significant asymmetry was in the TP, the mean left volume being 11% greater than the right. It is difficult to compare this finding with previous work as our system of measurement has not been used by other workers. The TP, in our definition, is a composite structure but a substantial proportion of it is comprised of the STG. Several studies have found the left STG to be significantly larger in comparison to the right in normal subjects, although not all workers have found this asymmetry and there may be gender differences (DeLisi, 1994; Bryant et al., 1999). It is possible that the asymmetry we identified is concordant with these findings, although it is impossible to make a direct comparison.

It will be interesting to determine whether extrahippocampal atrophy has any relationship with seizure outcome after epilepsy surgery. If the presence of atrophy reflects involvement of a region in seizure generation, it might be expected by analogy with the hippocampus that excision would be required to prevent seizures. The correlation between mesial and lateral atrophy, however, may make it difficult to explore this hypothesis. In our surgery programme, a standard anterior temporal lobectomy with amygdalohippocampectomy is performed in patients with unilateral MTS. Such patients tend to be selected for surgery because of the recognized relationship between the finding of MTS on MRI and good outcome. It will also be of interest to examine the extrahippocampal substructures in ‘MRI-negative’ patients, i.e. those patients with temporal lobe seizures without MTS or other abnormalities on MRI. These patients tend to have less good outcome after temporal lobe resection compared with patients with MTS (Cascino et al., 1992). Atrophy in the extrahippocampal structures, if found, might reflect a seizure generation mechanism not dependent on the hippocampus. In a proportion of such cases, this is supported by the occurrence of EEG abnormalities and seizure semiology suggestive of lateral temporal cortex seizure onset (Hajek et al., 1993). The detection of extrahippocampal atrophy in MRI-negative patients may contribute to the development of surgical strategies in such patients with medically intractable seizures.

Our technique for temporal lobe volumetry requires an average of 5 h per case to perform and is therefore not feasible as a routine clinical procedure. If extrahippocampal volumetry proves to be of clinical value, its implementation will require less time-consuming techniques. We performed measurements in each 1.5-mm slice but, at least for the larger structures, this may be unnecessary. For example, for the STG, we have found that measuring every second slice produces an error of 5% compared with including every slice. We are also investigating methods to perform automated
or semi-automated volumetric measurements of temporal lobe substructures.

In conclusion, we have demonstrated that MTS in patients with medically intractable TLE is associated with significant atrophy of the extrahippocampal temporal lobe structures using MRI volumetry. The degree of extrahippocampal atrophy is correlated with the degree HA and is not related to the occurrence of generalized seizures or the duration of epilepsy. This is consistent with a common process responsible for both MTS and extrahippocampal temporal atrophy. The significance of extrahippocampal atrophy to the outcome of temporal lobe resection for relief of seizures remains to be investigated. Analysis of the extrahippocampal temporal structures in MRI-negative patients with TLE may also prove of interest.

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