Abnormalities in hippocampi remote from the seizure focus: a T2 relaxometry study

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Summary
The aim of this study was to determine whether partial epilepsy is associated with abnormalities in hippocampi that are not the primary seizure focus. As hippocampal T2 relaxometry is useful for identifying abnormalities that are not obvious on visual assessment of MRI, this was the method employed. Of 457 consecutive children and young adults from whom T2 relaxometry data were obtained, 96 had well characterized partial epilepsy and were enrolled, along with 27 control subjects. The patients were divided on the basis of clinical, video-EEG and visual MRI assessment into three groups: (i) those with temporal lobe epilepsy (TLE) and mesial temporal sclerosis (MTS) (MTS-TLE); (ii) lesional TLE (l-TLE); or (iii) extratemporal epilepsy (ETE). There was a significant and similar prolongation of T2 relaxation time identified in hippocampi remote from the seizure focus in all patient groups when compared with control subjects. In the non-sclerotic hippocampus of patients with MTS, T2 relaxation time was prolonged by a mean of 3.3 ms [95% confidence interval (CI), 0.8–5.9 ms; P = 0.01], patients with l-TLE had prolongation of T2 relaxation time by a mean of 4.3 ms (95% CI, 1.8–7.1 ms; P = 0.001) and those with ETE had prolongation of T2 relaxation time by a mean of 3.7 ms (95% CI, 1.6–6.6 ms; P = 0.006) compared with control subjects after adjustment for age. Unsurprisingly, in patients with MTS-TLE, T2 relaxation time in the sclerotic hippocampus was prolonged by a mean of 19 ms (95% CI = 14.6–22.4 ms; P < 0.001). The similarity in the extent of prolongation of T2 relaxation time in hippocampi that are not the primary epileptogenic focus, the wide variety of structural associations and the varied sites of epileptogenic foci, considered together, suggest that the abnormalities are likely to be caused by ongoing seizure activity rather than by underlying aetiology or site of epileptogenic focus.

Keywords: hippocampus; MTS; MRI; T2 relaxometry

Abbreviations: AI = asymmetry index; CI = confidence interval; ETE = extratemporal epilepsy; MTS = mesial temporal sclerosis; TLE = temporal lobe epilepsy

Introduction
Mesial temporal sclerosis (MTS) is the most common structural correlate of temporal lobe epilepsy (TLE) in adults who undergo temporal lobe resections for treatment of epilepsy. Although MTS may be the consequence of an initial insult, it remains unclear whether recurrent seizures further damage either an already sclerotic hippocampus or those that are remote from the seizure focus. It is now well established that MTS can be reliably detected using visual analysis of MRI (Cross et al., 1993; Jackson et al., 1993a; Kuzniecky et al., 1997; Lee et al., 1998) in association with quantitative techniques such as T2 relaxometry and hippocampal volumetry (Jackson et al., 1993b; Van Paesschen et al., 1997a; Namer et al., 1998). The MRI findings have been reported to be related both to the degree of histological abnormality and to the side of seizure origin (Kuzniecky et al., 1997; Van Paesschen et al., 1997a). It has also been suggested that there is an association between degree of hippocampal atrophy identified by hippocampal volumetry or histological severity of MTS, and age of onset and total duration of epilepsy (Davies et al., 1996; Mathern et al., 1996; Kalviainen et al., 1998; Fuerst et al., 2001). This has been attributed to ongoing damage caused by frequent complex partial or secondarily generalized seizures.
It is also possible that hippocampi remote from a seizure focus may be injured by recurrent seizures. Although MTS is frequently severe in one, rather than both hippocampi, bilateral histological hippocampal abnormalities have long been recognized at post-mortem in individuals who had chronic epilepsy. In vivo studies using quantitative MRI methods have also identified hippocampal abnormalities contralateral, as well as ipsilateral, to the seizure focus in patients with MTS and in patients with extra-hippocampal seizures (Jackson et al., 1993b; Barr et al., 1997; Namer et al., 1998; Bernasconi et al., 2000; Mackay et al., 2000). There is also histological evidence of hippocampal neuronal loss in patients with extra-hippocampal seizures (Babb et al., 1986; Levesque et al., 1991; Fried et al., 1992), although the hippocampal abnormalities seen in addition to extra-hippocampal pathology may be qualitatively different from classical MTS (Babb et al., 1986; Levesque et al., 1991). Neuronal densities within the hippocampus in patients who have undergone temporal lobe resections for foreign tissue lesions have been reported to have significantly lower densities in all hippocampal fields compared with autopsy control subjects (Fried et al., 1992), but the amount of hippocampal cell loss is less than that seen in established MTS (Levesque et al., 1991). The causes of these hippocampal abnormalities remain uncertain, although ongoing epilepsy rather than an acute insult may play an important role. Assessment of hippocampal pathology has not been determined by interictal or ictal EEG, but by the amount of hippocampal abnormalities consistent with damage caused by seizures.

The above data suggest that recurrent seizures may be harmful to hippocampi remote from the primary seizure focus. The aim of this study, therefore, was to determine whether hippocampal abnormalities can be identified in vivo in hippocampi that are not the primary source of seizures in children and young adults with well characterized focal epilepsy. T2 relaxometry was the chosen method given earlier demonstrations of the sensitivity of T2 relaxometry in the identification of hippocampal abnormalities.

Methods
This study was approved by the Great Ormond Street Hospital local research ethics committee. Children and young adults with partial epilepsy evaluated within the Great Ormond Street Hospital epilepsy surgery programme were enrolled. Consent was obtained either from the individual undergoing the investigation or one of their parents. Localization of the seizure focus was carried out at a case review conference attended by paediatric neurologists, neurophysiologists, neuroradiologists, neuropsychologists and a neuropsychiatrist. Each professional presented data to the meeting and localization was decided by consensus of this multidisciplinary team.

Clinical localization was by seizure semiology. Clinical localization to the temporal lobe was considered if there was any one of the following: behavioural arrest; oro-alimentary automatisms; stereotyped complex automatisms with post-ictal confusion; psychic aura such as fear or deja vu; an aura of a formed auditory or visual hallucination; a distinct epigastric aura; speech impairment prior to or immediately following the seizure; or non-specific aura or automatisms followed by confusion post-ictally (French et al., 1993; Duchowny et al., 1994). Localization to the frontal lobe was considered if seizures were brief, there was rapid onset or offset to the seizure, a nocturnal bias, a preponderancy to clusters, bizarre behaviour or vocalization (Stores et al., 1991; Jayakar et al., 1992). An occipital origin was suggested if there were elemental visual hallucinations, contralateral eye deviation or ictal blindness. Lateralization was based on lateralized motor phenomena (e.g. limb jerking or dystonia) or lack of speech during or speech disturbance immediately following the seizure (Gabr et al., 1989).

Neurophysiological data included interictal and ictal surface video-EEG, and magnetic resonance data included axial and coronal T1- and T2-weighted images optimized for imaging of the hippocampus. For the purposes of contributing to localization, these images were visually assessed. After presentation of the data, each case was discussed in an open forum and if clear localization was possible, the patient was assigned to one of the following groups:

(i) TLE in conjunction with MTS (MTS-TLE). Two patients were retrospectively classified as belonging this group following histological evidence that they had MTS.
(ii) Lesional TLE (l-TLE), encompassing patients with lesions other than MTS.
(iii) Extra-temporal epilepsy (ETE).

Only patients in whom consensus was reached are included in the current study.

Control subjects were also enrolled. In order to obtain control data for the children in the younger age range who require sedation, children who were undergoing MRI investigation to exclude neurological disorders were enrolled. This includes children undergoing magnetic resonance investigations to exclude neurocutaneous disorders (e.g. Sturge-Weber syndrome), those undergoing staging of malignancies and those with eye or ear disorders. To be eligible for inclusion as control subjects, children needed to be neurodevelopmentally normal and to have normal MRI on visual assessment of T1 and T2 weighted axial and coronal images by consensus decision of two neuroradiologists.

All patients and control subjects underwent MRI investigations, including T2 relaxometry. The MRI investigations were carried out on either a Siemens (Erlangen, Germany) 1.5 T SP whole body system (pre-1999) or a Siemens 1.5 T Vision whole body system (post-1999). T2 maps were calculated from 16 images obtained at echo times of 22–262 ms using a modified Carr–Purcell–Meiboom–Gill sequence in a tilted coronal plane through the body of the hippocampus as reported previously (Scott et al., 2001). The slice was oriented on a line that crossed the pons on the anterior border of the brain stem of the sagittal scout image.
The slice thickness was 8 mm. T2 maps were generated by fitting single exponentials to the image data of corresponding pixels from all 16 echoes. In this way, a T2 relaxation time was calculated for each pixel, and an image was then constructed in which pixel intensity corresponded to the calculated T2 relaxation time. After identification of the anatomical boundaries of the hippocampus, mean T2 hippocampal relaxation times were measured. A region of interest was placed in the largest possible area within the hippocampus while avoiding boundaries where partial volume effects may occur and the mean T2 value was noted (see Fig. 1). T2 relaxation time values have the same mean and SD in adult control subjects investigated on both scanners.

**Data analysis**

SPSS version 10 (SPSS Inc, Chicago, IL, USA) was used for the analysis. An initial analysis was carried out to identify significant differences in right to left symmetry of T2 relaxation time in the patient groups when compared with control subjects. To achieve this, an asymmetry index (AI) was calculated in each individual, with AI defined as:

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AI = \frac{|R - L|}{\frac{1}{2}(R + L)}
\]

where \(R\) is right hippocampal T2 relaxation time and \(L\) is left hippocampal T2 relaxation time. We used the modulus of the difference between right and left hippocampal T2 relaxation times so that the value for the AI would always be positive. The AI in each group was compared with control subjects using a Mann–Whitney U test.

Subsequently, multiple linear regression was used to investigate differences in T2 relaxation times between patient and control groups after adjustment for age (Scott et al., 2001, 2002). The dependent variable was the mean of right and left T2 relaxation times if no significant group asymmetry was identified. If a significant group asymmetry was identified, T2 relaxation times ipsilateral to the seizure focus were analysed separately from T2 relaxation times contralateral to the seizure focus. The logarithm of age was a covariate. Other covariates investigated included whether a patient had surgery and whether patients who had surgery became seizure free. Interaction terms were investigated and found to be unnecessary. After adjustment for age, abnormal T2 relaxation times were considered to be those that lie above the 95% prediction limit for the control subjects. Correlation between T2 relaxation time and length of time the patient had had epilepsy was also investigated.

**Results**

**Patient population**

Of 457 consecutive children and young adults with epilepsy and related disorders who had had T2 relaxometry of the hippocampi as part of their MRI examination, 96 had well characterized focal epilepsy localized on the basis of clinical, video-EEG and visually assessed MRI data. There were 35 patients in the MTS-TLE group (median age 152 months, range 34–213 months), 33 of whom had evidence of MTS on visual assessment of MRI, and two who were included after histological confirmation of MTS. Thirty-one patients underwent temporal lobe resection, and MTS was confirmed by histological assessment of resected hippocampi in all cases. Twenty-six (84%) of these patients are seizure free. Postsurgical follow-up has been for at least 1 year in all patients. There were also 33 patients (median age 135 months, range 33–233 months) with l-TLE. Of these, 31 have had a surgical resection of the lesion. All patients had a lesionectomy and the hippocampus was not routinely removed. 19 (61%) of these patients have been seizure free for at least one year. There were 28 patients (median age 121 months, range 41–257 months) with ETE included in the current study. Of these, 16 had surgery and six (38%) have been seizure free for at least 1 year. Twenty-seven control subjects (median age 127 months, range 11–216 months) were also enrolled.

**T2 relaxation times**

Hippocampal T2 relaxation times were dependent upon age in all groups \((P < 0.001)\), in both hippocampi, except in the sclerotic hippocampus in patients with MTS. There was no correlation between T2 relaxation time and length of time the patient had had epilepsy in any of the groups. T2 relaxation time was no different in patients who had surgery compared with those who did not, and no difference in T2 relaxation time was identified in patients who became seizure free compared with those who did not. In addition, on individual assessment there was no difference between the numbers of...
patients with abnormal \( T_2 \) relaxation times who became seizure free and those who did not.

In the patients in the MTS-TLE group, 22 patients had MRI features compatible with left sided MTS and ten had features compatible with right sided MTS on visual assessment of the MRI scans. One of the patients with evidence of right sided MTS also had increased signal on \( T_2 \)-weighted imaging in the anterior temporal lobe consistent with widespread gliotic change. One additional patient had evidence of hippocampal atrophy, confirmed to be MTS on histological assessment, within the context of Rasmussen’s encephalitis involving the temporal lobe. Two patients had normal MRI scans on visual assessment, but were subsequently confirmed to have MTS on histological assessment. On the basis of EEG and clinical data, both had a temporal lobe resection and both are seizure free. On histology, one had end folium sclerosis and one had typical Ammon’s horn sclerosis on visual analysis of the histology. No hippocampal volumetry was carried out in these patients. The quantitative \( T_2 \) relaxation times in these two patients were bilaterally normal. On individual analysis in the group with evidence of MTS, 26 out of 35 (74%) had a unilateral increase in \( T_2 \) relaxation time and three out of 35 (9%) had bilateral prolongation of \( T_2 \) relaxation time compared with control subjects. The patients with bilateral abnormalities had the higher \( T_2 \) relaxation time on the side of the seizure focus, i.e. \( T_2 \) relaxometry correctly lateralized the seizure focus in 83% of patients. In no patient was the \( T_2 \) relaxation time falsely lateralising on the basis of the clinical, video-EEG, visual MRI and histological analysis.

On group analysis of the patients with MTS, there was marked hippocampal asymmetry (AI defined in data analysis section of Methods) \((P < 0.001)\). The subsequent regression analysis revealed that ipsilateral to the seizure focus, \( T_2 \) relaxation time was prolonged by a mean of 19 ms [95% confidence interval (CI) 14.6–22.4 ms] compared with control subjects \((P < 0.001)\) (see Fig. 2). There was also prolongation of \( T_2 \) relaxation time by a mean of 3.3 ms (95% CI, 0.8–5.9 ms, \( P = 0.01) \) contralateral to the seizure focus (see Fig. 3A).

In the patients with l-TLE, 15 had MRI features consistent with a dysmyeloplastic neuroepithelial tumour in the left temporal lobe and 13 had such evidence in the right temporal lobe. Two patients had temporal cortical dysplasia, one had a left temporal tuber in the context of tuberose sclerosis, one had a right sided pial angioma consistent with Sturge–Weber syndrome, one had an epidermoid in the right mesial temporal lobe and one had bilateral temporal polymicrogyria. No patients had evidence of hippocampal abnormality on visual assessment. Individual assessment of \( T_2 \) relaxation time in this group revealed six out of 32 (19%) patients with unilateral prolongation and four out of 32 (13%) with bilateral prolongation of the \( T_2 \) relaxation time compared with the control subjects. In the patients with unilateral abnormalities and prolongation of \( T_2 \) relaxation time, the most prolonged \( T_2 \) relaxation time was on the side of the lesion in all patients. However, the AI was not different in the patients with l-TLE compared with control subjects \((P = 0.11)\) and therefore the mean of right and left \( T_2 \) relaxation time was used in the group analysis, which revealed prolongation of \( T_2 \) relaxation time by a mean of 4.3 ms (95% CI, 1.8–7.1 ms, \( P = 0.001) \) in patients compared with control subjects (see Fig. 3B). Subsequent analysis confirms that the \( T_2 \) relaxation time is prolonged both ipsilateral and contralateral to the lesion.

Visual assessment of the MRI of the 28 patients with ETE gave the following results. Fourteen patients had normal neuroimaging, four had evidence of an extra-temporal DNET (dysmyeloplastic neuroepithelial tumour), two had cortical atrophy and there was one each of cerebellar atrophy, periventricular grey matter heterotopia, frontal cortical dysplasia, bilateral occipital ulegyria, widespread \( T_2 \)-weighted signal change post-encephalitis, previous trauma, asymmetrical ventricles and tuberose sclerosis. Only two patients had evidence of hippocampal abnormality on visual assessment. On assessment of the quantitative \( T_2 \) data, five out of 28 (18%) had a unilateral increase and one out of 28 (4%) had a bilateral increase in \( T_2 \) relaxation time compared with control subjects. The child with bilateral abnormalities had widespread abnormalities on \( T_2 \)-weighted images on visual assessment. There was no difference in AI in the patients compared with control subjects \((P = 0.31)\) and therefore the means of right and left \( T_2 \) relaxation times was used for group analysis, which revealed prolongation of \( T_2 \) relaxation time by a mean of 3.7 ms (95% CI, 1.1–6.6 ms, \( P = 0.006) \) in patients compared with control subjects (see Fig. 3C). There was no difference in mean increase in \( T_2 \) relaxation time between patients with lesional ETE and those with non-lesional ETE.
Discussion

T₂ relaxometry is a quantitative magnetic resonance tool that can be used to increase the sensitivity of identifying hippocampal abnormalities above that of visual assessment alone and can detect changes that would not be considered to be hippocampal sclerosis. Because it does not depend on side-to-side comparison, it is particularly useful in detecting subtle abnormalities and, as in this paper, to interrogate the hippocampus when it is not involved directly in the seizure origin.

The main finding in this study is that there is a subtle prolongation of T₂ relaxation time in the hippocampi of patients with partial epilepsy when the hippocampus is not the primary seizure focus. This includes the hippocampus contralateral to the seizure focus in patients with MTS, patients with lesional TLE where the lesion is the primary seizure focus, and patients with ETE where the primary seizure focus is outside the temporal lobe. Significant prolongation of the T₂ relaxation time was identified in each group. Interestingly, the degree of T₂ prolongation was similar in all groups and less than is typically seen in sclerotic hippocampi. These abnormalities, which were not identified on visual assessment alone, are consistent with observations that the hippocampus can be abnormal secondary to seizures arising elsewhere. For example, there are histologically identified hippocampal changes in patients with extrahippocampal pathology that is presumed to be the seizure origin, and these pathological abnormalities are more subtle, with less neuronal loss, than those seen in typical hippocampal sclerosis (Babb et al., 1986; Levesque et al., 1991).

The data from the current study are most consistent with hippocampal injury in the hippocampi that are at a distance from the presumed seizure focus occurring as a consequence of ongoing seizures once partial epilepsy has been established. This is supported by the similarity in the degree of prolongation of T₂ relaxation time between the groups despite the wide variability in site of origin of partial epilepsy and in the number of different causes of the epilepsy. In addition, the number of patients with MTS and bilaterally abnormal T₂ relaxation times in our study (9%) is less than the number of patients with bilateral abnormalities identified in adult studies (18–40±%) (Jackson et al., 1993b; Namer et al., 1998; Bernasconi et al., 2000; Mackay et al., 2000). This may be because the adult patients have had a longer period of epilepsy, and therefore may have had a greater number of

![Fig. 3 Scatter plots of hippocampal T₂ relaxation time against age in control subjects (open square, lower regression line) and in the hippocampus contralateral to the seizure focus in patients with MTS (filled square, upper regression line) (A). Hippocampi in patients with lesional temporal lobe epilepsy (filled diamond, upper regression line) (B). Hippocampi in patients with extratemporal epilepsy (filled triangle, upper regression line) (C). These graphs were generated from a single regression analysis and are shown separately for clarity. Note that the x-axis is in a logarithmic scale.](https://academic.oup.com/brain/article-abstract/126/9/1968/367470)
seizures than the young patients described in the present study. In support of the idea that seizures can affect the hippocampus, it has been shown recently, with hippocampal volumes in adult onset MRI negative TLE, that subtle hippocampal abnormalities may be associated with the number of generalized tonic clonic seizures between measurements (Briellmann et al., 2002). In one patient, this progressed to classical hippocampal sclerosis.

While we favour the view that seizures that involve the hippocampus or spread secondarily to the hippocampus are the likely cause of our findings, there are other potential reasons for $T_2$ abnormalities in hippocampi that are not the primary source of partial epilepsy. It is possible that the $T_2$ relaxation time abnormalities are the result of a pre-existing abnormality such as dysgenesis, present prior to the onset of epilepsy, i.e. patients with dual pathology. However, patients with disorders ranging from neuronal migration disorders to tuberous sclerosis, encephalitis or Sturge–Weber Syndrome would then need to have such pre-existing hippocampal changes. This, clearly, is not likely to be the case. It is also possible that both hippocampi are injured at the time of an acute initial insult such as a prolonged febrile convulsion or head injury, and in the case of MTS, that one hippocampus is more severely affected than the other. Although this may be plausible or even likely in patients with MTS, it is an unlikely explanation for the bilateral hippocampal abnormalities identified in patients with l-TLE and ETE, in whom an acute insult is not identified.

It is also possible that in the patients with l-TLE, the hippocampus is required for seizure generation and may be part of a seizure focus, rather than remote from the seizure focus. Damage in these hippocampi could be greater than damage in hippocampi that are not part of a seizure focus, e.g. those contralateral to the seizure focus. However, although it is true that $T_2$ relaxation time is higher on the side of the lesion in patients with l-TLE than on the contralateral side, there is no significant side-to-side asymmetry relative to control subjects. In addition, the prolongation of $T_2$ relaxation time is far less than the prolongation recognized in patients with MTS. Thus, although we cannot rule it out, we suggest that this interpretation for our data is unlikely.

As well as this small $T_2$ relaxation time change in hippocampi remote from the seizure focus, there is also the more obvious, and typical, prolongation of $T_2$ relaxation time that is characteristic of the epileptogenic ipsilateral sclerotic hippocampus in our TLE patients. In the current study, the most severely abnormal $T_2$ relaxation time was correctly lateralising in 83% of patients with MTS and incorrectly lateralising in none. This is consistent with reports of adult patients in the literature (Lee et al., 1998; Bernasconi et al., 2000; Mackay et al., 2000). There are two patients in the TLE-MTS group who did not show evidence of MTS on visual assessment of MRI and who had normal $T_2$ relaxation times. Adult patients with these characteristics have been reported previously (Van Paesschen et al., 1997b). As well as suggesting that hippocampi may show abnormalities second-


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