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MR detection of hippocampal disease in epilepsy: factors influencing T2 relaxation time.

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MR Detection of Hippocampal Disease in Epilepsy: Factors Influencing T2 Relaxation Time

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PURPOSE: To assess the reproducibility and stability of hippocampal T2 relaxation times and examine the effects of patients' age, seizures, and duration of epilepsy on this measure. **METHODS:** Hippocampal T2 relaxation times were measured in 63 patients with chronic epilepsy (55 with partial and 8 with idiopathic generalized seizures) using a Carr-Purcell-Meiboom-Gill sequence, echo times 22 to 262 millisecond, on a 1.5-T clinical MR imaging system. Twenty-three patients on stable medication regimens underwent repeated T2 relaxometry after an interval of between 115 and 331 days. In 4 patients with partial seizures, hippocampal T2 relaxation times were measured interictally and again within 45 minutes of seizures. **RESULTS:** In the 55 patients with partial epilepsy, hippocampal T2 relaxation times did not correlate with seizure frequency, duration of epilepsy, or age, but they were significantly more abnormal in those patients with a history of prolonged (more than 30 minutes) early childhood seizures than in those without. Eight patients with idiopathic generalized epilepsy had normal MR and hippocampal T2 relaxation times. In the 23 patients who underwent repeated T2 relaxometry there was no evidence of qualitative changes in T2-weighted images of the hippocampi or systematic changes of hippocampal T2 relaxation times with time. In 4 patients recent complex partial or secondary generalized seizures did not acutely alter hippocampal T2 relaxation times. **CONCLUSION:** Hippocampal T2 relaxation time is a precise, reliable, stable, noninvasive measurement sensitive to hippocampal disease. These results do not suggest progression of hippocampal disease in patients with intractable partial seizures during periods of up to 331 days.

Index terms: Seizures; Hippocampus; Magnetic resonance, tissue characterization; Brain, magnetic resonance

Hippocampal sclerosis is associated with characteristic magnetic resonance (MR) abnormalities, including hippocampal volume loss and T2-weighted signal changes on appropriately oriented images (1–3). Disruption of internal structure and the presence of T1 signal abnormalities have been described recently (4).

Visual assessment of abnormal T2-weighted signal in the hippocampus is subjective, and reported prevalence of visible T2 signal abnormalities varies widely. T2 relaxation times may be quantified on many commercial clinical MR systems in vivo, and such quantification has been shown to reduce the subjectivity and increase sensitivity of detection of hippocampal disease (5). Good interobserver reliability has been found for quantification of T2 relaxation times in normal and abnormal hippocampi (5). The range of T2 relaxation times in the normal hippocampus was small (99 to 106 milliseconds with a maximum side-to-side difference of 5 milliseconds) (5), although the actual values are potentially variable between instruments. Hippocampal signal abnormalities were identified consistently when present; in patients with hippocampal sclerosis, visually apparent T2 signal abnormalities were pres-

ent in 77%, but measured T2 relaxation times were always at least 10 milliseconds greater than the normal range (4, 5).

The underlying cause of such abnormalities of hippocampal T2 relaxation time is not yet determined. Prolonged hippocampal T2 relaxation times could indicate the presence of gliosis, a histopathologic feature of hippocampal sclerosis. Hippocampal T2 relaxation times also could be transiently affected by recent seizures or may change with duration of epilepsy or possibly as a result of drug-related neuropathologic changes in the brain. In rats, vigabatrin administration is associated with intramyelinic edema and astrocytosis, which is detectable by T2 relaxometry (6); similar changes have not been detected in humans (7).

The quantitative and noninvasive nature of hippocampal T2 relaxation time measurement allows comparison between repeated measurements. This enables investigation of the factors that influence hippocampal T2 relaxation times and study of the natural history or progression of hippocampal disease. We have tested the hypotheses that hippocampal T2 relaxation times are stable and reproducible during periods of up to 10 months in patients with epilepsy on stable medication; may be affected by a history of prolonged early childhood convulsion, difficult birth, birth hypoxia, and long duration of habitual epilepsy; and may alter transiently after a seizure.

Methods

Patients

Fifty-five outpatients with partial epilepsy and 8 with idiopathic generalized epilepsy were studied. The study was approved by the hospital ethics committee, and all patients gave informed consent.

The patients with partial epilepsy had seizures refractory to current antiepileptic medication. These patients underwent detailed assessment by two independent neurologists, electroencephalography (including additional video electroencephalography in 26, ictal electroencephalography in 15 patients), MR, and quantitative T2 mapping. Histories of early childhood convulsions were obtained by questioning the patients and families, supplemented, where possible, by review of the original hospital notes. Seizure frequencies were determined from seizure diaries, recording all such events during the 8-week period before scanning. All patients recorded the numbers of simple partial, complex partial, and secondary generalized seizures on seizure calendars.

Twenty-three patients with partial and secondary generalized seizures who remained on stable antiepileptic drug regimens throughout the study period underwent further

T2 relaxometry after an interval of between 115 and 331 (median, 169) days.

Four of the 55 patients with partial seizures underwent postictal and interictal T2 relaxometry. These patients had generalized tonic clonic or complex partial seizures between 10 and 45 minutes before study. They returned for repeat relaxometry after seizure-free periods of at least 72 hours.

Eight patients with idiopathic generalized epilepsy were also studied. Patients with juvenile myoclonic epilepsy were selected, because this is the best-defined and most easily diagnosed adult idiopathic generalized epilepsy syndrome (8, 9). All these patients had characteristic myoclonic jerks on awakening, generalized tonic clonic seizures, and generalized electroencephalographic abnormalities.

MR

T1-weighted inversion-recovery oblique axial and oblique coronal images (3500/26 [repetition time/echo time[, 300-millisecond inversion time, 5-mm section thickness every 7.5 mm) and oblique coronal T2-weighted images (second echo of a double-echo inversion-recovery sequence, 4000/85, 145-millisecond inversion time, 5-mm section thickness every 7.5 mm) covering the whole brain were acquired using a Siemens (Iselin, NJ) 1.5-T SP63 Magnetom scanner. These sequences were selected to demonstrate hippocampal anatomy and features of hippocampal sclerosis optimally (4).

T2 maps were calculated in each of 3 coronal sections from 16 images obtained at echo times of 22 to 262 using a Carr-Purcell-Meiboom-Gill sequence (imaging time approximately 12 minutes). The section thickness was 8 mm. T2 maps were generated by a computer program that fitted single exponential to the signal-intensity data of corresponding pixels from all 16 echoes (10). In this way 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 (Fig 1). The central section from which hippocampal T2 data were acquired was oriented on a line that crossed the pons on the anterior border of the brain stem of the sagittal scout image (Fig 2). Mean hippocampal T2 relaxation times were measured within the anatomic boundaries of the hippocampus by placement of the largest possible circular region of interest within the hippocampus, consistent with avoidance of boundaries where partial volume effects might occur (Fig 1).

Results

Patients with Partial Seizures

Patient Characteristics. Twenty-eight female and 27 male patients with intractable partial epilepsy were evaluated. The median age of the patients was 29 years (range, 15 to 61 years); the median age at onset of habitual epilepsy was 11 years (range, 3 months to 34 years); and the median duration of epilepsy 20 years (range, 4 to 36 years). Median seizure frequency was 10 sei-
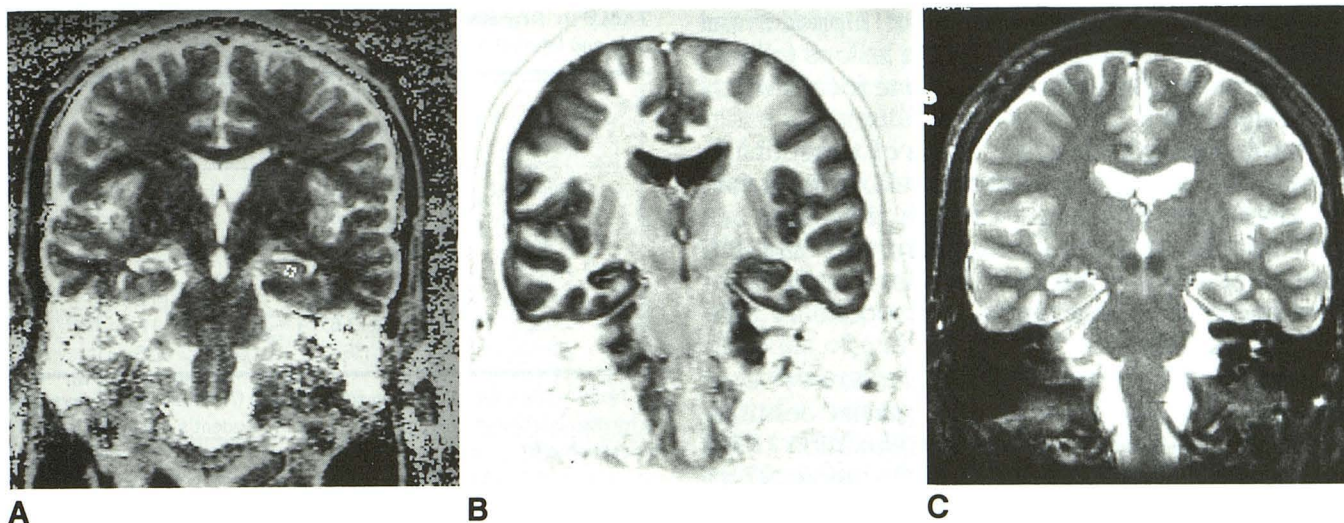
A   **B**   **C**

Fig. 1. *A,* T2 map calculated from 16 tilted coronal images (echo times, 22 to 262). Pixel intensity represents T2 relaxation time, calculated by fitting a single exponential to signal-intensity values of corresponding pixels from each constituent image. The largest possible region of interest (containing 10 pixels in this case) has been placed within the anatomic boundaries of the left hippocampus (hippocampal T2 relaxation time = 109 milliseconds), consistent with avoidance of boundaries between hippocampus and surrounding cerebrospinal fluid, where partial volume effects occur. This value of hippocampal T2 relaxation time is outside the normal range (98 to 106 milliseconds), as is not infrequently seen in patients with contralateral hippocampal sclerosis. In the smaller right hippocampus the hippocampal T2 relaxation time (120 milliseconds) is within the range characteristic of hippocampal sclerosis. Histologic analysis of resected hippocampal tissue confirmed hippocampal sclerosis.

B, T1-weighted image corresponding to T2 map. Note the atrophy and loss of internal hippocampal structure in the left hippocampus.

C, T2-weighted image corresponding to T2 map. High signal is seen in the right (sclerotic) hippocampus. The left hippocampus appears normal, despite a slightly abnormal hippocampal T2 relaxation time.
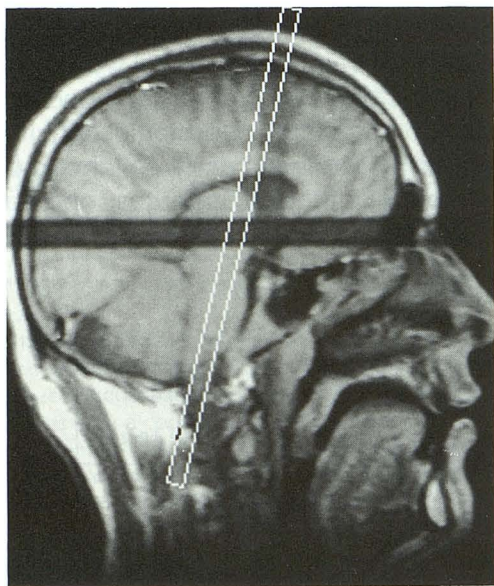

Fig. 2. Sagittal image showing alignment of acquisition plane for T2 maps. The central section from which hippocampal T2 data were acquired was oriented on a line that crossed the pons on the anterior border of the brain stem of the sagittal scout image.

zures per month (range 0 to 62), including simple partial (range, 0 to 45), complex partial (range, 0 to 62), and secondarily generalized seizures (range, 0 to 8).

Based on clinical, electroencephalographic, and MR evaluation, 44 of the 55 patients had diagnoses of temporal lobe epilepsy, 22 with left-sided focus, 17 with right-sided focus, and 5 undetermined. Of the remaining 11, 2 had unequivocal frontal onset of seizures, one frontoparietal, and in the remaining 8 seizure onset was multifocal or undetermined. There were 28 cases in which structural MR diagnoses of unilateral hippocampal sclerosis were made on the basis of visual assessment of the images (Figs 1B and 1C) but excluding T2 relaxometry data: 18 on the left and 10 on the right. Temporal lobe epilepsy was the clinical and electroencephalographic diagnoses in 25 of these; 1 patient had an extratemporal seizure origin, and 2 had undetermined seizure origin. Temporal lobectomy has subsequently been performed in 15 patients; the pathologic diagnoses confirmed the MR diagnoses in the 10 cases in which sufficient hippocampal tissue was available for assessment. In the remaining 5 cases, the tissue available for histology was inadequate for pathologic analysis. There was no patient with qualitative MR evidence of bilateral hippocampal sclerosis. Eighteen patients had atrophy or increased T2-weighted signals of the ipsilateral temporal lobes; 11 of these 18

patients also had MR evidence of hippocampal sclerosis. Three had foreign-tissue lesions (glioma or dysembryoplastic tumor) and one focal cortical microgyria.

Acute Postictal Studies. Three of the four patients who underwent postictal relaxometry had temporal lobe epilepsy (two with right and one with left temporal seizure onset); two had MR evidence of hippocampal sclerosis. The final patient had cryptogenic partial and secondary generalized seizures.

Stability of Repeated T2 Relaxometry over Time. In the 55 patients with partial seizures, baseline mean hippocampal T2 relaxation times was 112.9 milliseconds (SD, 12.9; range, 97 to 187; n = 110; Fig 3). There was no patient with qualitative or quantitative (hippocampal T2 relaxation times more than 116 milliseconds in our hands [5]) evidence of bilateral hippocampal sclerosis. There was no significant change between first and second measurements of hippocampal T2 relaxation times in the 23 patients who had repeat relaxometry after 115 to 331 days while on stable medication (Table 1 and Fig 4A); the mean difference (SD) between first and second measurements of hippocampal T2 relaxation times was −1.1 (6.4) milliseconds and the difference between measurements normally distributed. The limits of agreement were −13.9 to 11.7 milliseconds, and the coefficient of repeatability (11) was 12.8 milliseconds. The 95% confidence limits for the mean difference was −3 to 0.8 milliseconds, for the upper limit of agreement 9.8 to 13.6 milliseconds, and for the lower limit of

agreement −15.9 to −12.0 milliseconds. There was no suggestion of an increase in hippocampal T2 relaxation times with longer interscan intervals (Fig 4B).

Relationship between Hippocampal T2 and Early Medical Events. There was no significant correlation between patient age, age of onset of habitual epilepsy, or duration of epilepsy and hippocampal signal abnormality. In 49 of the 55 patients with partial epilepsy a reliable history of childhood seizures was available. Eighteen had suffered early childhood convulsions, lasting longer than 30 minutes in 16. Two of the prolonged early childhood convulsions had been associated with postictal neurologic deficits. Two patients had experienced early childhood convulsions lasting less than 30 minutes: one had unilateral hippocampal sclerosis with a T2 of 120

TABLE 1: Repeated measurements of hippocampal T2 relaxation time and interval between measurements

	T2 Right Hippocampus, ms	T2 Left Hippocampus, ms
Baseline	(n = 23)	(n = 23)
Mean	112.8	113.0
SD	13.0	13.0
Repeat		
Mean	114.3	113.3
SD	13.6	11.3
P	NS	NS

Note.—The interval between scans ranged from 115 to 331 days, with a median interval of 169 days; P values by Student's t test; NS indicates not significant.

Fig. 3. Hippocampal T2 relaxation times in patients with partial seizures and idiopathic generalized epilepsy (normal range, 99 to 106 milliseconds). IGE indicates hippocampal T2 relaxation time values of patients with idiopathic generalized epilepsy (juvenile myoclonic epilepsy); partial, hippocampal T2 relaxation times of patients with partial epilepsy. All values of hippocampal T2 relaxation times in patients with idiopathic generalized epilepsy are in the normal range (99 to 106 milliseconds). In patients with partial seizures, hippocampal T2 relaxation times of more than 116 milliseconds are consistently associated with other MR evidence of hippocampal sclerosis. Values of hippocampal T2 relaxation times between 106 and 116 milliseconds may represent minor degrees of hippocampal abnormality.
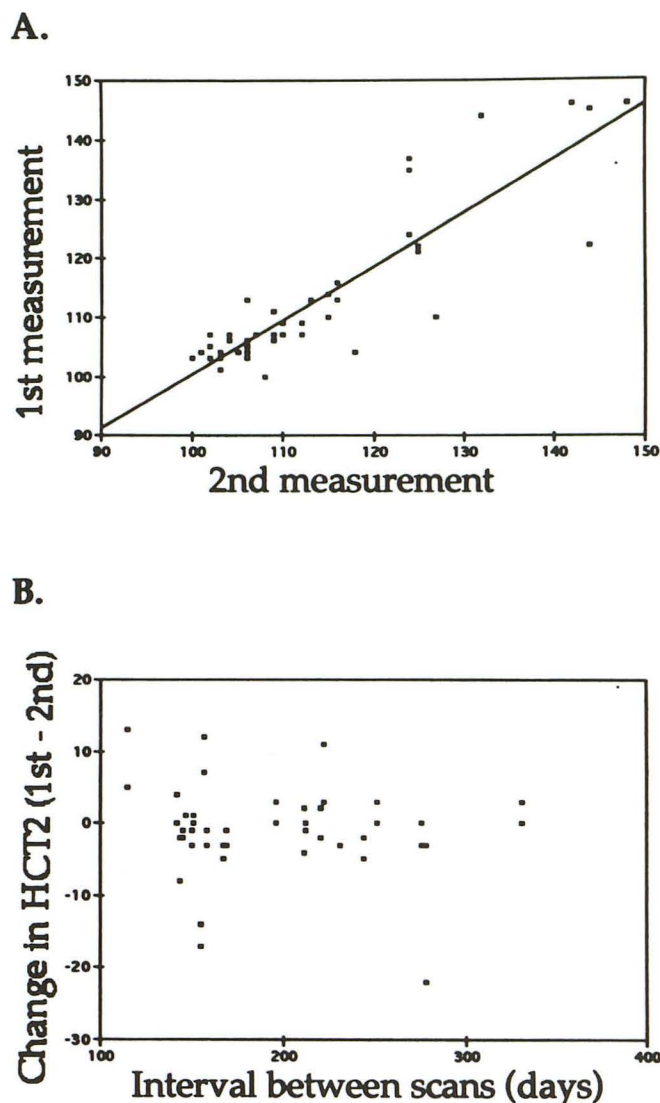
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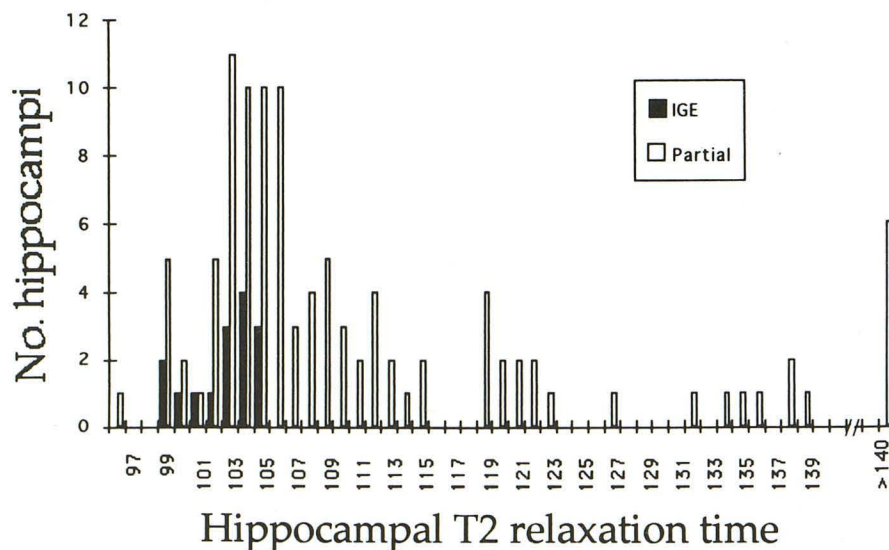
Fig. 4. Successive measurements of hippocampal T2 relaxation times.

A, Comparison between repeated measurements of T2 relaxation times within the same hippocampus. There is good agreement between successive measurements of hippocampal T2 relaxation times with a correlation coefficient of .88.

B, Plot of change in measured hippocampal T2 relaxation times against the interval between successive measurements. No time-dependent systematic change is evident.

milliseconds; the other had normal hippocampi with a T2 of less than 106 milliseconds bilaterally.

A history of early childhood convulsions lasting more than 30 minutes was significantly associated with hippocampal T2 relaxation time–defined hippocampal sclerosis (hippocampal T2 relaxation times more than 116 milliseconds under these conditions [5]). Fifteen of 16 patients with histories of prolonged early childhood convulsions but only 11 of the 31 patients with no such histories had hippocampal T2 relaxation times of more than 116 milliseconds ($P < .002$ by Pearson's χ^2). The mean hippocampal T2 relaxation times on the more abnormal side were also significantly greater in patients with histories of early childhood convulsions lasting more than 30 minutes than in those without (Table 2). There were no significant differences in the prevalence of abnormal hippocampal T2 relaxation times or of mean hippocampal T2 relaxation times in the less affected hippocampi of patients with and without histories of early childhood convulsions.

Relationship of Seizures to Hippocampal T2 Signal Change: Long-Term Effects. In the group with partial seizures there was no significant correlation between hippocampal T2 relaxation times and the frequency of simple partial, complex partial, and secondary generalized seizures, or total seizures assessed over the 8 weeks before initial MR scanning (Fig 5). There was no correlation between estimated total number of simple partial, complex partial, and secondary generalized seizures, or total seizures recorded between scans and change in hippocampal T2 relaxation times.

Short-Term Effects. There was no significant difference in hippocampal T2 relaxation times measured in four patients within 45 minutes of seizures, compared with measurements performed in the same patients during a period of more than 72 hours without seizures (Table 3). Three of these four patients had temporal lobe seizure foci.

Patients with Idiopathic Generalized Epilepsy

The eight patients with juvenile myoclonic epilepsy had a median age of 28 years (range, 19 to 43 years). Generalized tonic-clonic seizures began at a mean age of 17 years (range, 13 to 25 years) and myoclonic jerks at 17 years (range, 12 to 26 years). The median duration of this epilepsy was

TABLE 2: Hippocampal T2 relaxation times in patients with early childhood convulsions and controls

	T2 Better Side, ms	T2 Worse Side, ms
Prolonged early childhood convulsions (n = 16)		
Mean	105.5	131.9
SD	3.5	17.7
No early childhood convulsions (n = 31)		
Mean	105.9	116.4
SD	3.7	13.6
P	NS	.002

Note.—*P* values by Student's *t* test; NS indicates not significant.
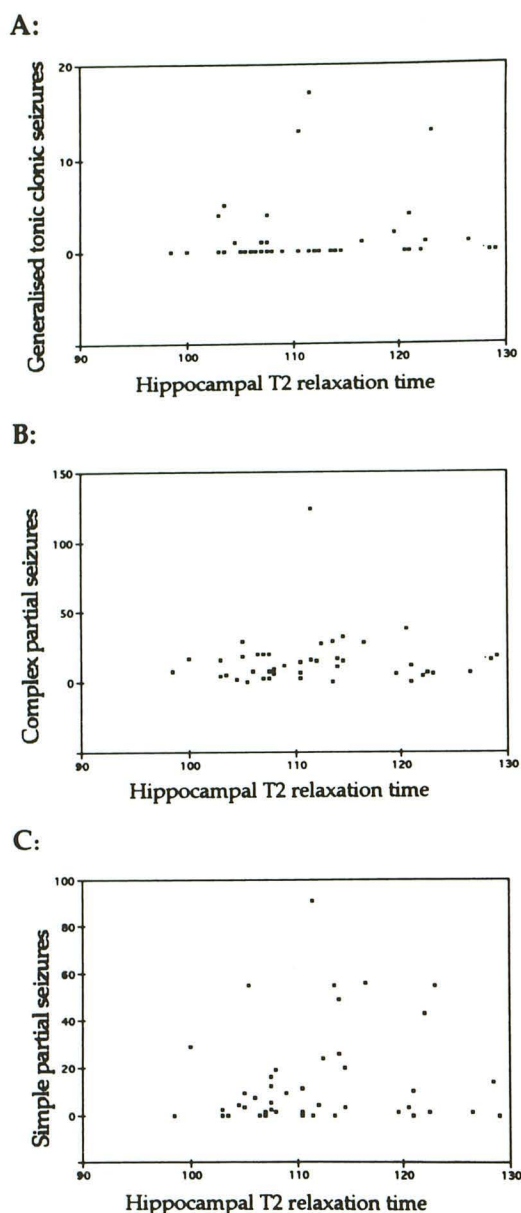
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Fig. 5. Correlation between hippocampal T2 relaxation times and seizure frequency at baseline (measured as number of seizures during 8 weeks) in patients with partial epilepsy. There is no relationship between simple partial, complex partial, or secondarily generalized seizure frequency and hippocampal T2 relaxation times.

20 years (range, 4 to 25 years). Two of the eight patients also had typical absences. Five of the eight patients had well-controlled seizures, although all had suffered periods of poor control (more than two generalized tonic-clonic seizures per month) in the past.

All eight patients with juvenile myoclonic epilepsy had hippocampal T2 relaxation times within the normal range (mean, 103.8 ± 2.0 millisec-

conds, n = 16; Fig 3) and normal conventional MR of the brain.

Discussion

Hippocampal sclerosis is associated with T2 signal abnormalities (1–4), and T2 relaxometry has been shown to increase the sensitivity of its detection by MR (5). Using identical instrument and imaging methods as in the present study, hippocampal T2 relaxation times of more than 116 milliseconds correlated with pathologic and/ or MR evidence of hippocampal sclerosis (5). Healthy subjects have hippocampal T2 relaxation times of 99 to 106 milliseconds. There is a further group of patients with hippocampal T2 relaxation times between 106 and 116 milliseconds; such hippocampal T2 relaxation time abnormalities are usually not detectable by visual assessment of T2-weighted images and are often found contralateral to a clearly sclerotic hippocampus. Lesser degrees of neuronal loss or gliosis have been reported in pathologic studies to exist contralateral to a sclerotic hippocampus (12–14). It has therefore been postulated that such minor hippocampal T2 relaxation time abnormalities may represent lesser degrees of hippocampal disease and that hippocampal T2 relaxation time prolongation may depend on the severity of hippocampal damage. Hippocampal T2 relaxation time potentially represents a useful noninvasive measure of hippocampal abnormality and may enable longitudinal studies of the development or progression of hippocampal disease.

The usefulness of T2 relaxometry as a tool to identify abnormalities and follow medium- and long-term changes in the brain depends on the stability and reproducibility of the measurement, factors that have not been studied previously. Reproducibility of T2 relaxometry in the hippocampus depends on numerous factors. By repeating measurements on the same MR system, we have minimized technical and machine variables. For longitudinal studies of changes in hippocampal T2 relaxation times, signal variation along the length of the hippocampus was a further potential source of error, necessitating precise and reproducible orientation of imaging planes with reference to standard anatomic landmarks, in this case along the anterior border of the brain stem on the sagittal scout image. The T2 maps were orientated at right angles to the long axes of the hippocampi, and measurements were taken from a region well within the anatomic borders of the hippocampi to minimize partial

TABLE 3: Immediately postictal and interictal hippocampal T2 relaxometry

Patient	First Scan			Type of Seizure (onset)	Second Scan			
	Hippocampal T2 Relaxation Time (right), ms	Hippocampal T2 Relaxation Time (left), ms	Time Since Seizure, min		Hippocampal T2 Relaxation Time (right), ms	Hippocampal T2 Relaxation Time (left), ms	Time Since Seizure, h	Interval, d
1	112	109	45	Complex partial (unlocalized)	112	109	>120	7
2	113	120	45	Complex partial (left temporal)	109	120	>72	14
3	129	115	10	Complex partial (right temporal)	130	113	>168	21
4	105	109	10	Secondary generalised tonic clonic (left temporal)	108	108	>72	21

volume effects with surrounding cerebrospinal fluid (5). Using these techniques, we have demonstrated good stability and reproducibility of hippocampal T2 relaxation times during periods of up to 11 months.

Abnormalities of computed tomographic brain scans have been reported in association with flurries of partial seizures, resolving in 5 days to 3 weeks (15–17). Transient focal changes in visually assessed T2 MR signals after episodes of partial status epilepticus have been reported (18, 19). Such changes have been attributed to impairment of the blood-brain barrier by seizures and status epilepticus, resulting in local edema (20). We found no difference between hippocampal T2 relaxation times measured soon after a single seizure and that measured after 72 hours free of seizures. This implies that there were no immediate changes in hippocampal tissue water, and that hippocampal T2 relaxation time measurements obtained at this time reflect chronic and fixed abnormalities. It is likely that changes in T2 signal after single seizures, at least in the hippocampi, are exceptional.

Patterns of hippocampal damage have been studied by Margerison and Corsellis in postmortem tissue of patients with intractable partial seizures (13). Classical Ammon's horn sclerosis, with severe neurone loss in the pyramidal cell layer and end folium, was found in 40% and lesser degrees of damage with sclerosis of the end folium but preservation of the pyramidal cell layer in a further 25%. Bilateral hippocampal sclerosis was reported in 31% of cases. More recently, Ammon's horn sclerosis has been distinguished from nonspecific hippocampal sclerosis, in which there is only moderate neuron loss in the end folium and/or CA1 zone of the hippocampus but sparing of the dentate gyrus granule cells (21,22). Only Ammon's horn sclerosis was associated with a history of prolonged early childhood convulsions, whereas nonspecific hippocampal sclerosis was found in patients with long histories of epilepsy.

It has been suggested that seizures may be responsible in part for neuronal cell damage in hippocampal sclerosis (23–25), although susceptibility to such damage also may depend on other factors, such as patient age (27), fever (28), vascular perfusion, and tissue oxygenation (29). Appropriate studies using T2 relaxometry may enable assessment of the contribution of such factors.

Hippocampal T2 relaxation times of more than 116 milliseconds, a constant feature of hippocampal sclerosis in an earlier study (5), were much more common in patients with histories of prolonged early childhood seizures than those without, reflecting the recognized association between early childhood seizures and hippocampal sclerosis (21, 22). Mean hippocampal T2 relaxation times were greater in those with a history of prolonged early childhood convulsion than in those without. This is consistent with the hypothesis that greater hippocampal T2 relaxation time abnormality is associated with more severe hippocampal disease such as Ammon's horn sclerosis and less prolonged but abnormal hippocampal T2 relaxation times with lesser damage in nonspecific hippocampal sclerosis.

In neither the whole group nor in a selected subgroup with less severely abnormal hippocampal T2 relaxation times (between 106 and 116 milliseconds) was there a correlation between duration of epilepsy or seizure frequency and hippocampal T2 relaxation time. We found no evidence that seizures produce progression of hippocampal damage as assessed by hippocampal T2 relaxation times in any patients. Patients with idiopathic generalized epilepsy had no evi-

dence of hippocampal T2 signal change despite many years of recurrent generalized tonic-clonic seizures. Similarly, in the patients with partial seizures, hippocampal T2 relaxation times were independent of the severity or duration of epilepsy, and no consistent change in hippocampal T2 relaxation times was observed in our 23 patients during interscan intervals of 115 to 331 days. These observations suggest that hippocampal sclerosis (including Ammon's horn sclerosis and nonspecific hippocampal sclerosis) was static by the time these patients were scanned. We cannot exclude changes occurring during an interval of many years or changes that have plateaued. A study of hippocampal T2 relaxation times from the onset of epilepsy and of infants after febrile convulsions would enable analysis of factors that contribute to hippocampal damage.

Hippocampal T2 relaxation time measurements provide a sensitive technique for noninvasive assessment of hippocampal disease, and in contrast to volumetric assessment of the hippocampus, allow detection of mild, bilateral abnormalities because of the small range of control hippocampal T2 relaxation time values. These measurements are reproducible and in patients with chronic epilepsy are unaffected by recent or recurrent seizures during periods of up to 10 months. Medical histories of our patients are consistent with the hypothesis that hippocampal sclerosis is established before adulthood, often related to prolonged early childhood convulsions, and not progressive in adults with recurrent seizures, during periods of up to 10 months.

Acknowledgments

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