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# MR and Positron Emission Tomography in the Diagnosis of Surgically Correctable Temporal Lobe Epilepsy

R. Heinz, N. Ferris, E. K. Lee, R. Radtke, B. Crain, J. M. Hoffman, M. Hanson, S. Paine, and A. Friedman

**PURPOSE:** To determine the association of an MR abnormality and a positron emission tomography (PET) abnormality with a good outcome in patients with temporal lobe epilepsy after lobectomy, the association of combined PET and MR findings with good outcomes after lobectomy, and MR and PET pathologic correlation. **METHODS:** MR and PET were performed on 27 patients in a blinded study. Histologic studies were correlated with foci of increased T2 signal. **RESULTS:** Increased signal or decreased volume of the hippocampus was noted in 13 of 15 patients with mesial temporal sclerosis. Twelve of 15 had positive PET findings. MR identified 20 (83%) of the 24 patients with good outcomes. PET identified 71%. When MR and PET were combined, they detected 95% of the patients with good outcome. Region of interest measurements of the hippocampus in 11 study patients and 7 control subjects documented a significant increase in signal in the patients with seizures. Histologic correlative studies demonstrated that increased T2 signals related to astrocytosis in the hippocampus and adjacent white matter. **CONCLUSION:** MR (increased signal and decreased volume of the hippocampus) significantly improved the capability to identify those persons who would be helped by lobectomy. MR sensitivity exceeded that of PET.

**Index terms:** Seizures; Brain, temporal lobe; Positron emission tomography (PET); Magnetic resonance, in treatment planning

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Neuroimaging has been used in the preoperative assessment of patients with temporal lobe epilepsy for the last 40 years. When there is an accurate preoperative lateralization of the epileptogenic focus, temporal lobectomy can result in complete cure of, or significant improvement in, seizure activity (1). In the past, electroencephalography has provided most information on lateralization in these patients. In the last decade, positron emission tomography (PET) has provided new information about metabolic changes occurring at the seizure focus (2). More recently, magnetic resonance (MR) has been useful in establishing the site of epileptogenic foci (3–11). Despite significant improvements in the rate of detection of epileptogenic foci with MR (from 20% to 65%). PET has been superior, with detection rates consistently in the range of 70% to 80% (2). We report a series of 27 patients with temporal lobe epilepsy who had MR studies in 1990 and 1991 followed by lobectomy within 1 year. The patients have had follow-up of at least 1 year (mean, 21 months). The purpose of the study was to answer four questions: (*a*) What is the association of an MR abnormality and a good outcome after surgery? (*b*) What is the association of a PET abnormality and a good surgical outcome? (*c*) Does the combination of PET and MR result in greater sensitivity than that achieved with either test alone? (*d*) How well do MR and PET findings correlate with histopathologic findings of the resected tissue?

## Materials and Methods

Thirty-one consecutive patients who had been evaluated by MR and PET at Duke University for medically intractable temporal lobe epilepsy went on to have anterior

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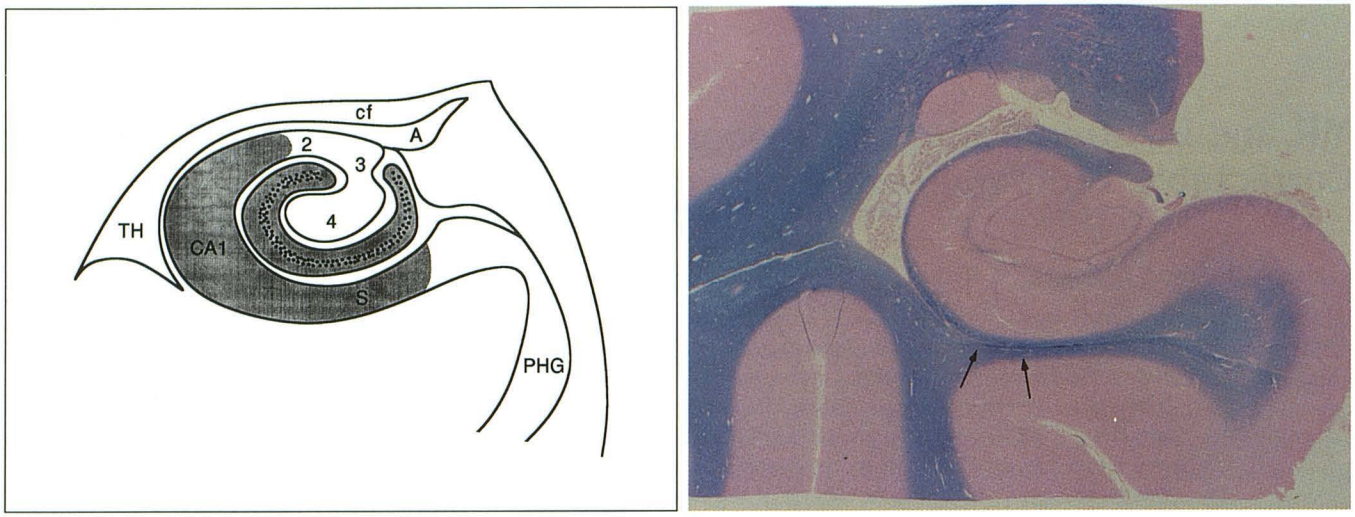



Fig 1. Temporal lobe and hippocampal anatomy.

*A*, Coronal section through the body of the right hippocampus and parahippocampal gyrus. Note that Sommer sector CA4 (designated 4 in drawing) invaginates the cuplike dentate gyrus. *A* indicates alveus; *Cf*, choroidal fissure continuous with temporal horn; *TH*, temporal horn; and *PHG*, parahippocampal gyrus.

*B*, Coronal section through body of the right hippocampus (hematoxylin and eosin stain) Note that CA4 and dentate gyrus are confluent. *Arrows* designate the collateral white matter.

temporal lobectomies in 1990 and 1991. These patients constitute the study group. In addition, because this study is directed more toward MR, 11 control subjects who had the same MR studies at the same time were included as MR controls. The control subjects had pseudoseizures or conversion reactions. Of the original 31 patients, 4 were excluded from the study, 1 because no PET scan was done and 3 because the surgery was modified in light of the imaging findings (1 local excision of a cavernous hemangioma, 1 limited resection and drainage of an encephalocele, and 1 resection of bilateral temporal lobe cysts), leaving 27 patients available for study. All patients were followed up for at least 1 year (mean, 21 months). There were 15 male and 12 female patients. Age at surgery ranged from 11 to 59 years (mean, 28.2 years); the duration of seizures ranged from 2 to 37 years (mean, 21.3 years).

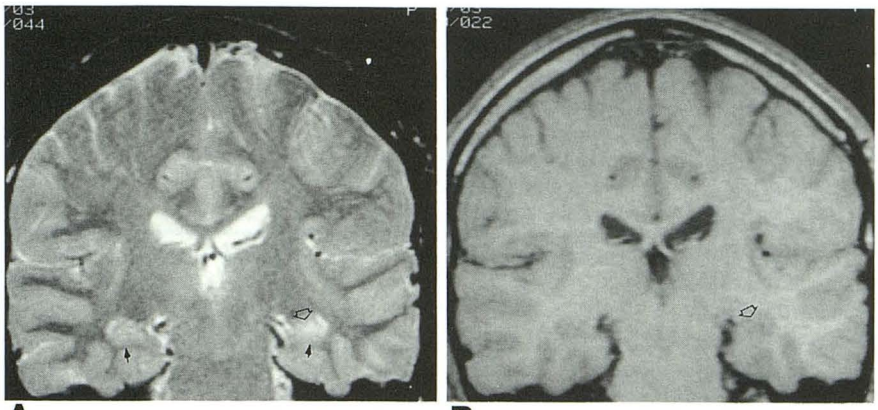
### *MR Studies*

Studies were performed on a 1.5-T magnet using spin-echo sequences in 1990. These consisted of axial and coronal T1-weighted images (500/25/1 [repetition time/echo time/excitations]) and T2-weighted images in both axial and coronal planes. Each section was 5 mm thick with a 2.5-mm intersection gap. The MR images of the temporal lobes of each patient were evaluated with regard to a series of parameters, and the findings recorded by each neuroradiologist independently. Studies were evaluated by two neuroradiologists, each blinded to all clinical and laboratory data. After the completion of each part of the study, the findings of the two neuroradiologists were compared; where significant differences were noted, the relevant images were reviewed, and a consensus finding adopted.

The signal intensity and volume of the head and body (Figs 1–3) of the hippocampus were assessed on each side and compared. Signal intensities were graded from 0 (normal) to +2 (significantly increased). Volumes were assessed as normal, increased, or decreased. In addition, the appearance of the collateral white matter was compared between the two sides. The collateral white matter refers to the white matter that lies between the collateral sulcis and the subiculum/CA1 sector of the hippocampus. The collateral white matter was rated as normal or abnormal; abnormality was defined as loss of the normal sharp demarcation of the gray/white matter boundary at the subiculum-CA1 junction, increased signal in the collateral white matter on T2-weighted images, or decreased volume of white matter (Figs 2 and 6).

Finally, each neuroradiologist made an overall assessment of each hippocampal complex, classifying it as either (*a*) normal, (*b*) abnormal or probably abnormal, or (*c*) indeterminate. This last category was reserved for cases with subtle or apparently contradictory findings. These overall assessments were correlated with the clinical outcomes after surgery, to determine the utility of the assessment method.

After the subjective analysis of the temporal lobe was completed, signal intensity of the hippocampus was measured by region-of-interest measurements of the hippocampi in nine patients with temporal lobe epilepsy who proved to have mesial temporal sclerosis. Circular cursors with an area of 4 $mm^2$ were centered on CA4 bilaterally. Similar measurements were made with seven of the control subjects; the data were no longer available on the



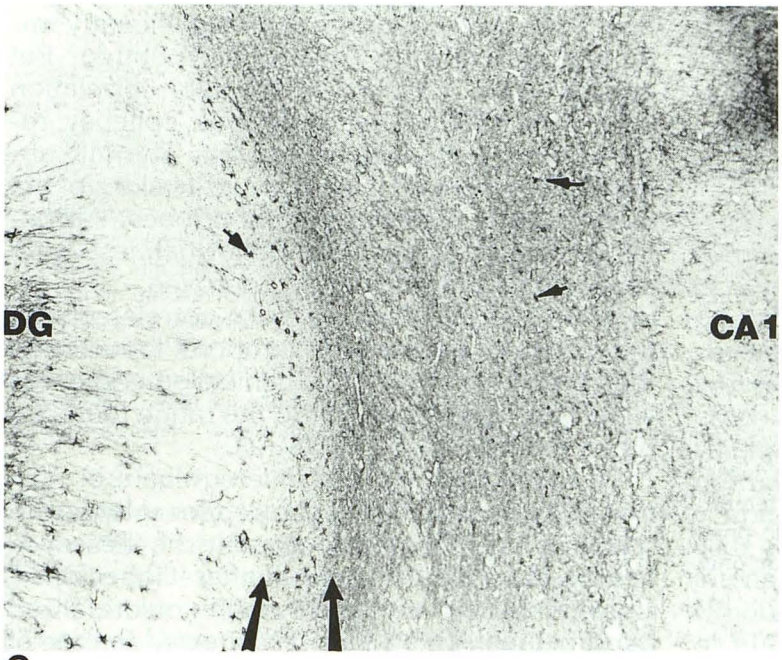




Fig 2. Case 1, 19-year-old man with mesial temporal sclerosis.

*A*, Spin-echo T2-weighted coronal image 2500/70. Note that the volumes of right and left hippocampi are equal; however, the signal of the left hippocampus is markedly increased (*large arrow*). In addition, the sharp margin between the hippocampus is lost, and the adjacent collateral white matter has increased signal (*arrow*). Compare with normal right side (*arrow*).

*B*, Spin-echo T1-weighted 500/20 coronal image also shows the left hippocampus to be as large or larger than the right.

*C*, Microscopy of hippocampus (×68). Section of hippocampus (CA1 and dentate gyrus, *left*) with dark-stained reactive astroglial cells (glial fibrillary acidic protein stain, *small arrows*). The glial cells are seen in the stratum oriens, stratum pyramidale, stratum radiatum, stratum lacunosum, and stratum moleculare. They are particularly well seen between the two *larger arrows*. This gliosis is thought to be responsible for the increased hippocampal signal on T2-weighted images. *CA1* indicates hippocampal area CA1; and *DG*, dentate gyrus.

remaining six patients with mesial temporal sclerosis and four control subjects. An exact version of the Wilcoxon Rank Sum Test was performed to test the difference in the median values between the groups.

### *PET Studies*

Fluorodeoxyglucose PET studies were performed on a PET scanner with a resolution of 8.6 mm full width at half-maximum. Patients fasted for 4 hours, and then received intravenous injections of 10 mCi of fluorodeoxyglucose. During the 30-minute uptake period, patients were kept in a quiet, dim room with their eyes open and ears unoccluded. Electroencephalographic monitoring during the uptake phase has been a part of our routine protocol. No patient in this study demonstrated electroencephalographic seizure activity during the uptake phase.

Patients were imaged along the canthomeatal line with a section thickness of 8 mm. A total of 12 to 15 images

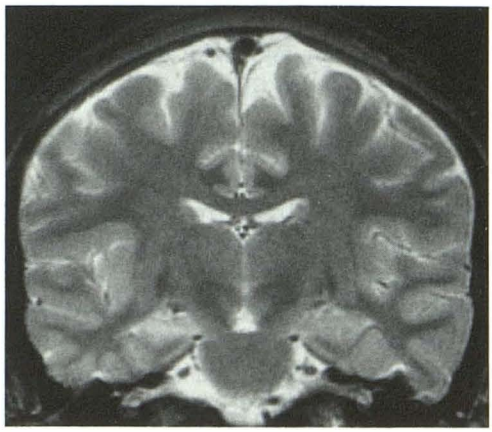


Fig 3. Case 2, 23-year-old man with right mesial temporal sclerosis. Spin-echo T2-weighted coronal image 2500/80. The right hippocampus is slightly smaller (mainly less vertical diameter) when compared with the left, and there is very high signal. This is the typical MR appearance of hippocampal sclerosis.

were obtained with interleaving over the temporal lobe regions. All PET studies were obtained early in the preoperative evaluation while patients remained on at least one anticonvulsant medication and before any major change in seizure frequency occurred.

Each study was analyzed visually by two observers who were not aware of any clinical information. When interpretations differed, a consensus opinion was reached upon joint review. To be judged significant, any metabolic asymmetry had to be apparent on at least two adjacent image planes and could not be a reflection of partial volume effect when correlated with MR. The observers rated the degree of hypometabolism on a five-point scale. The degree of hypometabolism served as the basis for labeling findings as normal or abnormal. For clinical purposes, studies scored as grade 4 (moderate asymmetry) or grade 5 (severe asymmetry) were considered abnormal studies; PET studies labeled as grade 1 (no asymmetry), grade 2 (minimal asymmetry), or grade 3 (mild asymmetry) were considered normal studies. These findings were then compared with the clinical outcome.

### *Histology*

The surgical specimens were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. A diagnosis of mesial temporal sclerosis was rendered when either focal or diffuse neuronal loss was qualitatively present in the CA subfields of the hippocampus. A single case with mild gliosis but no apparent neuronal loss was categorized with the normal histology cases. In three cases with signal abnormalities in the collateral white matter, an immunohistochemical stain for glial fibrillary acidic protein was performed. All diagnoses were reviewed by one neuropathologist.

### *Clinical Outcome*

Patients were considered seizure-free if they had no clinical seizures (excluding auras). Patients were considered clinically improved if they had fewer than 10 seizures per year and at least a 90% reduction in seizures from the preoperative year.

## Results

### *Outcome*

A structural temporal lobe abnormality was identified with MR in 20 of the 24 improved patients with temporal lobe epilepsy. Seven patients were evaluated as indeterminate or normal; 3 of these 7 patients did not improve. Thirteen of the 15 patients with mesial temporal sclerosis were identified by MR; 13 had hippocampal volume loss (both observers); 13 had increased signal (both observers); and 5 had abnormal collateral white matter (both observers).

**Correlation of pathology with abnormal findings on MR and PET**

| | MR+ | PET+ |
|---|---|---|
| Mesial temporal sclerosis (n = 15) | 13 | 12 |
| Ganglion cell tumor (n = 2) | 2 | 2 |
| Pilocytic astrocytoma (n = 1) | 1 | 0 |
| Hamatoma (n = 1) | 1 | 1 |
| No pathologic diagnosis (n = 7) | 2 | 4 |

Note.—Hippocampal tissue was not available in one patient.

The most important result of this study is that MR showed an abnormality in 83% of the patients who were seizure-free or significantly improved at follow-up (mean, 21 months). Put another way, MR showed an 83% correlation with patients with temporal lobe epilepsy responsive to temporal lobectomy. The MR abnormalities were all ipsilateral to the sides of the subsequently resected temporal lobes. All patients with definite MR abnormalities were seizure-free or significantly improved.

When the PET findings were correlated with the clinical outcome after temporal lobectomy, the correlation with a good clinical outcome was 71%. This figure is similar to the range found by other authors (70% to 80%)(2).

Of seven patients with indeterminate or normal findings on MR, four showed focal hypometabolism on PET. However, one of these patients did not improve after lobectomy. Conversely, of nine patients with nonlateralized hypometabolism on PET, six showed unilateral focal abnormalities on MR.

If an abnormality on either MR or PET was taken as a "positive" imaging study, the correlation with this combined test for lobectomy-responsive temporal lobe epilepsy was 23 of 24 or 96%.

### *Histopathology*

MR showed 89.5% correlation with histologic abnormality. Previous experience has shown that there may be a good clinical outcome in some patients with temporal lobe epilepsy after temporal lobectomy even when no definite disease is identified in the resected tissue; that was also noted in this series. PET showed a correlation of 71% with a histologic abnormality.

Imaging findings correlated with histopathologic diagnoses are tabulated in the Table. In the 15 patients with mesial temporal sclerosis (58%

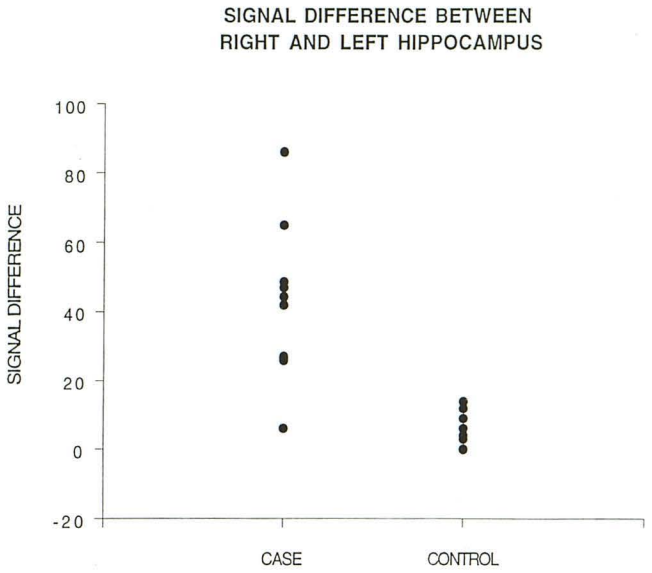



Fig 4. Patients with mesial temporal sclerosis on the *left* (case); control subjects are on the *right*. Each *circle* represents the difference between the signal in the right and left temporal lobes as measured by MR region-of-interest raw numbers. In all the patients with higher signal in one lobe, that lobe was determined to be the lobe with disease. The one patient who had a small difference between the lobes was identified as "abnormal" by decreased volume on MR. Determination of signal region-of-interest values could not be performed on the remaining seven patients with mesial temporal sclerosis, because their data were no longer available. Wilcoxon Rank Sum Test, $P = .0012$.

of our temporal lobe epilepsy group; 79% of those with a histologic abnormality), 13 of the 15 MR studies showed hippocampal volume loss. Thirteen of the 15 showed increased hippocampal signal on T2-weighted images. This increased signal was thought to be related to the finding of gliosis confirmed by glial fibrillary acidic protein staining (Fig 2). Region-of-interest analysis on 9 of these patients with mesial temporal sclerosis confirmed increased signal in the hippocampus where increased signal had been recorded earlier based on qualitative visual analyses. Region-of-interest data were unavailable on the 6 remaining patients with mesial temporal sclerosis (Fig 4). Seven of the 15 patients showed abnormalities of the collateral white matter (loss of the sharp corticomedullary junction line, slight increased signal on T2-weighted images, or volume loss). These collateral white matter changes, corresponding to astrocytosis at the gray-white matter junction (Figs 2 and 3) were seen only in the patients who also had increased hippocampal signals. PET disclosed focal hypometabolism in 12 of the 15 patients with mesial temporal sclerosis.

All four patients with neoplasms or hamartomata involving the hippocampus were identified as having mass lesions on MR.

All 11 of the control subjects were assessed as normal on MR. Seven of these controls had signal region-of-interest recordings of the hippocampi; none showed a significant disparity between the two sides (Fig 4).

Three of the 27 patients were not significantly improved after temporal lobectomy. Of these, 2 showed no abnormality on MR, PET, or histologic examination of the resected temporal lobe. One had normal MR findings, but showed lateralized temporal lobe hypometabolism on PET; the resected ipsilateral temporal lobe showed the histologic features of mesial temporal sclerosis.

## Discussion

Engle et al originally developed the standard technique for fluorodeoxyglucose PET location of a structural abnormality causing complex partial seizures (2); the ipsilateral temporal lobe showed decreased emission in 78% of patients interictally. Laster et al demonstrated that MR could show an abnormality in the temporal lobe when the computed tomographic findings were normal (3). In 1986, Radtke and colleagues described MR abnormalities in 12 of 22 patients with complex partial seizures, including hyperintense T2 signal in the mesial temporal lobe (Radtke et al, Usefulness of MRI in the Presurgical Evaluation in Intractable Complex Partial Seizures, American Epilepsy Proceedings, November 1986). In the following year, Kuzniecky et al described similar MR changes in 65% of patients with temporal lobe epilepsy (4). Heinz et al confirmed the presence of increased signal intensity in the hippocampus on coronal T2-weighted images (5) and correlated the abnormal hippocampal signal with the pathologic findings in 39 patients (6). In a later report, comparing MR with PET in 30 patients with temporal lobe epilepsy, MR findings were abnormal in 54% (7).

Bronen et al described decreases in hippocampal volume, best seen on coronal T1-weighted images, which showed good correlation with the presence of surgically resectable seizure foci in nine patients (8). Most of these patients (eight of nine) also showed increased signal in the hippocampus. Jack et al (9), using a computer-assisted volumetric method, identi-

fied temporal lobe losses, consistent with atrophy, in patients with temporal lobe epilepsy.

Despite the recent improvement in the detection rate with MR, PET studies have remained more sensitive in the detection of temporal lobe seizure foci. Schwartz (10) reported PET sensitivities of 85% overall, with MR sensitivity of 67% in 34 patients subjected to lobectomy. They stated that "PET was only slightly more sensitive than MR." Ninety-five percent of their patients were seizure-free or significantly improved after lobectomy. Theodore (11) reported 26 patients (81%) with abnormal PET scans. Five of 22 improved patients (23%) had abnormal MR scans. However, because these were patients sent to the National Institutes of Health clinical center, there may have been considerable preselection of patients treated locally who had abnormal MR scans. A recent comparative study (7) yielded a detection rate of 78% for PET, compared with 54% for MR, using MR criteria of focal hippocampal atrophy and signal hyperintensity.

In the present study, we compared MR and PET findings with the clinical outcome after temporal lobectomy. The MR studies were abnormal in 20 of the 24 patients in whom lobectomy improved seizure control; MR was normal or indeterminate in 3 patients who failed to improve with lobectomy. The correlation of MR with prediction of clinical improvement was 83%. PET was also interpreted as diagnostic in 17 of the 24 patients successfully operated on, for a sensitivity of 71%. The sensitivity of PET in this study is comparable with earlier studies, but that of MR represents a significant improvement from previous reports.

When the MR and histologic findings were correlated, MR abnormalities were identified in 17 of the 19 patients with histopathologic lesions (90%).

If the preoperative imaging assessment included both MR and PET, with abnormalities on either study being taken as positive findings, the correlation of this combined test was 91% with prediction of a good clinical outcome.

Because mesial temporal sclerosis is the most common pathologic diagnosis in our series (79%), it is helpful to review the imaging characteristics in this lesion. Volume loss was common (13 of 15; 87%). The decrease in volume is usually manifested as a loss of height of the hippocampus seen in the coronal view (Figs 2 and 3). Increased signal on T2-weighted images was noted (Figs 1–3) in 13 of 15 patients (86%). One patient with mesial temporal sclerosis was identified because of signal increase without the volume loss (Fig 2); in 4 other patients with mesial temporal sclerosis, the increased signal was markedly more prominent than the volume loss. The increased signal was measured by region of interest in several of these patients with mesial temporal sclerosis (Fig 4). This increased signal was particularly helpful when asymmetry of the hippocampi (Fig 5), which was not uncommon, made comparison very difficult. One patient was identified because of volume loss without significant signal change.

Changes in the collateral white matter were frequently an additional aid in the diagnosis of mesial temporal sclerosis; abnormalities were detected in 7 of the 15 cases (47%). The changes consist of loss of the sharp margin between the subiculum, CA1, and the subjacent collateral white matter on T2-weighted images and, in severe disease, decreased volume of the white matter (Figs 3 and 6). This finding may be called the "collateral white matter sign." These findings have not previously been reported; they seem to correlate with reactive astrocytosis at the gray-white matter junction (Figs 2A and 6A). Collateral white matter abnormalities are particularly useful in assessing whether asymmetric hippocampi, or those with subtle decreases in height, truly indicate disease. In such cases, evaluation of the collateral white matter and the hippocampal signal intensity on T2-

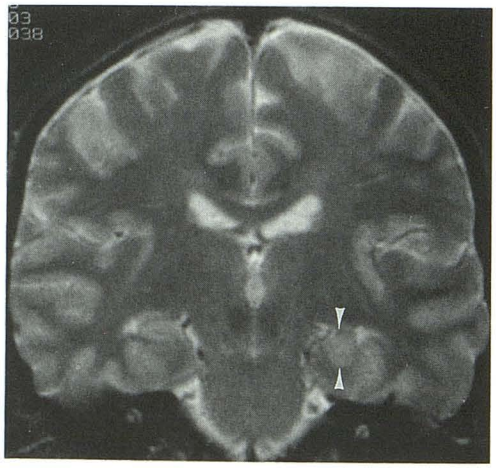


Fig 5. Thirty-one-year-old male control subject. T2-weighted image 2500/80. Note asymmetry between right and left hippocampi. Because left is globoid, one could question whether right has decreased volume. However, there is no signal abnormality, and collateral white matter is normal.

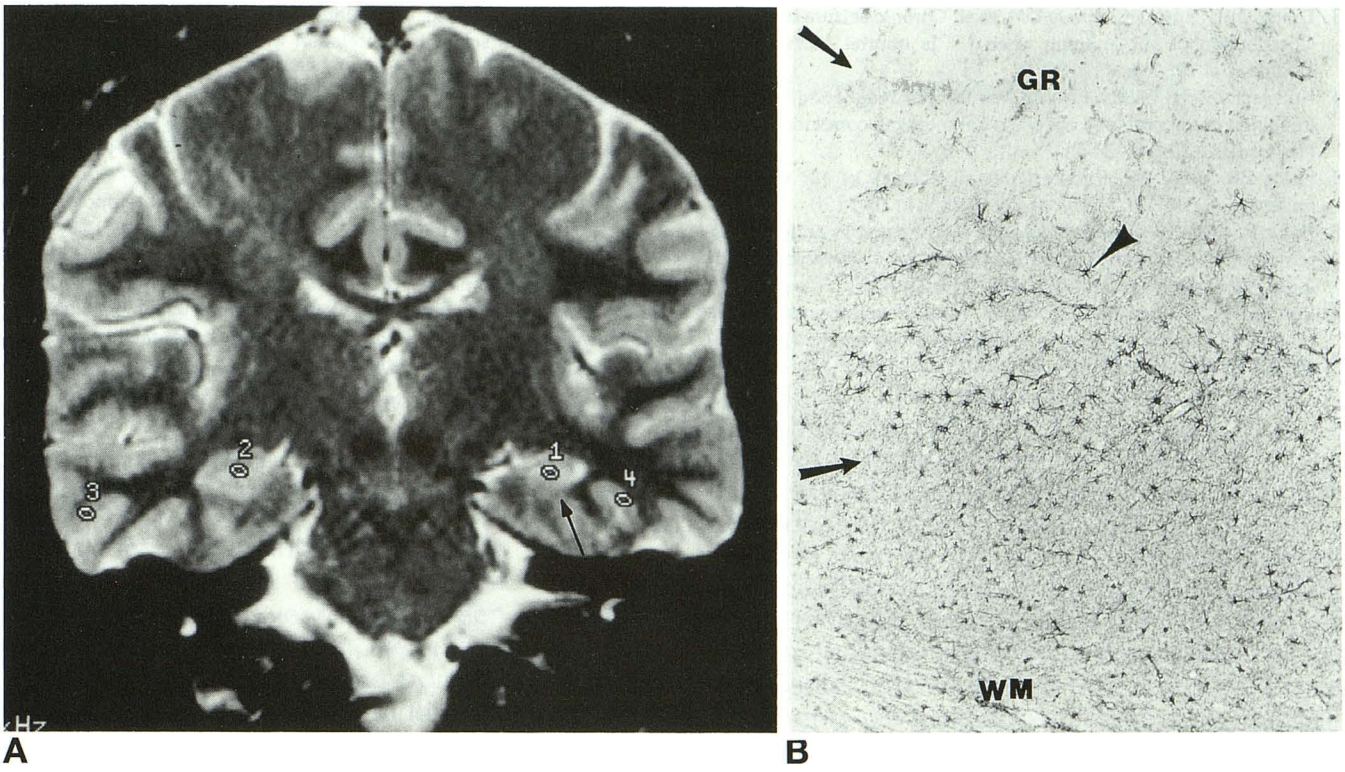



Fig 6. Case 3, 31-year-old man with mesial temporal sclerosis.

*A*, T2-weighted image (2500/80). Decreased volume, increased signal left hippocampus. Cursors (2 $mm^2$) 1 (left) and 2 (right) are placed in the center of hippocampus (CA4 area). Region of interest: right side, 416 ± 20; left side, 481 ± 17. The basal margin of the left hippocampus is indistinct (*arrow*). This is the collateral white matter sign.

*B*, Microscopic section of hippocampal area CA1-collateral white matter (×68). Note the dark staining reactive astroglial cells (*arrowhead*) at the junction between CA1 (*top*) and adjacent collateral white matter (*bottom*). The *double arrows* bracket the gray-white junction, where the reactive cells are most numerous. Section is prepared with glial fibrillary acidic protein stain to emphasize these glial cells, which are thought to cause the indistinct margin between hippocampus and nearby white matter—the collateral white matter sign. *GR* indicates gray matter; and *WM*, white matter.

weighted images may improve the detection rate of MR.

In the four patients with tumors or hamartoma, the diagnosis of a mass lesion was readily made on the basis of distorted anatomy, focal volume increases, and focal signal abnormalities (T2 hyperintensity). All four cases showed focal volume increases, and three of the four had signal abnormalities.

In the seven patients in whom no diagnosis could be made histologically, MR showed volume abnormalities in three, but none had a definite signal abnormality.

In summary, our findings suggest that MR now has a high sensitivity for the detection of temporal lobe abnormalities that are responsive to surgery for control of temporal lobe epilepsy; in this study it is at least comparable to PET. This improved MR capability has significant international health implications, because MR facilities are widespread, and PET facilities are very limited in number. The MR findings are based on decreased hippocampal volume, increased signal, and, to a lesser extent, indistinct collateral white matter. The signal increases noted in the visual evaluation could be confirmed on region-of-interest measurements. When MR and PET are used together, the predictive value for good postsurgical outcome is better than for either examination alone.

## Acknowledgment

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