Surgery is a safe and effective treatment for drug-resistant temporal lobe epilepsy (TLE). However, bilateral electroencephalographic (EEG) abnormalities are frequently present, making presurgical lateralization difficult. New magnetic resonance (MR) techniques can help; proton magnetic resonance spectroscopic imaging (MRSI) can detect and quantify focal neuronal damage or dysfunction based on reduced signals from the neuronal marker N-acetylaspartate, and magnetic resonance imaging (MRI)-based measurements of amygdala-hippocampal volumes (MRIVol) can improve the detection of atrophy of these structures. We performed proton MRSI and MRIVol in 100 consecutive patients with medically intractable TLE to determine how well these techniques agreed with the lateralization by extensive EEG investigation. We found that the EEG, MRSI, and MRIVol findings were highly concordant. The MRSI was abnormal in 99 of 100 patients (bilateral in 54%). The MRIVol was abnormal in 86 of 98 patients (bilateral in 28%). We obtained lateralization in 83% of patients using MRIVol alone, in 86% using MRSI alone, and in 90% by combining MRSI and MRIVol (vs 93% lateralization by EEG). MRSI was abnormal in 12 patients with normal MRIVol. The combination of proton MRSI and MRIVol can lateralize TLE accurately and noninvasively in the great majority of patients. By reducing reliance on EEG, these imaging techniques could reduce prolonged presurgical evaluation and make seizure surgery available to more patients.

demonstrated by subsequent histopathology [9–12, 16, 17, 21]. However, there remains a significant proportion of patients with TLE in whom no MRI changes can be detected.

Unlike conventional MRI, which provides structural information based on signals from water, proton magnetic resonance spectroscopic imaging (MRSI) provides spatially encoded chemical information, thus enabling the noninvasive assay of regional chemical composition [22–25]. Proton magnetic resonance spectra of normal human brain reveal a major resonance at 2.0 parts per million (ppm), from N-acetyl groups that originate largely from N-acetylaspartate (NAA), a compound localized exclusively in neurons and neuronal processes [26, 27]. Recent proton MRS studies have shown reduced signals from NAA, reflecting focal neuronal loss or damage in most patients with TLE [23, 28–35]. Thus, proton MRSI has promise for becoming an important part of the study of TLE.

We studied a large series of patients with TLE being evaluated for seizure surgery, to determine how lateralization based on proton MRSI and MRIVol alone or in combination would concur with lateralization by EEG.

Patients and Methods

We studied 100 consecutive epileptic patients being evaluated for medically refractory TLE who had no mass lesions on conventional MRI. Accurate identification of the type and localization of the seizures was determined by a comprehensive evaluation including a detailed history and neurological examination, serial EEGs with sphenoidal electrodes, and intensive video-EEG telemetry for recording of seizures [2, 4].

Informed consent was obtained from all subjects. This study is part of a research project approved by the Ethics Review Committee of the Montreal Neurological Institute and Hospital.

Electroencephalographic Investigation

Prolonged EEG recordings, using the International 10-20 system including sphenoidal electrodes, and long-term video-EEG monitoring were performed initially to record at least three habitual seizures in all patients. If discrepancies arose between the localization of ictal and interictal abnormalities, if EEG seizure discharges could not be localized due to movement or muscle artifacts, or if ictal behavioral manifestations strongly indicated a possible seizure generator in extratemporal structures (for example, elementary visual hallucinations), patients underwent intracranial EEG recordings with stereotactically implanted depth electrodes (SEEG). In these patients, the lateralization was defined according to the ictal onset during SEEG investigation. Twenty patients underwent SEEG investigation because the extracranial EEG recordings did not provide clear localization or lateralization of seizure onset. All these patients had SEEG seizure onsets in the temporal lobe regions.

Patients were classified according to the localization of EEG seizure onsets preceding the first clinical manifestations as (1) unilateral Left (L) or Right (R), if more than 90% of ictal onsets were unilateral or clearly lateralized to the left or right side, respectively; (2) L > R or R > L, if more than 70% of ictal onsets lateralized to the left or right side, respectively; or (3) bilateral (L = R), if less than 70% of ictal onsets lateralized to one side.

The electroencephalographers were unaware of the MRSI and MRIVol results before they reported the EEG findings.

Proton Magnetic Resonance Spectroscopic Imaging

Conventional MRI scans, as well as two-dimensional proton MRSI scans, were acquired by using either a 1.5-T ACS II or III imaging/spectroscopy system (Philips Medical Systems, Best, The Netherlands).

After scout images in axial and sagittal planes, multislice spin echo MRIs (repetition time [TR] 2,000 msec, echo time [TE] 30 msec) were obtained in the transverse plane along the axis of the temporal lobes and in the coronal plane perpendicular to the axis of the sylvian fissure. A large region of interest (ROI) behind the clivus, including both temporal lobes and excluding bone, was defined for selective excitation before phase encoding for the proton MRSI. The ROI was oriented in a similar position for all examinations to cover the entire extension of both hippocampi (85–100 mm left–right × 75–95 mm anteroposterior × 20-mm thickness) (Fig 1). A water-suppressed proton MRSI was obtained from that ROI by using a 90°-180°-180° pulse sequence with a 2-second interpulse delay (TR 2,000 msec, TE 272, 250 × 250-mm field of view [FOV], 32 × 32 phase-encoding steps), followed by a proton MRSI without water suppression (TR 850, TE 272, 250 × 250-mm FOV, 16 × 16 phase-encoding steps). After zero-filling the latter to 32 × 32 profiles, the water-suppressed MRSI was divided by the non-water suppressed MRSI to correct for artifacts resulting from magnetic field inhomogeneity. The resulting time domain signal was left shifted and subtracted from itself to improve water suppression [36]. This reduces the amplitude of creatinine (Cr) as well as water and results in relatively high ratios of NAA/Cr; however, this is consistent for all the control data and patient data. To enhance the resolution of the spectral peaks, a Lorentzian–Gaussian transformation was applied before Fourier transformation in three dimensions. The nominal voxel size in plane was approximately 8 × 8 mm and 12 × 12 mm after K-space filtering.

Resonance intensities on MRSIs were determined from peak areas by integration, using locally developed software. The values for NAA, choline (Cho), Cr, and NAA/Cr were determined for the middle (Mid) and posterior (Post) regions of each temporal lobe by averaging 12 ± 3 spectra in each region (Figs 1 and 2). We divided the temporal lobes into two anatomical regions, to avoid averaging too many voxels and to increase the likelihood of detecting more focal abnormalities. Spectra were excluded from the analyses if they were artifactually broadened (ie, full width at half maximum > 10 Hz) or if the Cho and Cr peaks were not resolved.

The intensity ratio NAA/Cr was used to simplify quantitation across patients. The observations do not depend on Cr being a stable internal reference. However, if Cr is assumed to be stable or only slightly changed in brain regions associ-
Fig 1. Proton magnetic resonance spectroscopic imaging (MRSI) region of interest. Conventional (water-based) axial T1-weighted magnetic resonance imaging through the temporal lobes with the original phase-encoding grid superimposed. The region of interest (ROI) for acquisition of the MRSI is outlined by the thick white line. Each temporal lobe inside the ROI is subdivided into two anatomical regions. One most anterior, defined as middle temporal (black line), comprises the region of the head and body of the hippocampus (lower arrow) and surrounding structures. The second, defined as posterior temporal (dashed line), includes the tail of the hippocampus and the medial aspect of the posterior temporal lobe. The pole of the temporal lobe and the amygdala (upper arrow) are not included in the ROI, to avoid artificial interference from the bone and fat tissue from the clivus and sphenoid bone.

ated with epileptic damage (which is a reasonable assumption) [23, 28, 33, 35], the decreases in the ratio NAA/Cr can be interpreted in terms of axonal loss or damage, which is useful for understanding the pathogenesis of TLE [23, 28–34].

Patient average NAA/Cr values for each side were compared with each other as well as with the values obtained in 21 healthy normal controls (12 men and 9 women; mean age, 28.2 years; SD = 4.5). A normalized measure of asymmetry of the signal intensity between the two temporal lobes was defined as (Left − Right)/[(Left + Right)/2].

Magnetic Resonance Imaging

The MRI volumetric measurements were performed by using two acquisition protocols. For the first 34 patients, due to constraints imposed by our MR system at the time, we acquired 3-mm contiguous slices perpendicular to the plane of the sylvian fissure, with a three-dimensional (3D) fast-field echo (FFE) or an inversion recovery (IR) sequence. For the subsequent 64 patients, we acquired 1-mm-thick slices by using a 3D FFE sequence with isotropic voxels. Two patients did not have MRIVol. The images were transferred to a computer workstation and the ROIs were outlined, using a locally developed interactive software program [16, 37]. Volumes were compared with age-matched healthy volunteers who had the same MRI acquisition protocol (n = 30 for 3-mm-thick [17 men and 13 women; mean age, 32.4 years, SD = 11.3] and n = 22 for 1-mm-thick MRIs [12 men and 10 women; mean age, 29.5 years, SD = 10.2]). We analyzed the absolute volume of the amygdala (AM) and hippocampal formation (HF) as well as the asymmetry between sides ((Right − Left)/(Right + Left)/2)). The anatomical guidelines used for identification and segmentation of the AM and HF have been described by Watson and colleagues [37].

Statistical Analysis

GROUP COMPARISONS. We performed analyses of variance (ANOVAs) to compare all six groups [38]. We then performed post hoc comparisons using Tukey's HSD (honestly significant difference) test to compare all possible pairs of groups [39].

CLASSIFICATION OF INDIVIDUAL PATIENTS BASED ON MRSI OR MRIVOL ALONE. In addition to the group differences, we also determined how accurately MRSI and MRIVol, alone or in combination, were able to lateralize each patient. For the classification of individual patients, we combined the "Left" and "L > R" EEG groups into one "Left-TLE" group and the "Right" and "R > L" EEG groups into one "Right-TLE" group. For the analysis of individual subjects, we considered values 2 SD below the mean of the control group to be abnormal. Abnormalities in either region were counted. We classified patients, based on their right-sided, left-sided, and right–left asymmetry values on each examination, as follows: Lateralized (left or right): (1) abnormal values from one side only, or (2) abnormal values from both sides with significant asymmetry, or (3) normal values on both sides (within 2D of controls), but abnormal asymmetry ratio; bilateral without lateralization: abnormal values on both sides without significant asymmetry; or normal: values from both sides and asymmetry index within normal range.

COMBINATION OF MRSI AND MRIVOL. Results from MRSI and MRIVol examinations, using the criteria defined above, were tabulated. The classification for each patient was defined as follows: Lateralized (left or right): (1) both MRSI and MRIVol are lateralized to the same side, or (2) either MRSI or MRIVol is lateralized and the other is normal or bilateral; bilateral without lateralization: (1) both MRSI and MRIVol are bilateral, or (2) either MRSI or MRIVol is bilateral and the other is normal; or normal: both MRSI and MRIVol are normal.

CORRELATION BETWEEN MRSI AND MRIVOL. We performed Pearson correlation analyses between MRIVol and
Normal control                  Patient with Left TLE

![Illustrative spectra from a normal control and a patient with left temporal lobe epilepsy (TLE). Each spectrum represents the average of 12 ± 3 voxels from the middle temporal regions of the left and right temporal lobes. Note the relatively low N-acetylaspartate (NA) resonance in the left side of this patient with left TLE. TL = temporal lobe; Mid = middle; Cho = choline; Cr = creatinine.]

MRSI by using Z scores of absolute values and asymmetries in NAA/Cr, AM, and HF volumes.

Results
The 100 patients were comprised of 45 men and 55 women (mean age, 35.1 ± 12.4 years).

Clinical-EEG Investigation
According to the criteria described above, the TLE in the 100 patients was classified as left (n = 47), L > R (n = 21), right (n = 19), R > L (n = 6), and bilateral (n = 7).

Magnetic Resonance Spectroscopic Imaging
GROUP DIFFERENCES. The ANOVAs for NAA/Cr Mid and NAA/Cr Post values from both temporal lobes showed a significant difference between the normal control individuals (n = 21) and the five groups of patients (based on the EEG), with F = 20.4 and p < 0.0001 (Fig 3).

POST HOC PAIRWISE COMPARISONS. The NAA/Cr values for Mid and Post temporal lobe ipsilateral to the main EEG focus from all TLE groups were significantly different from controls (p < 0.001). The NAA/Cr values for the contralateral temporal lobe were also lower than controls, but this was not significant for the Right-TLE (Mid and Post temporal lobe) and Left-TLE (Post temporal lobe) groups, which were comprised of patients with the least bilateral EEG abnormalities. The more unilateral were the EEG abnormalities, the more asymmetric were the MRSI abnormalities.

The asymmetry ratios were less pronounced in patients with more frequent bilateral (ictal and interictal) EEG abnormalities (R > L and bilateral groups versus controls, p > 0.5; and L > R group versus controls, p = 0.02) compared with patients with more unilateral EEG abnormalities (Left- and Right-TLE groups versus controls, p < 0.0001) (see Fig 3).

ANALYSIS FOR INDIVIDUAL PATIENTS. The NAA/Cr values were abnormally low in at least one temporal lobe in all but 1 patient and were low bilaterally in 54% (considering both Mid and Post temporal lobe regions). There was a lateralized abnormality in 86% of patients, ie, 84 of 93 patients who had lateralization by ictal EEG and 2 of 7 patients who had no definite EEG lateralization. In addition, 12 patients with normal MRIVol had reduced NAA/Cr values in a temporal region; 7 of them underwent surgery, and pathological examination of the resected tissue revealed mild astrogliosis and neuronal loss of mesial temporal structures based on a qualitative histopathological evaluation [6–8] (see Table 1).

NAA/Cr was abnormal in 96 of 100 patients in the Mid temporal lobe and in 85 of 100 patients in the Post temporal lobe region.

MRI Volumetric Studies
GROUP DIFFERENCES. To make the values from our two acquisition protocols comparable, we transformed...
AM and HF volumes from the two MRI acquisition protocols (3-mm and 1-mm thickness) into Z scores (standardized scores that express the original raw score as a deviation from the mean of the appropriate control group in units of that control group's standard deviation).

The HF Z scores are presented in the form of a box and whiskers plot in Figure 4.

There was a significant difference among the six groups' HF Z scores, both on the left ($F = 18.8, p < 0.0001$) and on the right side ($F = 18.1$ and $p$ <
The six groups also differed in their left AM Z scores ($F = 9.6$, $p < 0.0001$) but not in their right AM Z scores ($F = 2.0$, $p = 0.08$).

**POST HOC PAIRWISE COMPARISONS.** For all groups, except for the bilateral TLE group, HF Z scores ipsilateral to the main EEG focus were significantly lower than in controls ($p < 0.05$). The HF Z scores contralateral to the EEG focus, however, did not differ from controls ($p > 0.5$). The bilateral TLE group had significantly lower Z scores than controls for both the left and the right HF ($p < 0.003$). HF asymmetry ratios were significantly different from controls in the Left-TLE and Right-TLE (both $p < 0.0001$) and L > R TLE ($p = 0.01$) groups but not in the R > L TLE and bilateral TLE groups ($p > 0.5$) (see Fig 4).

AM Z scores were significantly different from controls only for the ipsilateral temporal lobe in the Left-TLE ($p < 0.001$), L > R TLE ($p < 0.001$), and Right-TLE ($p = 0.02$) groups. In a similar manner, the AM asymmetry ratios were significantly different from controls in only the Left-TLE ($p < 0.001$), L > R TLE ($p = 0.02$), and Right-TLE ($p < 0.01$) groups.

In summary, the more unilateral the EEG abnormalities, the more asymmetric the MRIVol abnormalities were in both the AM and the HF.

**ANALYSIS FOR INDIVIDUAL PATIENTS.** The AM–HF volumes combined were abnormal in 86 of 98 (87.7%) patients. The AM–HF atrophy was bilateral in 27 (28%) patients; there was no lateralization in 5 of these patients. The AM–HF volumes were normal in 12 patients; all these 12 patients had lateralized MRSI abnormalities in agreement with the lateralization by EEG (Table 1).

The AM volumes alone were abnormal in 58 of 93 (62.4%) patients, and the HF volumes alone were abnormal in 84 of 98 (85.7%) patients.

We found no significant difference for the MRIVol lateralization in the patients who had 3-mm-thick MRI slices (28 of 34, 82.4%, lateralized) versus the group with 1-mm slices (53 of 64, 83%, lateralized). This lack of a difference between the overall lateralization, using these two protocols, may reflect differences in the clinical characteristics of the two groups of patients, rather than the sensitivity of measurements performed on 3-mm versus 1-mm-thick images in general. Increased sensitivity of thin slices is expected mainly in patients with subtle atrophy that would be missed with the use of 3-mm-thick slices. Proper comparison of the effect of slice thickness on sensitivity requires making both measurements in the same subjects. We have done this in a small group of patients and normal controls and found an increased sensitivity, using 1-mm-thick slices, that was greater for AM volumes than for HF volumes. This increase was due, at least in part, to less variation in the normal control data (data not shown here).

**Proton MRSI and MRIVol Interrelationships**

Z scores for absolute values and asymmetries in NAA/Cr and AM and HF volumes were highly interrelated and concordant (Table 2).

**Combination of MRSI and MRIVol**

All 98 patients (2 patients did not have MRIVol available) were classified as abnormal, ie, 88 of 98 (90%) as unilateral and 10 of 98 (10%) as bilateral. Only 1 patient was lateralized contralateral to the EEG classification (see Table 1).

**Results in Disagreement with EEG**

There were 4 patients who had some imaging results in disagreement with the EEG investigation. One patient had both MRIVol and MRSI lateralization opposite to the EEG, 2 patients had only MRIVol, and another 1 had only MRSI lateralization contralateral to the EEG (see Table 1).

One patient had MRSI (both for Mid and Post temporal regions) and MRIVol (right HF atrophy and normal AM volumes) lateralization to the right temporal lobe, whereas intracranial EEG investigation revealed a clear predominance of seizure onsets from the left mesial temporal structures. This patient underwent a left

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**Table 1. Classifications Based on Normal Control Cutoffs (Mean – 2 SD)**

<table>
<thead>
<tr>
<th>MR Examination</th>
<th>Bilateral on EEG</th>
<th>Left on EEG</th>
<th>Right on EEG</th>
<th>Normal (%)</th>
<th>Abnormal (%)</th>
<th>Lateralization with EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRIVol (n = 98)</td>
<td>1 2 1 3</td>
<td>3 4 6 3</td>
<td>1 0 5 19</td>
<td>12 (12)</td>
<td>86 (88)</td>
<td>81 (83)</td>
</tr>
<tr>
<td>MRSI (n = 100)</td>
<td>5 1 1 3</td>
<td>7 5 1 2</td>
<td>1 0 0 24</td>
<td>1 (1)</td>
<td>99 (99)</td>
<td>86 (86)</td>
</tr>
<tr>
<td>MRIVol + MRSI (n = 98)</td>
<td>2 2 0 3</td>
<td>7 5 0 1</td>
<td>1 0 0 24</td>
<td>0 (0)</td>
<td>98 (100)</td>
<td>88 (90)</td>
</tr>
</tbody>
</table>

MR = magnetic resonance; EEG = electroencephalography; Bilat = bilateral; NI = normal; MRI = magnetic resonance imaging; MRIVol = MRI volumetric analysis; MRSI = proton magnetic resonance spectroscopic imaging.
Table 2. MRSI and MRIVol Intercorrelations

<table>
<thead>
<tr>
<th>Left-Sided Measures</th>
<th>Left NAA/Cr Post</th>
<th>Left HF Z Score</th>
<th>Left amygdala Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMCr</td>
<td>0.64 (p &lt; 0.0001)</td>
<td>0.31 (p = 0.004)</td>
<td>0.13 (p = 0.228)</td>
</tr>
<tr>
<td>Post</td>
<td></td>
<td>0.26 (p = 0.015)</td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td></td>
<td>0.56 (p &lt; 0.0001)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right-Sided Measures</th>
<th>Right NAA/Cr Mid</th>
<th>Right NAA/Cr Post</th>
<th>Right HF Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMCr</td>
<td>0.79 (p &lt; 0.0001)</td>
<td>0.30 (p = 0.005)</td>
<td>0.12 (p = 0.261)</td>
</tr>
<tr>
<td>Post</td>
<td></td>
<td>0.14 (p = 0.193)</td>
<td>0.47 (p &lt; 0.0001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left-Right Asymmetry Values</th>
<th>NAA/Cr Mid Asymmetry</th>
<th>NAA/Cr Post Asymmetry</th>
<th>HF Asymmetry</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS NMCr Post asymmetry</td>
<td>0.68 (p &lt; 0.0001)</td>
<td>0.51 (p &lt; 0.0001)</td>
<td>0.84 (p &lt; 0.0001)</td>
</tr>
<tr>
<td>AS HF asymmetry</td>
<td>0.55 (p &lt; 0.0001)</td>
<td>0.54 (p &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>AS Amygdala asymmetry</td>
<td>0.43 (p &lt; 0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pearson product-moment correlation analyses.

MRSI = proton magnetic resonance spectroscopic imaging; MRIVol = magnetic resonance imaging volumetric analysis; NAA = N-acetylaspartate; Cr = creatinine; Mid = middle; Post = posterior; HF = hippocampal formation.

Discussion

We compared the lateralization of TLE by MRSI, MRIVol, and the combination of the two, using EEG lateralization as the "gold standard." We found that the EEG, MRSI, and MRIVol results were highly concordant. The MRSI was abnormal in 99 of 100 patients (bilateral in 54%) and the MRIVol was abnormal in 86 of 98 patients (bilateral in 28%). Proton MRSI alone lateralized 86% of patients, and MRIVol alone lateralized 83% of patients. The combination of the two MR techniques lateralized 90% of patients (vs 93% lateralization by EEG).

Choice of Outcome Measure

We elected to use EEG seizure localization as the standard against which data obtained by proton MRSI and MRIVol were compared, realizing that the EEG may not have always provided correct localization and lateralization. Because the EEG, proton MRSI, and MRIVol data represent three sets of independent variables, concordance of the results provided by these three methods strengthens the validity of the diagnostic conclusions derived from any method individually and thereby increases the likelihood that the area from which the patient's seizures originates is being localized and lateralized accurately. Freedom from seizures after surgery is another potential outcome measure that might be considered more important. However, surgical outcome requires at least 2 years' follow-up for proper evaluation and is not itself without problems as an outcome measure, because surgical factors, such as insufficient removal of epileptogenic tissue, may be responsible for some patients not becoming seizure free, although their lateralizations were correct [40].

Relationship Between Metabolic and Structural Disturbances

Because low NAA is associated with neuronal loss or dysfunction [23, 24, 27], decreased NAA/Cr values in the temporal regions of patients with TLE would be
expected to be associated with medial temporal lobe atrophy. In accordance with this, we found that the NAA/Cr values correlated well with volume loss on MRIVol in our patients (see Table 2). However, 12 patients with normal MRI had reduced NAA/Cr values in the temporal region; 7 of these patients underwent surgery. Qualitative histopathological examination of the resected tissue revealed mild astrogliosis and neuronal loss of mesial temporal structures [6–8]. Four of these patients are seizure free, or have auras only, after surgery [1], with a follow up of at least 1 year. The remaining 3 patients have undergone surgery recently and the outcomes are not yet available. These data imply that proton MRS evidence of neuronal damage is detectable in vivo before structural changes are seen by conventional MRI [41].

Consistent with this, we found that proton MRSI demonstrated more diffuse abnormalities within the temporal lobes than did MRI. The presence of bilateral proton MRSI abnormalities may preclude lateralization by MRSI in some patients. MRIVol provides lateralization in some of these patients, at least some of whom can still benefit from surgery. The significance of bilateral proton MRSI abnormalities and their relationship to postoperative outcome in TLE must be investigated further.

Patients with bilateral ictal EEG abnormalities had more severe bilateral proton MRSI and MRIVol abnormalities than patients with all or more than 90% of their seizures originating from one temporal lobe. Using NAA/Cr values from the Mid and Post temporal regions together allowed us to lateralize more patients than using each one of these regions separately. To a lesser extent the same was true for the AM and the HF volumes.

We obtained lateralization in 83% of patients by using MRIVol alone and in 86% of patients by using proton MRSI alone. By combining MRSI and MRIVol results all patients could be classified as having temporal lobe abnormalities, and 90% of patients could be lateralized. EEG investigation lateralized 93% of patients. Thus, combining data sources resulted in classification of more patients with a higher degree of accuracy.

Relationship of Metabolic and Structural Disturbances to EEG Findings
The side of maximal proton MRSI and MRIVol abnormalities correlated with the side from which most seizures originated, according to the EEG investigation, in all but 4 patients. However, when MRSI and MRIVol findings were combined, only 1 patient had lateralization on the side opposite to the most frequent EEG seizure onsets. The reason for the incongruent proton MRSI and MRIVol in this patient remains unclear. She has undergone surgery on the side of predominant intracranial EEG seizure onsets, opposite to the side of greater atrophy and NAA/Cr decrease, and has had a poor outcome after a 22-month follow-up. It is not clear whether the EEG lateralization was misleading in this patient, or whether the poor outcome was related to bitemporal seizure onsets or to other factors such as the amount of epileptogenic tissue resected.

The relative merits of ictal EEG findings versus associated structural or metabolic abnormalities in lateralizing the most epileptogenic area remains to be determined. The primary importance of the EEG in the diagnosis of epilepsy is self-evident because epileptic seizures are an electrical phenomenon. However, it is well known that seizures may appear to begin on both sides in many patients with TLE, and that the first recorded seizure may not originate from the main seizure generator [4, 5]. The structural and, presumably, the metabolic abnormality in TLE may reflect the pathological substrate of the seizure generator. Thus, these image-based abnormalities may bear a sufficiently consistent relationship to the origin and severity of seizures to obviate the need to record multiple ictal events to determine the side from which most seizures originate. We do not believe that EEG will ever be replaced by imaging alone. However, the results of the present study, together with previous publications [9–13, 16, 17, 20, 28, 29, 33–35, 42–45], support the preoperative strategy, proposed by Cascino and associates [45], that selected patients with a history and ictal semiology consistent with medial TLE may undergo surgery if interictal epileptiform discharges recorded during serial routine EEGs or long-term video-EEG monitoring consistently lateralize to one temporal lobe, in agreement with strong functional and structural imaging evidence of unilateral medial temporal lobe damage. Recording of ictal events by surface or intracranial EEG would still be imperative in those patients without abundant interictal abnormalities, in patients with normal imaging studies, in patients with bilateral imaging or bilateral interictal EEG abnormalities, and in patients with discordant preoperative studies [2, 4, 45].

The present series included only patients with TLE, and therefore, it is not suitable for assessment of the specificity of MRIVol or MRSI abnormalities. Our previous studies in patients with TLE and extratemporal epilepsy, however, indicated that abnormalities on both MRIVol [16, 44] and MRSI from the temporal lobes [46] can be specific for TLE in this setting. Because specificity always depends on the patient population under study, the specificity we have found may not apply to other patient populations.

The use of proton MRSI for the presurgical evaluation of extratemporal epilepsies has potential [47, 48] but poses greater technical difficulties and must be evaluated further.
Conclusions

Although the improved sensitivity achieved by combining MRSI and MRIVol is relatively small (83–90%), we believe that this is a worthwhile improvement for the following reasons: (1) In this series of difficult cases, 7 additional patients could be lateralized; (2) the use of these two MR examinations, which can be performed on an outpatient basis, increased our confidence of the lateralization of the seizure focus; and (3) the EEG lateralization in 20% of these patients required invasive intracranial recordings after long-term extracranial EEG investigations had failed to provide lateralization. It is possible that intracranial recordings could be avoided by use of multimodal MR examinations.

One could question whether patients with TLE must have both of these MR examinations in addition to an extensive EEG investigation. Although the different examinations may agree on lateralization, they provide different kinds of information, namely, electrophysiological, structural, and functional information, that are helpful in understanding the significance of abnormalities in individual patients and making decisions regarding the use of surgical therapy in difficult cases.

Our results suggest that proton MRSI and MRIVol represent powerful new tools for the noninvasive presurgical lateralization of TLE.

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References