Electroencephalographic, Volumetric, and Neuropsychological Indicators of Seizure Focus Lateralization in Temporal Lobe Epilepsy

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Context: Anterior temporal lobectomy is an effective treatment for medically intractable temporal lobe seizures. Identification of seizure focus is essential to surgical success.

Objective: To examine the usefulness of presurgical electroencephalography (EEG), magnetic resonance imaging (MRI), and neuropsychological data in the lateralization of seizure focus.

Design: Presurgical EEG, MRI, and neuropsychological data were entered, independently and in combination, as indicators of seizure focus lateralization in discriminant function analyses, yielding correct seizure lateralization rates for each set of indicators.

Setting: Comprehensive Epilepsy Program, Shands Teaching Hospital, University of Florida, Gainesville.

Patients: Forty-four right-handed adult patients who ultimately underwent successful anterior temporal lobectomy. Left-handed patients, those with less-than-optimal surgical outcome, and any patients with a history of neurological insult unrelated to seizure disorder were excluded from this study.

Main Outcome Measures: For each patient presurgical EEG was represented as a seizure lateralization index reflecting the numbers of seizures originating in the left hemisphere, right hemisphere, and those unable to be lateralized. Magnetic resonance imaging data were represented as left-right difference in hippocampal volume. Neuropsychological data consisted of mean scores in each of 5 cognitive domains.

Results: The EEG was a better indicator of lateralization (89% correct) than MRI (86%), although not significantly. The EEG and MRI were significantly superior to neuropsychological data (66%) ($P=.02$ and $.04$, respectively). Combining EEG and MRI yielded a significantly higher lateralization rate (93%) than EEG alone ($P<.01$). Adding neuropsychological data improved this slightly (95%).

Conclusions: The EEG and MRI were of high lateralization value, while neuropsychological data were of limited use in this regard. Combining EEG, MRI, and neuropsychological improved focus lateralization relative to using these data independently.

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ANTERIOR TEMPORAL lobectomy (ATL) is an effective treatment for medically intractable seizures that originate in the temporal lobe.¹ Surgical success depends on the selection of candidates with discrete and identifiable epileptogenic foci.²³ Removal of such a focus will theoretically result in seizure-free status.⁴

Electroencephalography (EEG)—scalp, invasive, or both—has traditionally been the standard criterion of seizure focus identification. High correct lateralization rates have been achieved using scalp EEG, although these rates have varied greatly, ranging from 15% to 99%, as a function of patient selection⁴⁴ and methods.

Brain magnetic resonance imaging (MRI) allows for detailed analysis of mesial temporal lobe structures, an essential part of testing as mesial temporal sclerosis is the most common neuroanatomical finding associated with seizure focus among candidates for ATL.⁶ Studies have yielded a wide range of MRI-based lateralization rates,⁷⁸ with one recent investigation¹¹ indicating that, among patients with postoperatively confirmed mesial temporal sclerosis, hippocampal volumes were used to correctly lateralize 93% of the cases.

The few studies¹⁴-¹⁷ that have assessed the use of neuropsychological data in indicating seizure focus lateralization in individuals have revealed that these data are of limited value. A recent investiga-
PATIENTS AND METHODS

PATIENTS

Forty-four patients with medically intractable unilateral temporal lobe epilepsy who underwent comprehensive presurgical epilepsy evaluations and subsequently underwent right (n=26) or left (n=18) ATL were enrolled in this study. All patients had experienced highly successful surgical outcomes and were assessed as having Engel scores16 of 1 at least 12 months after surgery. This allowed for the assumption that lateralization of surgical resection was the same as lateralization of the actual seizure focus. Of 61 potential patients who met all other inclusion criteria, 17 were excluded owing to having postsurgical Engel scores greater than 1 (Engel II; 14 patients; Engel III; 2 patients; and Engel IV, 1 patient). All patients were right-handed, at least 18 years old, and underwent presurgical neuropsychological assessment and continuous inpatient (noninvasive) video-EEG (VEEG) monitoring. Nineteen patients (12 patients who underwent right ATLs, 7 patients who underwent left ATLs) also required invasive EEG prior to surgery. All patients except for 1 in each group underwent presurgical brain MRI. Left-handed patients, those with incomplete neuropsychological data, and those with a history of neurological insult that occurred after the onset of epilepsy or that was deemed to be unrelated to their epilepsy were excluded from the study (Table 1).

MRI DATA

Presurgical imaging consisted of magnetization prepared rapid gradient echo imaging. Data were as follows: repetition time = 10 milliseconds, echo time = 4 milliseconds, flip angle = 10°, acquisition matrix = 130 × 256 pixels, volume = 160 mm, and section thickness = 1.25 to 1.40 mm, producing a gapless series of high-quality images. On the computer monitor, the hippocampus was outlined on every section that it appeared in the sagittal plane. Volumes were then calculated by measuring the hippocampal area for each section and multiplying it by the thickness of the section. The resulting volumes were summed to obtain a total volume. Each patient’s right and left hippocampus was measured twice by an individual (D.J.M.) blind to patient information. The mean of these 2 values represented the right and left hippocampal volumes, expressed in cubic centimeters.

EEG DATA

Prior to surgery, each patient was admitted to the hospital for continuous scalp VEEG monitoring. All VEEG recordings were analyzed by the electroencephalographer (R.L.G.), who logged each seizure’s clinical description, type, and, if possible, lateralization and localization of onset. Scalp electrodes were placed according to the International 10-20 System,9 with frequent additional use of bilateral sphenoidal electrodes. Various electrode montages and filters were used.

Each patient’s VEEG event log was reviewed on a seizure-by-seizure basis and the electroencephalographer’s interpretation of each event was entered into a database. When 2 or more seizures occurred within a 3-hour interval and were of identical lateralization and localization, they were statistically regarded as 1 event, as such circumstances make it difficult to determine whether the events are truly independent of each other. All EEG recordings significantly obscured by artifact were excluded.

The following values were obtained for each patient: total number of seizures, number of seizures lateralized to the right hemisphere, number of seizures lateralized to the left hemisphere, number of nonlateralized seizures (seizures that could not be lateralized to one hemisphere over the other). Once these data were collected, it was necessary to quantify them in a manner that would indicate difference in frequency of right and left hemispheric events, that would consider the occurrence of nonlateralized seizures, and that would place these values within the context of the total number of events recorded. Therefore, a seizure lateralization index (SLI) was calculated using the following equation:

\[
SLI = \frac{|N - R - L - R + L|}{R + L + N}
\]

where \( R \) indicates the number of seizures originating in the right hemisphere; \( L \), the number of seizures originating in the left hemisphere; and \( N \), the number of nonlateralized seizures. Nonlateralized seizures were given a weight of 0.5 which is that of a lateralized seizure, as they have a theoretically equal chance of having originated in either hemisphere.

The SLI equation yielded values ranging from 1.00 (all events lateralized to the right hemisphere) to −1.00 (all lateralized to the left hemisphere) for all patients. Values closer to 0.00 indicated varying degrees of right or left seizure frequency. The equation was designed in such a way that the occurrence of nonlateralized seizures would result in an SLI value that was less lateralizing (closer to 0.00) than it would have been had nonlateralized seizures been excluded.

NEUROPSYCHOLOGICAL DATA

Neuropsychological data were obtained from the patients’ presurgical files from assessments administered 1 to 3 years prior to surgery. To date, at least 1 investigation18 has examined EEG, MRI, and neuropsychological data in the same preoperative cohort of patients who had mesial temporal lobe epilepsy. Eighty-seven percent of these patients showed apparently lateralizing ictal scalp EEG changes, with 76% of the total group being correctly lateralized. Of only 28 patients who underwent MRI, the MRI findings in 23 were interpreted as having unilateral hippocampal sclerosis, 91% of which were confirmed via pathological testing. Regarding neuropsychological testing, 58 (87%) of the 67 patients were deemed to have lateralized data profiles, 56 (84%) of which (48 patients) 73% of the total group) were correctly lateralized.18
In the current study, we used presurgical EEG, MRI, and neuropsychological data to lateralize seizure foci in a group of patients who underwent successful ATL. This not only allowed for direct comparison of these individual techniques within a single patient population, but also enabled us to explore the degree to which combining these domains of data would increase correct lateralization rates. We hypothesized that EEG would yield the highest correct lateralization rate, followed by MRI, and then neuropsychological data. We also predicted that combining EEG, MRI, and neuropsychological data would increase correct lateralization rates compared with using them in isolation.

RESULTS

The groups who underwent right and left ATLs did not differ statistically significantly for demographic or illness-
related variables (Table 1). Table 2 contains descriptive statistics regarding the number and lateralization of seizures experienced by all patients and the groups who had right and left ATLs during inpatient VEEG monitoring, and the resulting mean SLI values for these groups. A 2-tailed t test revealed that the group who underwent left ATL had a statistically significant lower mean SLI ($t_{15.10} = 9.21, P < .001$) than did the group who underwent right ATL.

Table 3 contains descriptive statistics regarding hippocampal volumes. Two-tailed t tests revealed that the group who underwent right ATL had a significantly smaller mean right hippocampal volume ($t_{10} = -4.65, P < .001$) and a significantly lower mean DHF ($t_{10} = -7.34, P < .001$), than did the group who underwent left ATL, and the group who underwent left ATL had a significantly smaller mean left hippocampal volume than the group who underwent right ATL ($t_{10} = 3.06, P < .004$).

Table 4 contains descriptive statistics for the 5 neuropsychological domain scores. Two-tailed t tests revealed that the group who underwent left ATL had significantly lower mean language and verbal memory domain scores ($t_{12} = 2.07, P = .04; t_{12} = 2.22, P = .03$, respectively) than the group who underwent right ATL, while other differences were statistically nonsignificant.

The rates at which SLI, DHF, and the 5 neuropsychological domain scores, used independently and in combination, were used to correctly predict seizure focus lateralization are given in Table 5. The following classification rates were compared: SLI vs DHF, SLI vs the 5 neuropsychological domain scores, DHF vs the 5 neuropsychological domain scores, SLI and DHF combined vs SLI, the 5 neuropsychological domain scores and SLI combined vs SLI, and finally, the 5 neuropsychological domain scores, SLI, and DHF combined vs SLI and DHF combined. The results of these tests are presented below.

McNemar tests for $2 \times 2$ tables were used to test the first 3 of the above comparisons (ie, SLI vs DHF, SLI vs the 5 neuropsychological domain scores, and DHF vs the 5 neuropsychological domain scores). Again, the exact statistical significance of each comparison was obtained.

### Table 1. Descriptive Statistics for Demographic and Illness-Related Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 44)</th>
<th>LATL† (n = 26)</th>
<th>RATL† (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34.14 (9.95)</td>
<td>33.65 (10.26)</td>
<td>34.83 (9.75)</td>
</tr>
<tr>
<td>Education, y</td>
<td>12.85 (2.35)</td>
<td>12.81 (2.19)</td>
<td>12.92 (2.64)</td>
</tr>
<tr>
<td>Age at onset of epilepsy, y</td>
<td>11.21 (10.86)</td>
<td>11.90 (11.92)</td>
<td>10.22 (3.34)</td>
</tr>
<tr>
<td>Duration of epilepsy, y</td>
<td>23.02 (10.50)</td>
<td>22.12 (10.42)</td>
<td>24.33 (10.78)</td>
</tr>
<tr>
<td>% Female</td>
<td>54.54</td>
<td>61.11</td>
<td>50.00</td>
</tr>
</tbody>
</table>

*All values are expressed as mean (SD). When compared for statistical significance, all groups were not significantly different at the level of .05.
†LATL indicates patients who eventually underwent left anterior temporal lobectomy; RATL, patients who eventually underwent right anterior temporal lobectomy.

### Table 2. Descriptive Statistics for Electroencephalographic Variables

<table>
<thead>
<tr>
<th>Seizure Variable</th>
<th>All Patients (N = 44)</th>
<th>LATL† (n = 26)</th>
<th>RATL† (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total‡</td>
<td>5.36 (3.10)</td>
<td>5.19 (2.68)</td>
<td>5.81 (3.68)</td>
</tr>
<tr>
<td>Hemispheric onset, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>1.95 (3.27)</td>
<td>2.07 (1.04)</td>
<td>4.39 (3.85)</td>
</tr>
<tr>
<td>Left</td>
<td>2.70 (2.56)</td>
<td>4.12 (2.08)</td>
<td>0.67 (1.64)</td>
</tr>
<tr>
<td>Nonlateralized</td>
<td>0.70 (1.81)</td>
<td>0.81 (2.12)</td>
<td>0.56 (1.29)</td>
</tr>
<tr>
<td>SLI§</td>
<td>−0.23 (0.87)</td>
<td>−0.83 (0.36)</td>
<td>0.63 (0.60)</td>
</tr>
</tbody>
</table>

*All values are expressed as mean (SD). †LATL indicates patients who eventually underwent left anterior temporal lobectomy; RATL, patients who eventually underwent right anterior temporal lobectomy.
‡Indicates the total number of seizures experienced during videoelectroencephalographic recording.
§SLI indicates seizure lateralization index. (See equation 1 in the “EEG Data” subsection of the “Patients and Methods” section for an explanation of the calculation.) The patients in the LATL group differed significantly (P < .001) from the patients in the RATL group.

### Table 3. Descriptive Statistics for Volumetric Variables

<table>
<thead>
<tr>
<th>Volumetric Variable</th>
<th>All Patients (N = 44)</th>
<th>LATL† (n = 26)</th>
<th>RATL† (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal volume, cm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean right</td>
<td>3.13 (0.71)</td>
<td>3.47 (0.55)</td>
<td>&gt;2.63 (0.62)</td>
</tr>
<tr>
<td>Mean left</td>
<td>3.14 (0.73)</td>
<td>2.89 (0.77)</td>
<td>&lt;3.52 (0.46)</td>
</tr>
<tr>
<td>DHF‡</td>
<td>−0.02 (0.97)</td>
<td>0.58 (0.62)</td>
<td>&gt;−0.90 (0.68)</td>
</tr>
<tr>
<td>%RHS§</td>
<td>30.95</td>
<td>0.00</td>
<td>76.47</td>
</tr>
<tr>
<td>%LHS§</td>
<td>30.95</td>
<td>52.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*All values are expressed as mean (SD). The greater than (> ) or less than (< ) sign indicates the directionality of the statistically significantly differences between the groups (P < .01).
†LATL indicates patients who eventually underwent left anterior temporal lobectomy; RATL, patients who eventually underwent right anterior temporal lobectomy.
‡DHF indicates mean difference in hippocampal formation volume (right−left, in cubic centimeters).
§%RHS indicates percentage of each group meeting criteria for significantly smaller right hippocampus (DHF < −0.45 cm³); %LHS, percentage of each group meeting criteria for significantly smaller left hippocampus (DHF > +0.55 cm³).

### Table 4. Descriptive Statistics for 5 Neuropsychological Domain Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (N = 44)</th>
<th>LATL† (n = 26)</th>
<th>RATL† (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>−1.20 (1.19)</td>
<td>−1.50 (1.11)</td>
<td>&lt;−0.78 (1.19)</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>−1.26 (1.29)</td>
<td>−1.60 (1.28)</td>
<td>&lt;−0.76 (1.19)</td>
</tr>
<tr>
<td>Nonverbal memory</td>
<td>−0.44 (1.03)</td>
<td>−0.33 (0.92)</td>
<td>&lt;−0.61 (1.18)</td>
</tr>
<tr>
<td>Visuoconstructive</td>
<td>−0.35 (0.82)</td>
<td>−0.29 (0.85)</td>
<td>&lt;−0.44 (0.79)</td>
</tr>
<tr>
<td>Motor</td>
<td>0.45 (2.36)</td>
<td>0.39 (1.94)</td>
<td>0.54 (2.92)</td>
</tr>
</tbody>
</table>

*All values are expressed as mean (SD). The less than (< ) sign indicates the directionality of the statistically significantly differences between the groups (P < .05). See equations 2 through 6 in the “Neuropsychological Data” subsection of the “Patients and Methods” section for an explanation of the calculations for each variable.
†LATL indicates patients who eventually underwent left anterior temporal lobectomy; RATL, patients who eventually underwent right anterior temporal lobectomy.
Table 5. Correct Seizure Focus Lateralization Rates Using NP, SLI, and DHF as Indicators

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>LATL (n = 26)</th>
<th>RATL (n = 18)</th>
<th>All Patients (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP, DHF, and SLI</td>
<td>96.00 (25)</td>
<td>94.12 (17)</td>
<td>95.24 (42)</td>
</tr>
<tr>
<td>DHF and SLI</td>
<td>92.00 (25)</td>
<td>94.12 (17)</td>
<td>92.86 (42)</td>
</tr>
<tr>
<td>NP and SLI</td>
<td>92.31 (26)</td>
<td>88.89 (18)</td>
<td>90.91 (44)</td>
</tr>
<tr>
<td>SLI</td>
<td>92.31 (26)</td>
<td>83.33 (18)</td>
<td>88.63 (44)</td>
</tr>
<tr>
<td>DHF</td>
<td>88.00 (29)</td>
<td>82.35 (17)</td>
<td>85.71 (44)</td>
</tr>
<tr>
<td>NP and DHF</td>
<td>84.00 (25)</td>
<td>76.47 (17)</td>
<td>80.95 (42)</td>
</tr>
<tr>
<td>NP</td>
<td>69.23 (26)</td>
<td>61.11 (18)</td>
<td>65.91 (44)</td>
</tr>
</tbody>
</table>

*All values are expressed as percentage correct, ie, percentage of each group for which lateralization of seizure focus was correctly predicted by entering various combinations of predictor variables into discriminant analyses (size of subsample). NP indicates all 5 neuropsychological domain z scores; SLI, seizure lateralization index (see equation 1 in the “EEG Data” subsection of the “Patients and Methods” section); DHF, difference in hippocampal formation volume (right – left, in cubic centimeters); LATL, patients who eventually underwent left anterior temporal lobectomy; and RATL, patients who eventually underwent right anterior temporal lobectomy.

from the binomial distribution, and it is this value that is reported below. The classification rate for SLI (88.10% correct) and that for DHF (85.71%) were not significantly different (P = .99, n = 42). Classification rate for SLI (88.63%) was significantly better than that for the 5 neuropsychological domain scores (65.91%) (P = .02, n = 44). Classification rate for DHF (85.71%) was also significantly better than that for the 5 neuropsychological domain scores (61.90%) (P = .04, n = 42). On an exploratory basis, the classification rate for DHF was also examined among only those 26 patients who met criteria for significant hippocampal asymmetry (DHF < -0.45 cm³ or DHF > 0.55 cm³). Of these 100% were correctly lateralized using DHF.

F tests were used to test the final 3 comparisons described above (ie, SLI and DHF combined vs SLI, the 5 neuropsychological domain scores, SLI, and DHF combined vs SLI and DHF combined). Results indicated that classification rate for SLI and DHF combined (92.86% correct) was significantly better than that for SLI alone (88.10% correct), (F₁,₄₀ = 13.76, P = .001, n = 42). Classification rate for the 5 neuropsychological domain scores and SLI combined (90.91%) was not significantly different from that for SLI alone (86.63%) (n = 44). Finally, classification rate for 5 neuropsychological domain scores, SLI, and DHF combined (95.24%) was not significantly different from that for SLI and DHF combined (92.86% correct) (n = 42).

Exploratory examination of the data revealed that the patient in the right ATL group who was mislocalized had an SLI value of −1.00, because all of his seizures falsely appeared to originate in the left hemisphere on ictal scalp EEG. Furthermore, although he did not have a significant degree of hippocampal asymmetry, his MRI data were also mislocalizing when used as the sole predictor. In this study, only the 5 neuropsychological domain scores were able to lateralize this patient correctly. Clinically, this patient underwent invasive EEG monitoring that revealed the right hemisphere focus. The patient in the left ALT group who was mislocalized had an SLI value of 0.29, falsely indicating a tendency toward right lateralization. In this study, this patient would have been correctly lateralized had hippocampal volumes or the 5 neuropsychological domain scores been used to predict lateralization. Clinically, invasive EEG monitoring was used to identify the left hemisphere focus.

Following is a description of each set of predictors used in these discriminant analyses, the resulting Wilks λ values, and levels of statistical significance. Entering SLI as the sole predictor of seizure focus lateralization yielded the following results: Wilks λ = 0.292 (P < .001), n = 44. The DHF as the sole predictor: Wilks λ = 0.426 (P < .001), n = 42. The 5 neuropsychological domain scores as predictors: Wilks λ = 0.766, (P > .05), n = 44. Combined DHF and SLI as predictors: Wilks λ = 0.228 (P < .001), n = 42. Combined SLI and the 5 neuropsychological domain scores as predictors: Wilks λ = 0.262 (P < .001), n = 44. Combined DHF and the 5 neuropsychological domain scores as predictors: Wilks λ = 0.384 (P < .001), n = 42. Combined DHF, SLI, and the 5 neuropsychological domain scores as predictors: Wilks λ = 0.210 (P < .001), n = 42.

Our data support our hypotheses and are consistent with the existing literature. Ictal scalp EEG indicated seizure focus lateralization at a higher rate than MRI-based hippocampal volume differences, but this was not a statistically significant difference. Both EEG and MRI were significantly superior to the 5 neuropsychological domain scores. Combining EEG and MRI data yielded a significantly higher correct lateralization rate than using EEG alone. Despite its statistical significance, this improvement in lateralization was minor and of questionable clinical importance. Combining all 3 domains of data yielded the highest correct lateralization rate, but this was not a statistically significant improvement over using combined EEG and MRI data.

The fact that ictal scalp EEG data indicated lateralization at a rate approaching 90% is not surprising. This is consistent with existing studies and with the fact that this group of patients had discrete unilateral seizure foci. The inclusion of interictal and invasive EEG data would likely have yielded an even higher lateralization rate.

Magnetic resonance imaging–based hippocampal volume differences also indicated lateralization with a high degree of accuracy, despite the fact that only 62% of our patients met criteria for significant hippocampal asymmetry. Therefore, these volumes lateralized foci quite accurately, despite the fact that these data were statistically forced to indicate lateralization in many cases in which most clinicians would have interpreted the MRI as nonlateralizing. Among those meeting criteria for significant hippocampal asymmetry (n = 26), the correct lateralization rate was 100%. This is consistent with very high MRI-based lateralization rates reported in the literature, involving patients with postoperatively confirmed mesial temporal sclerosis.

Consistent with past studies, 14-18 neuropsychological data correctly lateralized seizure foci in only 63% of
cases. Despite this, both patients who were mislateralized when EEG, MRI, and neuropsychological data were combined, were correctly lateralized based on neuropsychological domain scores alone. Clinically, both required invasive EEG monitoring prior to surgery, as did 43% of all patients in the study.

It is surmised that neuropsychological performance is sensitive to factors such as education, affective issues, medication, seizure frequency, age of epilepsy onset, and duration of illness—factors that may not similarly reduce the usefulness of MRI or EEG. Despite these limitations, presurgical neuropsychological data remain valuable in the prediction of postsurgical functioning,31 and neuropsychological tasks are a critical component of the intracarotid amobarbitol procedure.14 Other neuropsychological services of significant benefit to patients and their families include cognitive rehabilitation and presurgical and postsurgical counseling.

That the combination of EEG, MRI, and neuropsychological data correctly lateralized temporal lobe seizure focus at a rate exceeding 95% in our study is certainly encouraging. However, it must be reiterated that this patient population had discreet seizure foci and, therefore, represent the cases most able to be lateralized. Additional studies are needed to investigate and improve lateralization and localization strategies in seizure disorders with more complex presentations.

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