Factors predictive of suboptimal seizure control following selective amygdalohippocampectomy

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Object. Selective amygdalohippocampectomy (SelAH) is used in the treatment of mesial temporal lobe epilepsy (MTLE). The goal of this study was to determine factors predictive of poor postoperative seizure control (Engel Class III or IV) following SelAH.

Methods. A retrospective study was conducted of 27 patients with poor seizure control postoperatively (Engel III/IV group), in comparison with 27 patients who were free from seizures after surgery (Engel I/II group). The results of electroencephalography, magnetic resonance (MR) imaging, and pathological studies were reviewed, and volumetric MR image analysis was used to compare the extent of the mesial structures that had been resected.

In 56% of patients in the Engel III/IV group, significant bitemporal abnormalities were displayed on preoperative EEG studies, compared with 24% of patients in the Engel I/II group (p < 0.05). An analysis of preoperative MR images disclosed five patients (19%) in the Engel III/IV group and no patient in the Engel I/II group with normal hippocampal volumes bilaterally. Thirteen patients in the Engel III/IV group subsequently underwent either extension of the SelAH (six cases) or a corticoamygdalohippocampectomy (seven patients). Three patients from the former and one patient from the latter subgroup subsequently became seizure free (four patients total [34%]). The remaining nine patients did not improve, despite the fact that they had undergone near-total resection of mesial structures.

Conclusions. The majority of patients receiving suboptimal seizure control following SelAH did not meet the criteria for unilateral MTLE, based on EEG, MR imaging, and/or histopathological studies. These patients were therefore unlikely to benefit from additional resection of mesial structures. With the benefits of modern imaging, and by strict adherence to selection criteria, SelAH can be predicted to yield excellent postoperative seizure control for nearly all patients with unilateral MTLE. There remains a subpopulation, however, that meets the criteria for MTLE, but does not become free from seizure following SelAH.

Key Words • amygdalohippocampectomy • seizure • resection

For many years, the standard surgical technique for the treatment of TLE was the CorAH—the so-called “anterior temporal lobectomy.” The rate of good seizure control (Engel Class I or II) following CorAH during the pre-MR imaging era was approximately 60%.

Although pioneered by Niemeyer in the 1950s and modified and popularized by Yasargil in the 1980s, the SelAH did not attain widespread popularity until the 1990s, following the general use of MR imaging and the advent of intraoperative neuronavigation. The late 1980s witnessed a gradual switch to SelAHs in patients with TLE. Although initially used for the more complex cases of TLE (typically those patients who required preoperative investigation with intracranial EEG), at a number of centers, SelAH has become the procedure of choice for patients with unilateral MTLE, whereas CorAH is reserved for those patients with a suspected or documented neocortical epileptogenic focus. The putative advantage of SelAH over CorAH lies in the fact that the former causes a smaller disruption of potentially functional temporal neocortex, while attaining the same postoperative seizure control rate as the latter. Early reviews have supported the belief that seizure control rates do not differ between SelAH and CorAH, but neurocognitive outcome analysis of these two groups is not yet complete.

For the majority of patients with unilateral MTLE undergoing SelAH at MNI during the MR imaging era, postoperative seizure control has been good (Engel Class I or II). Nearly half of the patients who did not attain good postoperative seizure control have undergone a second operation, during which a further resection of the amygdala and hippocampus has been performed.
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We retrospectively reviewed the preoperative clinical history, electrophysiological data, and MR images of all patients with Engel outcomes of Class III or IV following SelAH. Additionally, using volumetric analysis we assessed the extent of mesial temporal resection (amygdala, hippocampus, entorhinal cortex, and parahippocampal gyrus) in patients who underwent SelAH, to answer the following questions. What is the minimum resection required for good seizure outcome? Does the extent of resection—determined according to change in volume or by structures that were removed—distinguish those patients with poor outcomes (Engel III/IV group) from those patients with good postoperative outcomes (Engel I/II group)? Finally, we assessed the extent of additional mesial resection in those patients in whom initial selective resection failed, but who subsequently became free from seizure following extension of the mesial resection, to answer the question of what additional volume of resection is required for a good outcome. This information is crucial for the identification of the minimum resection volume required for optimal postoperative seizure control with the least possible neurocognitive disturbance, as well as for the identification of the structure(s) whose resection is both necessary and sufficient for optimal postoperative seizure control.

Clinical Material and Methods

Inclusion and Exclusion Criteria

All patients included in this study had nonlesional TLE, that is, they did not harbor any known intracranial tumors, cortical dysplasias, or vascular lesions at the time of entry into the study. All patients underwent an SelAH, which was performed by a single surgeon (A.O.) between 1986 and 1998. Preoperative and postoperative MR images were included in this study. A minimum of 2 years of follow-up review was available for all patients. A list of all patients who underwent SelAH, which was performed at the MNI by a single surgeon (A.O.) between 1986 and 1998, was obtained postoperatively. All patients who underwent an SelAH, which was performed by a single surgeon (A.O.) between 1986 and 1998, were obtained from the epilepsy surgery database. All patients with postoperative Engel Class III or IV seizure control and a minimum of 2 years of follow-up review were then selected for an analysis. A list was compiled of an equivalent number of patients who attained postoperative Engel Class I or II. This list was compared with the former for patient age, sex, and year of operation within the surgical series. A retrospective analysis of hospital and clinic charts was then conducted. All patients were seen at follow-up examinations by the surgeon (A.O.) and the referring neurologists (F.A. and F.D.). The classification of postoperative seizure reduction was based on the scale advocated by Engel: Class I is defined as seizure free; Class II as three or fewer seizures per year; Class III as greater than 60% reduction in seizures, but more than three seizures per year; and Class IV as less than a 60% reduction in seizures.

At MNI the preoperative evaluation of patients with medically refractory MTLE includes scalp EEG, MR imaging, and neuropsychological testing. Language dominance was determined based on the results of the preoperative IAP, if performed. Not all patients in this study underwent a preoperative IAP. At the MNI the indications for obtaining an IAP are the following: 1) if the results of the dichotic listening test demonstrate an atypical pattern—that is, there is a lack of a right-ear advantage; 2) if there is a strong family history of left-handedness; or 3) if cognitive findings are at odds with other clinical findings (for example, if the results of the cognitive tests suggest that the seizure focus is on the left side, but the findings of EEG and MR imaging support a right-sided focus). For patients in this study who did not undergo an IAP, those who were right-handed and those in whom dichotic listening tests displayed a right-ear advantage were assumed to be left-brain dominant for language. Additionally, we have developed memory tests that have been shown to be highly reliable indicators of memory dysfunction in the left or right temporal lobe.

Magnetic Resonance Imaging and Analysis

Preoperative MR images were retrospectively reviewed to confirm or refute the diagnosis of unilateral mesial temporal sclerosis, based on hippocampal and amygdalar atrophy and an increased signal on T2-weighted and fluid-attenuated inversion recovery sequences. Hippocampal atrophy was defined as a reduction in hippocampal volume that was greater than two standard deviations from the mean. Volumetric analysis of the hippocampi was performed as previously described. All patients in whom there was no evidence of unilateral or bilateral atrophy of mesial structures on MR images or no evidence of MTLE on retrospective analysis of EEGs, underwent repeated MR imaging with three-dimensional curvilinear reconstruction to check for extratemporal lesions.

Determination of the Extent of Resection

Volumetric MR images were acquired using a 1.5-tesla MR imager (Gyroscan; Philips Medical System, Eindhoven, NL) with a T1-weighted three-dimensional gradient-echo sequence (TR 18 msec, TE 10 msec, signal average 1, flip angle 30°, matrix 256 × 256, field of view 250 mm, slice thickness 1 mm). Approximately 170 slices were acquired, each with an isotropic voxel size of 1 mm3. Preoperative and postoperative MR images were automatically registered into stereotactic space to adjust for differences in total brain volume and orientation. Images were examined using a mouse-driven software package (REGISTER) developed at the Brain Imaging Center at MNI. This software allows for the simultaneous display of two MR image volumes. The lengths of the amygdala, hippocampus, and entorhinal cortex were determined on the preoperative MR images by counting the number of consecutive 1-mm-thick MR slices containing each structure. Similarly, on the postoperative MR images, the number of consecutive slices containing the remainder of each structure was determined. This number was subtracted from the total length of the particular structure and transformed into a percentage, yielding
The extent of resection. The anatomical guidelines used for the identification of the entorhinal cortex, amygdala, and hippocampus have been described elsewhere.18,24

### Electrophysiology and Assessment of Laterality

The results of the preoperative scalp EEG, intracranial S-EEG, if performed, and intraoperative ECoG were reviewed for each patient. All patients in this study had undergone preoperative scalp EEG. The determination of medial, lateral, and/or neocortical onset was made by the epileptologist who was responsible for the scalp EEG report (F.A., F.D., and L.F.Q.) and was based on the following criteria. The designation of medial as opposed to lateral seizure onset on scalp EEGs was determined by whether the predominant epileptiform activity arose first in the zygomatic and/or sphenoidal electrodes (medial; 13 patients), or in the convexity electrodes (lateral). The designation of medial as opposed to lateral onset on S-EEG was determined by whether the epileptiform activity arose first in the mesial structures (depth electrodes) or in the electrodes arrayed along the cortical or neocortical surface. Note that the sphenoidal electrodes were used in the evaluation of eight of the 27 patients in the Engel III/IV group and in six of the 27 patients in the Engel I/II group. Zygomatic electrodes were used in five patients in the Engel III/IV group and in four patients in the Engel I/II group.

Patients in this series had undergone PET or, later, PET or SPECT and/or S-EEG investigations when the laterality of seizure onset could not be defined based solely on scalp EEG and MR imaging results. For cases in which the PET or SPECT results were not concordant with those of the S-EEG, the results of the S-EEG were considered the gold standard for the assessment of lateralization. For the remaining patients, PET and/or SPECT results were concordant with those of the S-EEG.

Patients in this study who also underwent S-EEG did so because either localization or lateralization of an epileptic focus could not be determined on the basis of scalp EEG. Bilateral temporal epilepsy was defined as EEG or S-EEG evidence of ictal onset in both temporal lobes, irrespective of the percentage of seizures arising from one or the other side. Bilateral interictal epileptiform activity was not viewed as indicative of bitemporal epilepsy.

### Surgical Procedure

All patients underwent transcortical SelAH, a procedure that has been described in greater detail elsewhere.19 Since 1993, all procedures have been performed using frameless stereotaxy under general anesthesia, regardless of the side of operation relative to cerebral dominance. Briefly, the procedure involves performance of a frontotemporal craniotomy, followed by a corticectomy along the superior bank of the middle temporal gyrus, subpial extension of this line of entry down along the superior temporal sulcus, across the temporal white matter, and into the temporal horn of the lateral ventricle. Once inside the ventricle, the hippocampus, amygdala, entorhinal cortex, and uncus are resected.

### Histopathological Study

Resected specimens were reviewed by a neuropathologist at the time of the operation for evidence of hippocampal sclerosis or the presence of other lesions. All specimens were then examined by routine and immunohistochemical staining with antibodies to glial fibrillary acidic protein.

### Patient Follow-Up Interviews

In addition to the follow-up interviews conducted by the neurologists (F.A. and F.D.), all patients were contacted by mail and asked to participate in a survey of seizure frequency since the time of the operation.

### Statistical Analysis

Two-sample t-tests were used to calculate the statistical significance of the extent of resection of amygdala, hippocampus, and entorhinal cortex between the good and poor seizure groups. The statistical significance of the differences in preoperative characteristics (for example, MR imaging findings and EEG results) was calculated using the two-tailed Fisher exact test.

### Results

#### Characteristics of the Patient Population

Of the 27 patients with good seizure control in this study, 48% were female and 52% were male. The median length of the follow-up period was 47 months (range 24–92 months). In none of these patients was there any evidence of an intracranial tumor, cortical dysplasia, or a vascular lesion on MR images.

For the 27 patients with poor postoperative seizure con-
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trol, 44% were female and 56% were male. The median length of the follow-up period was 58 months (range 24–156 months). Neither sex distribution nor length of follow up varied significantly between the two Engel outcome groups. The median age of the Engel I/II group (33 years [range 13–55 years]) was slightly older than that of the Engel III/IV group (27 years [range 10–44 years]), but there was no statistical significance (p = 0.041). The year of operation within this series was not found to correlate with seizure outcome (Table 1). In none of these patients was there evidence of a tumor or vascular lesion on preoperative MR images or histopathological slides, and in none was cortical dysplasia or heterotopia known to exist prior to this study (see later discussion). The side on which the operation was performed (left or right) did not correlate with the volume of resection or with the postoperative seizure outcome (Table 1).

Stratification of Outcome Based on Preoperative Patient Characteristics

Among the 27 patients with poor postoperative seizure control, there was evidence in 15 patients of bitemporal epilepsy on the preoperative EEG or S-EEG study, in comparison with seven of 27 patients in the group with good postoperative seizure control (Table 1). In three patients in the Engel III/IV group there was EEG evidence of extratemporal epileptic activity, whereas similar evidence was found in only one patient in the Engel I/II group (Table 1). In two patients in the Engel III/IV group there was evidence of exclusively temporal neocortical activity and no evidence of a mesial temporal focus (based on preoperative EEG and intraoperative ECoG studies), whereas this finding was found in no patient in the Engel I/II group (Table 1).

A significantly higher percentage of patients in the Engel III/IV group (10 [37%] of 27 patients) had undergone preoperative depth electrode investigation, compared with patients in the Engel I/II group (two [7%] of 27 patients) (p = 0.004; Table 1). Depth electrode implantation (S-EEG) is used at MNI when seizure onset is ambiguous with respect either to lateralization or to localization within a hemisphere.

Five of the patients in this study underwent preoperative PET scanning and three patients underwent preoperative SPECT scanning. Four patients in the Engel I/II group and five patients in the Engel III/IV group underwent PET, SPECT, and/or S-EEG studies during the preoperative evaluation. In one patient in the Engel III/IV group, both PET and SPECT scans were interpreted as disclosing no abnormalities, but the S-EEG study disclosed predominantly left-sided seizure onset. In another patient (Engel III/IV group), SPECT scans disclosed a left temporal lobe abnormality, but the S-EEG study disclosed clinically relevant seizures arising predominantly from the right mesial temporal structures. For the remaining patients, the PET or SPECT data were consistent with the S-EEG data.

A significantly higher percentage of patients in the Engel III/IV group (five [19%] of 27 patients) demonstrated normal hippocampal volumes bilaterally on MR images compared with the Engel I/II group, in which no patient was found to have normal volumes bilaterally (p = 0.008; Table 1). In approximately one third of the patients in the Engel III/IV group, there was MR imaging evidence of bilateral, asymmetrical hippocampal atrophy in comparison with 11% of patients in the Engel I/II group, although this difference did not attain statistical significance (p = 0.078; Table 1).

In one patient in the Engel III/IV group, there was evidence on MR images of an extratemporal cortical dysplasia, and in another patient bilateral periventricular heterotopias were identified. Each of these findings had been missed during previous reviews of pre- and postoperative MR images. Another patient had global hemispheric atrophy and malformation of the first branchial arch. Finally, in four (17%) of 23 patients in the Engel III/IV group, there was no evidence of histopathological abnormalities based on material resected at surgery, in contrast with findings in one patient (4%) in the Engel I/II group (Table 1).

Thus, in the majority of patients in whom suboptimal seizure control was achieved (Engel Class III or IV) following the initial SelAH there was no evidence of unilateral MTLE on the preoperative EEG, MR imaging, and/or histopathological studies.

Finally, 24 (89%) of 27 patients in the Engel III/IV group underwent IAPs (10 for memory, eight for speech, and six for memory and speech evaluation), as opposed to 12 (44%) of 27 patients in the Engel I/II group (five IAPs for memory, five for speech, and two for memory and speech evaluation).

Extent of Resection

All patients in this study underwent SelAH while in a state of general anesthesia, raising the question of whether the surgeon’s concern about cerebral dominance in an asleep patient might result in a more conservative resection and hence a poorer outcome. Nevertheless, the number of patients who underwent surgery on the established or presumed side of dominance was similar in each outcome group: in 17 (63%) of 27 patients in the Engel I/II group and in 19 (70%) of 27 patients in the Engel III/IV group, the side on which the operation was performed coincided with the established or presumed side of language dominance based on results of the preoperative IAP or on handedness and neuropsychological evaluation for patients in whom an IAP had not been performed. Furthermore, pre- and postoperative MR images were available for nine of 17 patients in the Engel I/II group and eight of 18 patients in the Engel III/IV group for whom the side of the resection and the presumed or proven language dominance coincided. For these patients, no statistically significant difference in the extent of resection was found between patients undergoing operations on the dominant compared with the nondominant side.

Figure 1 illustrates the percentages of resection of the amygdala (Fig. 1 left), hippocampus (Fig. 1 center), and entorhinal cortex (Fig. 1 right) in patients with good (Engel Class I or II) and poor (Engel Class III or IV) seizure outcome scores. No statistically significant difference was found between the good and poor outcome groups with respect to the extent of either the hippocampal or amygdalar resection (p = 0.053 and 0.37, respectively), although a trend toward significance was found in the greater extent of hippocampal resection for patients with good as opposed to poor outcomes. Of note, in patients in the Engel I/II outcome group a significantly larger resection of the entorhinal cortex was found compared with the Engel III/IV group (Table 1).
inal cortex was performed than in those in the Engel III/IV group (p = 0.006; Fig. 1).

Repeated Operation

All second resections were performed on the same side as the original surgery. In seven of the 13 patients unilateral EEG findings were observed before the initial surgery. The patients with unilateral MTLE based on preoperative EEG and imaging were not invasively studied before the second surgery. Of the remaining six patients who underwent a repeated operation, four had bitemporal onset indicated by the initial EEG study, one had bifrontal and unilateral frontocentral onset, and one had bilateral centroparietal onset shown on the EEG study. Of the patients not undergoing a second surgery, in one there were unilateral findings on the EEG study and in another, although there was no EEG report in his chart at the time of review for this study, the referring neurologist had reported unilateral findings.

In all, 13 (48%) of the patients who initially had an Engel Class III or IV outcome, underwent a second operation for seizure control (Table 2) consisting of either an additional SelAH (six patients) or a CorAH (seven patients). Note that gliosis from the previous surgery made the use and interpretation of intraoperative ECoG during the second surgery very difficult and, hence, useless as a predictive tool. Pathological specimens were not available in the reoperated cases. Three of six patients who underwent a repeated SelAH and one of seven patients who underwent a CorAH as a second operation improved to Engel Class I following the second surgery (four patients total [31%]). The remaining nine patients (69%) did not improve following the second surgery.

Of the 13 patients who underwent a second operation, preoperative MR images and two sets of postoperative MR images were available for seven patients. We calculated the extents of the resections of the amygdala, hippocampus, and entorhinal cortex for each of these seven patients by per-

![Bar graphs demonstrating the percentages of the amygdala (left), hippocampus (center), and entorhinal cortex (right) that were resected in the 27 patients in the Engel I/II group (white bars) and the 27 patients in the Engel III/IV group (shaded bars).](image)

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### Table 2

<table>
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<th>Case No.</th>
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<th>Op No. 1</th>
<th>Op No. 2†</th>
<th>Pathological Finding</th>
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<td>CorAH IV</td>
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* Patient outcomes are based on Engel classes. Abbreviations: FNLG = focal neuronal loss with gliosis; hippoc scl = hippocampal sclerosis; LHA = left-sided hippocampal atrophy; NL&G = neuronal loss and gliosis; RHA = right-sided hippocampal atrophy; 3 sz = possibly three seizures; — = volumetric analysis was not performed before surgery.
† All second operations were performed on the same side as the first operation.
‡ Suspected abnormality in the left superior parietal gyrus (investigation pending).
§ Left-hemisphere abnormality in the left superior parietal gyrus (investigation pending).
‖ Bitemporal epilepsy (greater on left side than on right side on S-EEG; greater on right side than on left side on MR imaging).
forming semi-quantitative volumetric analysis (see Clinical Material and Methods) following each operation (Fig. 2).

The four patients who improved to Engel Class I or II following a second surgery had all undergone surgery on the right side: MR images revealed right hippocampal atrophy in three of the four patients and bilateral hippocampal atrophy, with the left side more severely affected, in one patient. Of the nine patients who did not improve following a second surgery, eight underwent left-sided resections and one underwent a right-sided resection. Volumetric analysis of preoperative MR images disclosed normal hippocampal volumes bilaterally in three of the nine patients, and bilaterally symmetrical hippocampal atrophy in one patient. In one patient the atrophy was greater contralateral to the side of surgery and in two patients the side of the hippocampal atrophy was discordant with the side of surgery. We were unable to locate MR images and reports for the two remaining patients in whom a second operation was unsuccessful.

Of the 13 patients who underwent a second operation, one set of preoperative MR images and two sets of postoperative MR images were available for seven patients. We calculated the extents of the resections of the amygdala, hippocampus, and entorhinal cortex for each of these seven patients by performing semi-quantitative volumetric analysis (see Clinical Material and Methods) following each operation (Fig. 2). Although the sample size is small, it should be noted that three patients (Cases 1, 3, and 7 in Fig. 2) underwent total or near-total resections of the amygdala, hippocampus, and entorhinal cortex during the second operation, but did not improve to Engel Class I or II. Nevertheless, two patients (Cases 2 and 4 in Fig. 2) did become free from seizure following further resection of the mesial structures.

Discussion

All patients in this study underwent surgery performed by a single surgeon (A.O.) at a single institution, eliminating some potentially important variables in any assessment of surgical outcome. We chose a minimum of 2 years of follow up for inclusion in our study on the basis of evidence suggesting that freedom from seizures at 2 years is a good predictor of long-term remission.\(^7,23\) We compared 27 patients with Engel Class III or IV outcomes with a comparable group of patients with Engel Class I or II outcomes to determine whether preoperative factors were predictive of seizure outcome following SelAH. The 27 patients in the Engel III/IV group were compared with 27 randomly selected, age- and year-of-operation–matched controls (Engel I/II group). Although there is a possibility of bias in the selection of a comparison group from the larger series of patients, the matched-group comparison design was selected to provide a truer comparison of outcomes, by factoring out patient age, surgeon’s learning curve, and technological advances as potential variables in outcome.

We performed an audit of the range of the resections of the amygdala, hippocampus, and entorhinal cortex for these same two groups of patients, and attempted to stratify seizure outcomes for patients undergoing SelAH according to the extents of resection of the various mesial structures, to identify a resection profile that corresponds to a successful outcome. Given the recent international interest in the use of radiosurgery for the performance of SelAHs, the attempt to define the minimum volume of mesial resection necessary for optimal seizure outcome is a pressing concern. Although it seems reasonable to target the area encompassed by a standard mesial resection, we cannot affirm that this will result in an outcome that is comparable to surgery with respect to long-term postprocedural seizure control rates and cognitive results. As yet, there is no sufficient follow-up period after radiosurgery to make this comparison, and there is no published report of a randomized, blinded comparison of surgery and radiosurgery for the treatment of MTLE.

Criteria for a Diagnosis of MTLE

The diagnosis of MTLE rests on findings of the semiological investigation, EEG, and MR imaging, and it relies as much on what is not present as on what is present. The findings of complex partial seizures, interictal sharp waves arising in the mesial temporal structures without evidence of extratemporal epileptiform activity on EEG, and unilat-
eral mesial temporal sclerosis on MR imaging without extratemporal lesions, together yield the diagnosis of MTLE. A striking finding of this study was that the majority of patients who did not attain good postoperative seizure control following SelAH, did not fulfill these strict criteria for MTLE on preoperative evaluation. Based on the current study, we would not alter the evaluation of these atypical patients: to wit, those patients not meeting the criteria for MTLE (on semiological, EEG, and imaging studies) will continue to be evaluated by PET and SPECT scanning, other investigational imaging techniques as these arise, and invasive monitoring, as indicated by the particulars of each case.

Indications for SelAH

This study was conducted in a retrospective fashion, and the criteria for SelAH have evolved over the study years. For the most part, patients undergoing SelAH at MNI have met the following criteria: 1) the presence of a clinically significant epileptogenic focus in the mesiobasal limbic structures ipsilateral to the side of resection, and 2) a reasonable function of the contralateral mesiobasal temporal lobe. \[18\] A few patients have undergone SelAH as a palliative treatment, as occurred in one patient in this study (Case 8 in Table 2). As described by Wieser, \[26\] the palliative SelAH is reserved for patients in whom the mesiobasal structures form a “secondary pacemaker” for a seizure focus that is either larger than the structures to be resected, or in whom the epileptogenic focus lies in eloquent cortex entirely outside the area of intended resection, yet propagates by means of the mesiobasal temporal structures.

Procedure of SelAH

Multiple approaches to mesial structures of the temporal lobe have been published, including transsylvian, \[27\] transcortical via the first temporal gyrus, \[28\] subtemporal through the parahippocampal gyrus. \[29\] We favor a transcortical approach via the second temporal gyrus, which is performed while remaining anterior to the central sulcus—both factors minimize the risk of postoperative language deficits. \[10\] The details of this procedure are described elsewhere. \[18\]

Seizure Outcome

Although the median age of the patients in the Engel I/II group (33 years [range 13–55 years]) was slightly older than that of the patients in the Engel III/IV group (27 years [range 10–44 years]), recent work suggests that older age at surgery—formerly thought to be a factor in poorer seizure outcome—does not have an impact on postoperative seizure control. \[13\] The coincidence of the side of presumed or proven language dominance with the side of resection did not correlate with either the volume of resection or postoperative seizure outcome, suggesting that any concern on the part of the surgeon about potential hemispheric dominance had no significant impact on the extent of resection or on outcome. The year of the operation within this series did not correlate with seizure outcome, suggesting that the surgeon’s learning curve for the technique did not adversely affect postoperative seizure control.

The proportion of patients in whom there was evidence of bitemporal epilepsy on preoperative evaluation, but who, nonetheless, achieved good seizure outcome was 19% (five patients). Recent work by Ergene and colleagues, \[30\] however, suggests that the frequency of bitemporal abnormalities in cases of TLE is higher than previously reported and that this is evident when patients are monitored for a long enough period of time. Given the retrospective nature of this study, it is not possible to go back and standardize the preoperative EEG evaluation of the patients included in this study.

Of note, the designation “Engel Class III” includes patients who have had a significant reduction in seizure frequency, yet continue to experience disabling seizures. This category encompasses a broad range of outcomes, and includes patients who underwent surgery for the intent of palliation (for example, Case 8 in Table 2).

Extent of Mesial Resection in Relation to Postoperative Seizure Control

We measured the extents of the resections of the amygdala, hippocampus, and entorhinal cortex for patients with good seizure control and those with suboptimal seizure control following SelAH. Both pre- and postoperative MR images were available in 48% of patients in the Engel I/II group and in 56% of patients in the Engel III/IV group. The postoperative MR images available for this study were obtained within the first 6 months following surgery. Although it is potentially feasible, from a technical standpoint, to obtain postoperative MR images in the remaining patients, these studies would now be performed in a greatly delayed fashion, allowing for the possibility of significant retrograde degeneration and thus, introducing yet another confounding variable into the assessment. For patients in whom MR images were available, no significant difference was found in the extent of amygdalar resection between the two outcome groups. Although not statistically significant, a trend toward significance was found in the extent of hippocampal resection between the two groups. Finally, the extent of entorhinal cortex resected was significantly greater for patients with Engel Class I or II outcomes than for those with Engel Class III or IV outcomes postoperatively. Siegel, et al., \[30\] noted a positive correlation between postoperative seizure control (follow-up period lasting ≥ 1 year) and the extent of the parahippocampal resection in 21 patients with nonlesional epilepsy (no evidence of tumor or vascular lesion) who had undergone SelAH. These authors defined the parahippocampal gyrus as including the entorhinal cortex and subiculum, and also noted a “decisive” relationship between the extent of subicular resection and seizure outcome. The extent of the entorhinal cortex resection was not described independent of the findings for the parahippocampal gyrus, and 12 of the 21 patients who were described underwent surgery for reasons of palliation and, presumably, did not have unilateral MTLE, making the results difficult to compare with the findings of our study.

Despite the finding of a statistically significant difference in the extent of entorhinal cortex resection between the Engel I/II and Engel III/IV groups, it is important to note that preoperative patient characteristics are of critical importance in the prediction of freedom from seizure. This caveat is illustrated in Fig. 2, which demonstrates total or near-to-
tal resection of the amygdala, hippocampus, and entorhinal cortex in five patients who underwent a second operation for seizure control. Of 13 patients who underwent additional resections, only four became seizure free. Of these 13, postoperative images following the second surgery were available for seven patients. With two exceptions, these additional MR imaging-verified mesial resections did not improve seizure control significantly. The observation that two patients (Cases 2 and 4 in Fig. 2) did, however, become free from seizure following further resection of the mesial structures, implies that for a small subpopulation of patients in whom the initial SelAH fails, a further resection of the mesial structures is warranted.

Critical Volume of Mesial Resection Required for Seizure Freedom

There is no consensus regarding either the minimum necessary volume of resection14,16,29 or which structures must be resected30 for freedom from seizure following TLE surgery. To date, however, the most commonly cited reason for failed temporal lobectomy has been an inadequate hippocampal resection.14,16,29 In a recent article addressing this topic, McKhann and colleagues16 noted that a maximum hippocampal resection in all cases may not be necessary for seizure control and may contribute to postoperative memory deficits. With these caveats in mind, they performed a prospective, randomized study of patients undergoing CorAH by using intraoperative ECoG recordings from the ventricular surface of the hippocampus in an effort to answer the question of whether the extent of hippocampal resection correlated with seizure outcome. These authors found no correlation between the extent of the hippocampal resection (mean 27.9 mm, range 5–46 mm) and postoperative seizure control at a follow-up period of 18 months. Although they noted that the anterior and lateral neocortex, the cingulate cortex and the hippocampus, were also resected in each case, no comment was made about the extent of resection of each of these structures, or whether this correlated with outcome. The authors did note, however, that the presence of postresection hippocampal ECoG spikes was associated with patients in whom seizure control was worse than in patients without this hippocampal epileptiform activity (p < 0.001). It is unclear from their report whether residual hippocampal ECoG activity and, hence, poor outcome could be converted into a good outcome by further hippocampal resection to a point at which ECoG no longer demonstrated epileptiform activity.

In our study, the findings in four patients who became seizure free following a second operation, in which further resection of mesial structures was performed, suggest that there is a critical volume of amygdala, hippocampus, and or entorhinal cortex that must be resected to attain optimal seizure control. The small number of patients for whom this was true, however, did not permit the determination of how much of which structure or combination of structures was essential to achieve seizure freedom. Postresection ECoG was not routinely performed in our study because, in our experience, the increased interictal spiking observed following SelAH has not correlated with seizure outcome.3

As all reported series of temporal lobe resections for MTLE result in approximately the same reported rate of seizure control postoperatively, it is conceivable that techniques at the various centers all result in severing a critical proportion of the connections between the entorhinal cortex (primary hippocampal afferent) and the hippocampus, and between the fimbria–fornix (primary hippocampal efferent) and the hippocampus, thereby blocking the entrance and/or propagation of recurrent excitation. It is possible, therefore, that it is the percentage of afferent and efferent connections of the mesial structures and not the volumes of the structures themselves that is the critical factor in determining seizure outcome. At this time, however, no imaging modality exists that can trace and quantify this type of connectivity.

Repeated Operation

The results of our study do not alter our willingness to perform a second operation for further resection of mesial structures, once an exhaustive reevaluation has been conducted for the possibility of a focus outside of the mesial structures. It should be noted that the decision to reoperate is sometimes capricious, and may depend on the wishes and biases of the patient or on those of the treating surgeon or neurologist. Nonetheless, we consider patients who experience a prolonged seizure-free interval following initial surgery to be good candidates for further resection. Our study, which spans the years 1986 to 1998, covers a period notable for improvements in the quality of MR imaging. These improvements have enhanced our ability to detect extratemporal lesions, which constitute one possible source of the failure of SelAH to treat epilepsy. Furthermore, four of seven patients who underwent a second resection became free from seizure following this second resection, which is still a better outcome for medically refractory patients than any other option currently available. Unfortunately, the small number of patients who became free from seizure following a second resection did not permit the identification of factors predictive of a successful reoperation.

Because no conclusive evidence demonstrates that a more conservative resection spares cognitive function, why not perform maximum resection of mesial structures in all patients, rather than bring selected patients back for a second operation? The lack of a demonstrable cognitive benefit resulting from a more conservative mesial resection is not an indication that there is no difference (from a cognitive standpoint) between a conservative and an aggressive resection. Rather, it remains entirely possible that the current standard for cognitive testing is not a sensitive enough measurement to detect differences in cognition between more and less aggressive resections.

Furthermore, from an anatomical standpoint, the hippocampus extends around the splenium and rostral to the body of the corpus callosum, as the induseum griseum. Practically speaking, therefore, one must pick some point at which to halt the resection. There is no evidence that extending the resection posterior to the lateral medullary sulcus will improve seizure outcome. In addition, the risks of operating in an increasingly deep and narrow hole as the resection extends more posteriorly, seem too dangerous to advocate—particularly when surgery is performed in the dominant hemisphere.

Dual Pathological Conditions and the Concept of Pseudotemporal Epilepsy

A subpopulation of patients with semiological findings...
suggestive of MTLE harbors an extratemporal epileptogenic origin that may be clinically silent or subtle. The seizures become clinically manifest once they propagate to the mesial temporal structures, hence the term “pseudotemporal” epilepsy. Patients with pseudotemporal epilepsy may even, on occasion, have a second pathological condition, in addition to the hippocampal atrophy and sclerosis evidenced on MR imaging, and their seizure frequency may improve initially following SeAH or CorAH. Advances in imaging techniques over the last decade have increased our awareness of extratemporal lesions such as cortical dysplasias and nodular heterotopias. Two of the patients in the Engel III/IV group were found during this investigation to have MR imaging evidence of such extratemporal lesions. Nonetheless, it is conceivable that even the best of currently available imaging modalities is not yet sensitive enough to detect more subtle lesions of a structural or biochemical nature. This latter group may account for those patients who seem, for all intents and purposes, to represent clear-cut MTLE, yet who fail to respond to seemingly appropriate surgical treatment.

Goal of Surgery: Palliation Compared With Cure

Occasionally patients undergo surgical procedures aimed at ameliorating their seizures, thereby improving their quality of life, but with the expectation that the seizures will not be completely halted. An example would be a patient who has global hemispheric abnormalities and multiple seizure types, but is most debilitating by seizures arising in or propagating to the mesial temporal structures. For these patients, who do not meet the criteria for MTLE, a significant reduction in seizure frequency (Engel Class III) is considered a good outcome.

Conclusions

Factors Predictive of Poorer Postoperative Seizure Control

Apart from the occasional patient who undergoes surgery with the intent of palliation rather than the elimination of seizures, which patients can be predicted to have a poorer outcome following SeAH? Based on our retrospective review, the following types of patients were found among those obtaining suboptimal postoperative seizure control following SeAH: patients in whom there is evidence of significant bitemporal or extratemporal seizure onset; patients requiring depth electrode investigation to clarify seizure lateralization or localization, bilaterally normal hippocampal volumes on MR imaging, or “pseudotemporal” epilepsy; and, occasionally, patients in whom the resection of mesial structures has not been adequate. Ongoing improvements in imaging techniques have increased the likelihood of identifying extratemporal lesions in those patients without clear-cut MTLE. Remaining is a small group of patients who still cannot be distinguished from those with MTLE by all criteria, yet fail to respond to appropriate surgical therapy.

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References

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