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Is it necessary to define the ictal onset zone with EEG prior to performing resective epilepsy surgery?

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ABSTRACT

When evaluating candidates for neurosurgical treatment for medically intractable epilepsy, is it always necessary to define the region of seizure onset with EEG? A simple answer to this question is not possible. There are specific situations where surgery is commonly performed without clear EEG ictal localization, and other situations where electrical localization is mandatory. However, opinions differ in many other situations. What are the core issues for determining when EEG localization is necessary? Neuroimaging is imperfect. It does not always accurately identify the site of seizure origination, because seizures do not always arise from visible structural lesions. EEG localization is also imperfect, as well as expensive and time consuming. Sometimes the site of origin is not identified, or a region of spread is misidentified as site of origin. False localization and lateralization can occur. Finally, epilepsy surgery is imperfect. It can produce life-changing results, but it carries risk, and surgical failure is not rare.

The limitations of these methods, and the high stakes of epilepsy surgery imply that we should be very cautious to omit EEG studies. The desire to improve access to epilepsy surgery, and to minimize the expense and risk from inpatient EEG studies, must be weighed against the possibility of an ineffective resection. To improve outcomes, improvements in both neuroimaging and EEG techniques are needed.

1. Introduction

Although video/EEG monitoring is a key method for localizing the seizure onset zone in patients undergoing evaluation for possible neurosurgical treatment for medically intractable epilepsy, over the last 25 years, MRI and other neuroimaging methods have assumed an increasingly important place in this process. When is it possible to consider epilepsy surgery in the absence of clear localization of the ictal onset zone with EEG? Must the patient with nonlocalized scalp EEG seizures undergo intracranial EEG? Should the patient with a nonlocalized intracranial ictal electroencephalographic onset but a well-localized lesion still be offered surgery? Should such a patient even be exposed to the risk of intracranial EEG? A simple answer to these questions is not possible. Clearly, there are limited, specific situations in which surgery is commonly performed without clear electroencephalographic ictal localization and other situations where electrical localization must be viewed as mandatory. There are many situations between these extremes where opinions and practices differ. Here we review the arguments for and against requiring electrographic localization of the epileptogenic zone in all patients selected for resective epilepsy surgery.

2. Arguments for requiring electrical localization of the seizure onset zone

2.1. Anatomy is not physiology

In other words, the seizure onset zone does not always localize to a structural lesion visible on neuroimaging. This includes individuals without a structural lesion on MRI who nonetheless achieve seizure control after resection based on localization by interictal and ictal EEG, often with confirmatory tests such as ictal SPECT. However, there are also uncommon patients with a potentially epileptogenic structural lesion on MRI that are demonstrated to have seizures originating from a different region.

Good neurosurgical outcomes are possible in the setting of normal MRI in the subset of patients with electrographically well-defined temporal lobe epilepsy [1–4]. Overall rates of seizure freedom from 48% [1] to 56% [2] have been described. When all ictal and interictal abnormalities are confined to the basal temporal region, 78% were seizure free [1]. In addition, 77% were seizure free

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when there were accompanying lateralizing findings on neuropsychological testing [3]. On the other hand, seizure freedom is much lower after extratemporal neocortical resection if the MRI is normal [5–7]. For example, one series reported that only 17% of patients were seizure free after frontal lobe resections with a normal MRI [5].

Although surgical outcomes for MRI-normal neocortical epilepsy are poor, the good outcomes for MRI-normal temporal lobe epilepsy indicate that operating in that situation is worthwhile. In addition, a subgroup of patients initially thought to have a normal MRI on more careful examination may be found to have subtle lesions on MRI, particularly focal cortical dysplasia, and invasive EEG can be a useful confirmation of the focus in that situation.

Although MRI-defined structural lesions are a strong predictor of the seizure onset zone, there are reports of well-documented cases in which resections of EEG-defined seizure onset regions that spared structural lesions have resulted in seizure freedom. A series of 20 such cases were identified from one center, making up less than 5% of surgical cases over a 5-year period [8]. These patients had well-documented, unilateral, potentially epileptogenic structural lesions: hippocampal atrophy in 12; cortical atrophy or encephalomalacia in 4; focal cortical dysplasia in 2; focal calcification in 1; and cavernoma in 1. All patients had electroencephalographic localization of ictal onset to a different lobe, 11 to the contralateral hemispere; 16 underwent invasive monitoring [8]. After resection of the EEG-defined but MRI-normal seizure onset region, 50% were seizure free in 2 to 5 years of follow-up.

It has been reported that patients with unilateral mesial temporal sclerosis have roughly similar surgical outcomes in the settings of concordant and discordant noninvasive ictal EEG [9]. However, that study defined discordance as evidence of contralateral seizure origination, and did not address the possibility of additional extratemporal origination ("dual pathology"), nor was invasive monitoring performed in that series [9]. In addition, there is a report [10] of a small, well-documented subset of patients with temporal lobe epilepsy (5 of a series of 109 patients with temporal lobe epilepsy undergoing depth electrode recordings) with severe hippocampal sclerosis (a "burned out hippocampus") who have atypical spread of the ictal discharge, leading to false lateralization of the seizure on noninvasive EEG. In those patients, invasive monitoring demonstrates seizure onset from the sclerotic hippocampus, leading to resection and an excellent outcome [10]. Other investigators have also observed this phenomenon [11].

Despite this, there is also clear evidence that there is a different subset of patients with discordant localization with imaging and invasive monitoring, where resection of the electrically defined seizure onset zone can result in seizure freedom. This is suggested by the fact that a lack of concordance between MRI and scalp EEG findings was not found to be an independent predictor of prognosis in a multicenter study of surgical outcome [12]. It is typical practice to resort to invasive monitoring when MRI and scalp EEG disagree, demonstrating that localization of the seizure onset region with depth or subdural electrodes can successfully resolve such conflicts. Specific evidence of this comes from a large series of 119 cases (63 resected) with hippocampal atrophy [13]. In this series, the 6 surgical failures had concordant EEG and MRI. Of the 3 discordant cases, all underwent depth electrode recording and all were seizure free after resection of the EEG-defined seizure onset zone and sparing of the atrophied hippocampus.

In summary, even with classic epileptogenic lesions such as hippocampal sclerosis and cavernomas, there is a small subgroup of patients in whom seizures arise elsewhere. There are also patients with normal MRI scans that can be good surgical candidates. Careful localization of the seizure onset zone by scalp EEG, and, when appropriate, invasive EEG, is needed to ensure that these patient subgroups are identified and receive the correct operation. Anatomy does not always correspond to physiology.

2.2. Surgical failure must be due to incomplete resection of epileptogenic tissue, but is seldom the result of residual, MRI-detectable structural lesions

Failure is a significant risk for epilepsy surgery: 32% of patients with mesial temporal resections and 50% of those with neocortical resections do not achieve a 2-year seizure remission [12]. An additional 25% of patients with mesial temporal resections and 19% of those with neocortical resections subsequently relapse [12]. Why does surgery sometimes fail?

This question can be addressed by identifying the brain region where seizures recur after surgery fails. This was best studied by Hennessy et al. [14], who used EEG monitoring and MRI to reassess 44 of 51 patients with recurrent seizures out of a series of 282 individuals who received temporal resections. Only 4 of these 44 patients had residual epileptogenic structural lesions at the second evaluation. Of the 44, 29 recurred ipsilaterally.

Of the 20 patients who had mesial temporal sclerosis at the initial operation, 1 recurred in residual ipsilateral hippocampus, 13 recurred in ipsilateral neocortex, and 6 either recurred contralaterally or could not be localized. Of the 14 individuals with nonspecific pathology at initial resection, 1 recurred in the ipsilateral hippocampus, 7 in ipsilateral neocortex, and 6 either recurred contralaterally or could not be localized. An unusual feature of this series is that 10 patients who failed surgery had dysplastic neuroectodermal tumors initially: 7 recurred from ipsilateral neocortex and 3 either recurred contralaterally or could not be localized.

More studies of surgical failure are needed because the causes will depend on case selection, preoperative workup, and operative details. However, this study [14] demonstrates that the most common site of origin for recurrent seizures after mesial temporal resection is ipsilateral neocortex that appears normal on MRI. This finding raises the important question of whether better methods and more intense efforts to identify electrically abnormal neocortex during the initial presurgical evaluation leading to a different resection could someday lower the risk of surgical failure.

2.3. The relative value of different techniques for localization has changed over time, and will continue to change

In the earliest days of epilepsy surgery, interictal and ictal EEG was the primary method of determining the surgical target. For example, prior to the introduction of cranial MRI in 1985, mesial temporal sclerosis and small low-grade neoplasms were typically not found on imaging studies but only discovered on postoperative pathological examination of tissue removed on the basis of electroencephalographic localization [15]. In the subsequent 20 years, however, the role of neuroimaging has steadily increased. Higher-resolution MRI allowed routine detection of mesial temporal sclerosis, cavernomas, and small tumors, and is increasingly useful for detection of cortical dysplasia. Ictal SPECT has become a useful supplementary localization method, with digital subtraction of the interictal image and corregistration with MRI increasing its value. At the same time, there have been only limited advances in clinical neurophysiological methods of localization, but this is beginning to change.

In the last few years, new clinical neurophysiological methods have been developed for localizing the seizure onset zone. One new noninvasive technique is dense array EEG, which uses 256 or more electrodes to decrease interelectrode distances and to provide better coverage of anterior and inferior brain regions. Such recordings can be extended for 3 or 4 days to capture spontaneous seizures. This method has been shown to detect ictal discharges earlier and more often, and with the aid of source localization software, provide more precise delineation of the seizure onset zone [16]. Another approach to improving the utility of scalp EEG is the use of DC-coupled amplifiers to record infraslow (<0.5 Hz) activity [17] from the scalp. Because the

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ictal signal has greater power in the infraslow band than at higher frequencies, activity in this range localizes some focal seizures that cannot be localized with conventional EEG [18].

The most important advance in improving ictal localization with EEG, however, has certainly been the use of high-frequency EEG analysis in invasive monitoring [19]. This work has become possible because of the availability of commercial EEG equipment that has the necessary characteristics—bandwidth to 500 Hz and beyond and a sampling rate of at least 2000 Hz—to record at high-frequency ranges that have been ignored in the past. High-frequency oscillations (HFOs), ripples (80–250 Hz) and fast ripples (250–500 Hz), have been recorded in humans with microelectrodes and conventional depth electrodes. Some HFOs are recorded from normal brain and reflect synchronous inhibitory postsynaptic potentials (IPSPs) from interneurons; others are recorded during seizures [19–21] and also from abnormal brain capable of ictogenesis. These likely are due to synchronized abnormal neuronal firing [22].

A potential source of error in interpretation of conventional invasive ictal recordings is that surgically implanted electrodes may be placed in a location that does not adequately cover the seizure onset zone. When this occurs, the electrodes from which the ictal discharge first appears may represent only a region of secondary spread from an uncovered, and thereby unidentified, seizure onset zone. The potential value of recording HFOs would be to distinguish genuinely epileptogenic brain regions from sites of mere secondary seizure propagation. Direct evidence that this may be the case comes from a report of 20 patients in whom resection of regions generating HFOs correlated better with seizure-free outcome than removal of the "EEG seizure onset zone" as determined from the apparent region of seizure onset on conventional invasive EEG, or of regions generating interictal spikes [23].

Current and continuing innovations in electrical recording and neuroimaging have the potential to improve surgical outcomes. As progress is made in each area, the relative contribution of electrical and imaging methods in each surgical situation will be subject to change.

2.4. Summary of arguments for requiring electrical localization of the seizure onset zone

It may be reasonable to resect unilateral hippocampal sclerosis with some definitive corroboration from other techniques, such as PET, SPECT, and neuropsychology, as long as ictal EEG is unlocalized but not contradictory. However, almost all other situations require clear electrical ictal localization. Why is this so?

The main reasons are that there are patients with normal neuroimaging that can benefit from epilepsy surgery, and that there are also infrequent, but well-documented cases in which there is a potentially epileptogenic lesion on MRI, but the seizures actually arise from another, distant brain region.

In addition, surgical failure is a significant risk in all situations. This typically is due to an undetected second focus. It is important to carefully look for additional seizure onset regions to reduce the risk of surgical failure. When the seizure onset region is carefully localized with scalp EEG, and it contradicts neuroimaging data, invasive EEG is an appropriate and reliable method to resolve this conflict, and can lead to successful surgical treatment.

Any debate on the relative merits of localization by EEG and neuroimaging will be influenced by the era in which the discussion takes place. Newer methods, particularly the recording of HFOs during invasive monitoring, promise to increase the value of electrical localization.

3. Arguments for not requiring electrical localization of the seizure onset zone

The value of ictal recording in preoperative patient selection and surgical planning is inversely proportional to the degree of concordance of other streams of data including clinical and behavioral ictal semiology, background and interictal electrographic disturbances, anatomic and functional imaging findings, and localizing neuropsychological deficits. We therefore stipulate that ictal recording is absolutely required in patients in whom there is no detectable anatomic lesion, no localized interictal EEG-revealed abnormality, no specific localizing seizure semiology, and no discrete functional imaging abnormality. Nonetheless, it is notable that in this population, even with ictal recording, the rate of surgical cure is low. In one series of patients with frontal lobe epilepsy with negative SPECT findings, the postoperative seizure freedom rate was <25% [7]. By contrast, in patients with single well-delineated anatomic lesions known to be commonly associated with focal epilepsy, for example, cavernous angioma or mesial temporal sclerosis in the absence of dual pathology, concordant unifocal interictal epileptiform spikes, a typical concordant localizing seizure semiology, and unambiguous concordant functional imaging abnormality on PET or SPECT examination, studies of the predictors of surgical success have not demonstrated a measurable incremental contribution of ictal recording. It is therefore clear that the need for ictal recording varies based on the specifics of the individual patient's clinical situation, and a blanket or absolute requirement for ictal recording cannot be justified.

The arguments in favor of requiring ictal recording presented in the first part of this article are superficially attractive and initially compelling. They are weakened, however, when evaluated in the context of risk as well as benefit. Principal risks of ictal recording are that (1) recordings will be noninformative; (2) recorded data will be misleading; (3) injury will occur during the recording process; and (4) an absolute requirement for ictal recording will be prohibitive financially or logistically and therefore lead to denial of potentially curative treatment in specific populations of patients with epilepsy. In the following discussion we consider each of these risks individually.

3.1. Risk that ictal recordings will be noninformative

Ictal recordings may be noninformative either if the tracing is obscured by artifact or otherwise uninterpretable or if the recording is purely confirmatory and adds no incremental value. The latter situation is trivial and requires no further discussion. Obscured tracings are frequently encountered in frontal lobe epilepsy cases in which high-amplitude muscle and movement artifact overwhelms the lower-amplitude electroencephalographic activity. In cases in which there is a visible relevant frontal lobe lesion, if all else is consistent, there may be no need for additional attempts at ictal recording. In some cases the argument that intracranial recording is required to fully define the epileptogenic zone may be advanced; however, outcome studies show a strong correlation between positive surgical outcome and completeness of the anatomic resection, thereby mooting the need for additional electrical information. Less frequently, temporal lobe seizures are obscured by chewing artifact, sometimes making lateralization difficult. In these situations, if there is compelling lateralizing information from other streams, the need for invasive ictal recording should be carefully considered before committing the patient to the added delay, risk, and expense.

3.2. Risk that ictal recording will be misleading

In at least three situations scalp ictal recordings can be misleading. Well-documented examples demonstrate that the apparent distribution of ictal activity may represent the target of propagation rather than the site of origin or epileptic focus [9]. False lateralization of scalp EEG has been described in patients with gross focal lesions [11] and in patients with severe unilateral hippocampal atrophy [10]. Finally, experience with invasive or minimally invasive recording demonstrates that on occasion, the apparent distribution of ictal activity may be skewed by sampling bias. For example, using foramen ovale

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electrodes, we have observed that in 5% of seizures, onset in one mesial temporal lobe precedes scalp onset over the contralateral hemisphere by 10–30 seconds. In this situation, scalp EEG alone would have been misleading because of inadequate sampling from mesial structures. So, although it may be true that anatomy is not physiology, it is equally true that electroencephalography is not epilepsy!

3.3. Risk of injury during the recording process

Serious injuries occur in the course of epilepsy monitoring. Noe and Drazkowski reported an 11% incidence of injury or complication in one series of patients admitted to an epilepsy monitoring unit who experienced generalized convulsions, often in the setting of deliberate medication reduction [24]. Withdrawal of medication may be ill advised in patients predisposed to status epilepticus. Ictal behavior may be violent and self-injurious as evidenced by the occurrence of verterbral compression fractures, tongue lacerations, dental injuries, and shoulder dislocations associated with convulsive activity. Tolerable ictal behavior during scalp recording may be intolerable when intracranial electrodes are in place. Finally, postictal behavior including combativeness and frank psychosis may be dangerous for both patients and staff.

3.4. Risk that an absolute requirement for ictal recording will be prohibitive in specific populations of patients with epilepsy

There is general consensus that epilepsy surgery is underused. In the United States alone, conservative estimates suggest that there are 315,000 potential candidates for epilepsy surgery (50% of the 30% of patients with refractory partial epilepsy calculated using a 1% prevalence estimate for all epilepsy). By contrast, the annual number of surgical procedures for epilepsy in the United States can be generously estimated in the low thousands. The situation in other developed countries is similar, whereas in much of the developing world, access to epilepsy surgery is essentially unheard of. In this setting, erecting absolute barriers such as an insistence on ictal recording prior to any epilepsy surgery would effectively deny entire populations access to treatment. Regardless of the absolute availability of recording, in some parts of the world, patients would have to travel hundreds or even thousands of miles to access the technology. And finally, even if recording could be accessed, for some populations, it might be prohibitively expensive. As the epilepsy community struggles to address the treatment gap, we would argue that special care should be taken to avoid inadvertently worsening an already bad situation.

3.5. Summary of arguments for not requiring ictal recording prior to epilepsy surgery

The previous discussion of risks of ictal recording strongly supports the position that risks of recording are sometimes unwarranted, but does not resolve the issue of whether recordings are unnecessary. For this, only a controlled clinical trial would be sufficient, and such a trial has not been performed. Outcome studies in which success of surgery is assessed in a nonrandomized fashion, generally retrospectively, are not helpful as they cannot determine how surgical decisions would have been made in the absence of ictal data. We are therefore left with clinical experience to address the question for the time being. In our experience, ictal recording adds little to decision making in the settings of highly concordant data, and especially in patients with compelling anatomic data for whom other data streams are either unavailable or corrupted.

4. Conclusions

Neuroimaging is imperfect. It does not always accurately identify the site of seizure origination. It is clear that seizures may, on occasion, not arise from the structural lesions. EEG localization is also imperfect, as well as expensive and time consuming. Sometimes the site of origin is not identified, or a region of spread is misidentified as site of origin. False localization and lateralization can occur. Finally, epilepsy surgery is imperfect. It can produce life changing results, but it carries risk, and surgical failure is not rare. The limitations of the methods of localization and the high stakes of epilepsy surgery mean that we should be very cautious to omit EEG studies. The expense and the risks of both scalp and invasive EEG must be balanced against the consequences of an ineffective resection, and this calculus must take into account the need to optimize access to potentially life-changing treatment. To improve outcomes in the future, we need improvements in both neuroimaging and EEG techniques.

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