Electrophysiology in epilepsy surgery: Roles and limitations

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Abstract

Successful epilepsy surgery depends on the localization of the seizure onset zone in an area of the brain that can be safely resected. Defining these zones uses multiple diagnostic approaches, which include different types of electroencephalography (EEG) and imaging, and the results are best when all of the tests point to the same region. Although EEG obtained with scalp recordings is often sufficient for the purposes of localization, there are times when intracranial recordings directly from the brain are needed; but the planning, use, value, and interpretation of the these recordings are not standardized, in part because the questions that are to be answered vary considerably across many patients and their heterogenous types of epilepsy that are investigated. Furthermore, there is a desire to use the opportunity of direct brain recordings to understand the pathophysiology of epilepsy, as these recordings are viewed as an opportunity to answer questions that cannot be otherwise answered. In this review, we examine the situations that may require intracranial electrodes and discuss the broad issues that this powerful diagnostic tool can help address, for identifying the seizure focus and for understanding the large scale circuits of the seizures.

Key Words

Epilepsy surgery, electroencephalography, electrophysiology, intracranial electrodes

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Electrophysiology has been a tool for understanding epilepsy almost from the discovery of EEG in the early twentieth century, and it has been one of the key components used in localizing the seizure onset zone in preparation for surgery. Although EEG recorded with electrodes on the scalp often provides sufficient localizing information, monitoring for seizures and interictal activity from electrodes on and in the brain is often considered the most accurate method for identifying the seizure onset zone. One places the electrodes in the area (s) where the seizures are most likely to start and waits for them to give their hiding places away. However, the unfortunate reality is that success in controlling the seizures following resections guided by intracranial electrodes is no better than resections that are determined by the results of noninvasive evaluation. One may reasonably ask if the success is no better, why would one subject a patient to the extra risk and expense of intracranial monitoring. The

primary reason is that people who undergo this monitoring are those for whom the noninvasive evaluation did not reveal a likely seizure onset zone. For people to whom surgery would not otherwise be offered, intracranial monitoring offers a very real potential to find the seizure onset zone and bring the seizures under control. There are, however, very real limitations to the procedure. In this article, we will review the role of intracranial monitoring in epilepsy surgery; how it may best be applied, and what the limitations of the procedure are. One topic that we will not discuss is the EEG patterns that are considered most localizing. It is an area in which there is much interest but also very diverse views.

For a number of decades the basic parameters of successful epilepsy surgery have been well known: identify a structural abnormality and confirm with physiology (surface interictal and ictal EEG) that the seizures begin near the abnormality. If the area can be safely resected (e.g. temporal lobe or frontal pole) there is a high likelihood that the seizures will come under control. However, experience has taught us that this approach has a number of limitations. For example, with MRI scans we are frequently finding that a number of people with epilepsy have more than one structural abnormality that could be the source of the seizures.[1,2] In addition, prolonged EEG monitoring has shown that some people appear to have multiple seizure types with different ictal patterns on EEG even though they have a single overt

lesion on imaging. These scenarios raise the possibility of multiple distinct seizure onset zones[3] even when it is also possible that there is a single zone that may have different paths of spread from the focus or multiple foci within a single abnormality.[4] Another common situation is when there is no obvious abnormality on imaging, even when the seizures are probably focal in onset. It is in these situations in which there is a likely single focus, but several candidate seizure onset zones that intracranial monitoring has a role to play; but the use and placement of the electrodes have to be considered carefully to increase the chances that there will be a successful outcome.

Because it is not technically possible to cover the entire brain and potential seizure onset zones with electrodes, one has to focus the placement of the electrodes on the areas that are the best candidates to be the source of the seizures. For this reason, it is essential to have clear hypotheses about the likely sites of seizure onset, to be able to include or exclude them from potential resections. In deciding about the placement of the electrodes, one must also consider the likely type of surgery, so that there is a clear delineation of the seizure generators from the normal tissue and that an effective but safe surgery can be performed. Some understanding of the relation between the underlying pathology and seizure generation is essential. Is the abnormality likely the "focus" (e.g. a cortical dysplasia) or are the seizures more likely to be arising from the edges of the lesion (e.g. a tumor or an old injury)? Understanding these specific situations will guide the decision for optimal placement of the electrodes.

Using Intracranial Electrodes

The decision to use the electrodes is driven by the desire to increase the probability of making the patient seizure free. Our intention of performing the surgery is to make 100% seizure free in patients, but that goal is yet to be achieved. The highest success remains when there is a clear mesial or anterior temporal lobe abnormality on imaging and the interictal and ictal EEG are concordant with the imaging. Intracranial monitoring is almost never warranted in this situation, as resection of the abnormality will usually bring the seizures under control (70 to 90% probability depending on the lesion type).[5] On the other hand, when the lesion is less clear on imaging (or not immediately apparent) and the noninvasive physiology markers are less certain, intracranial electrodes may be needed.

Determining the Goals for Intracranial Recordings

Several common questions are asked in deciding where and how to use intracranial electrodes [Table 1]. The most common question, which is raised when there is a lesion (acquired, neoplastic or developmental) is, "Where do the seizures begin in relation to the lesion?" Answering the question will confirm that the lesion or perilesional cortex is the focus (not always the case) and determine the seizure onset zone in relation to that lesion, as the lesion itself can be electrically silent. Because the onset zone may be in or near essential cortex such

as speech or motor function, the second question is, "Will the planned surgery have significant impact on the person's overall function and independence?" In this case, functional mapping may be needed to define safe boundaries around the seizure onset zone for a planned resection. The third question asked when the seizure focus is less clearly defined-because of either poorly localized EEG ictal changes on scalp recordings or there are several potential foci. In this case, the question is "Can I identify a candidate region where the seizures are arising?" This third question is often highly speculative and carries the risk that a seizure onset zone will not be identified. It is clear that direct recording and stimulation has opened up the possibility of surgery for many patients especially for the nontemporal lobe patients. Unfortunately, for these people, the chance for seizure freedom following surgery remains less than that for the temporal lobe epilepsies with identified structural abnormalities.

One of the key goals for moving the field forward is to use these electrodes more effectively in defining the seizure onset zone, but unfortunately overall seizure freedom rates have not improved significantly and the reason remains unclear. Intracranial electrodes are expensive and a separate surgical procedure to implant the electrodes is needed. This method of localization, uses up significant medical resources, so that the potential benefits have to be weighed against the risks and costs. In many healthcare systems, the costs associated with intracranial monitoring, may be prohibitive or consume resources that could be used to make surgery available to more patients, if the evaluation were entirely noninvasive. The cost benefit analysis regarding the use of intracranial electrodes includes two primary questions: "What is the probability that we will make this patient seizure free?" and "Will significant reduction in seizure frequency or seizure freedom improve the person's quality of life?"

Developing Hypotheses to Guide Electrode Placement

Assuming that the odds for successful surgery and improved quality of life, following the use of intracranial electrodes are good, the major issues in proceeding with intracranial monitoring is where to place the electrodes and which type to use. It is not possible to record from all of the brain, so it is essential that clear hypotheses be developed regarding potential seizure onset regions, to select the most likely areas. These hypotheses can include data from ictal and interictal EEG, multimodality structural and functional imaging, and seizure symptoms and neuropsychological profile. As no one test is sufficient to define the focus, it is important to weigh all factors in developing the hypotheses that will guide the placement. Included in the consideration is whether mapping

Table 1: Roles of electrophysiology in epilepsy surgery

Identify the seizure focus (ictal recordings)

Define the resection area (interictal electrocorticography)

Learn about the pathophysiology of epilepsy (research)

Avoid causing functional impairment (cortical mapping)

Identify targets for intracerebral therapy (research)

of the cortex to identify regions that should not be removed because of their function. The choice of electrodes will then be driven by likely onset zones, the need for functional mapping, and the preferences of the surgeon.

Types of Electrodes

There are two basic types of electrodes for intracranial recording subdural and intracerebral [Table 2]. Each type has multiple different configurations (number and spacing of electrodes), but there is a clear division of function and method of placement that separates the two. Subdural electrodes are intended to record from the cortical surface and provide a broad area of coverage as possible, whereas intracerebral (also known as depth) electrodes are designed to record from areas that are beneath the cortical surface (e.g. deep dysplasias) or from regions that are less accessible to strips (e.g. the mesial temporal/limbic structures). Depth electrodes provide much less cortical coverage than the subdural variety. There is an overlap in how these electrodes are used, which is related to the technical issues of recording from a specific patient and the surgeon's comfort in placing an electrode in a given area.

Subdural strips are frequently placed through a burr hole, unless a grid is being placed, in which case, an appropriately sized craniotomy is required to place the electrode array precisely over the cortex under direct visualization. In some cases, it is not possible or is inadvisable to lift the dura for electrode placement. In these cases, epidural placement is possible with little degradation of recording quality. However, cortical stimulation and mapping is not possible with epidural electrodes because the electrical stimulation will activate the pain fibers in the dura.

Intracerebral (or depth) electrodes are most commonly placed through small holes using stereotactic frame that is attached to the skull. On some occasions, they are placed freehand into deeper structures to be used simultaneously with subdural grids. In this situation, the depth electrodes are placed following a craniotomy over the target region and the insertion point, and angle and depth of insertion are under direct visual control. Originally, the electrode strands were rigid and had to be fixed in place to avoid damage to the brain that would result from an unintended movement laterally. Today the electrodes are predominantly limp strands that are aided in insertion by

an internal removable wire or an external slotted needle. There is considerable effort and technical infrastructure involved in determining the coordinates for electrode insertion and care must be taken to ensure that major vessels such as the middle cerebral artery are not in the electrode trajectory.

It is a common observation that the best success in seizure control is achieved when there is an identified lesion and seizures arise from within or adjacent to the lesion. For this reason, it is important to know precisely where the electrodes are located; so placement must always be confirmed with a postoperative scan, ideally an MRI, so that the relation of the electrodes to the desired targets and any known lesions can be confirmed. In addition, it is important to rule out small hemorrhages that can sometimes cause seizures that have nothing to do with the real seizure focus and could lead to a false localization. Although, the grids can be placed precisely under visual control, the strips, which are inserted through the burr holes are not placed under direct visualization, and may not always end up where desired. Because the strip electrodes are generally intended to include or exclude an area from early seizure involvement, exact placement is less of an issue. With depth electrodes, it is a common experience that slight shifts in the angles of the trajectory can result in the electrode's being off the target by a few millimeters that can significantly change the interpretation of the recordings. With grid electrodes, it is especially important to know the relationship of suspected lesions to the ictal onset, as the grid itself with the known location of the lesion becomes the guide to the resection. That is, the area of resection is defined by specific electrodes and once the grid is removed, the seizure onset zone can be lost. Without knowing the position of the electrodes in relation to key structures (e.g. hippocampus) or lesions suspected of playing a role in the initiation of the seizures, it is very difficult to determine the significance of the EEG, especially if the site of onset is not clear.

Interpreting the EEG

In interpreting the seizure onset on intracranial monitoring for potential resections, there is one rule that must always be kept in mind: For an area to be considered as a candidate for the seizure focus, electrographic seizure onset must precede clinical onset. Although, resecting an area in which the seizure onset on EEG precedes clinical onset does not guarantee a successful surgery, resecting an area in which EEG onset follows clinical onset will almost certainly result in a poor outcome. Video EEG correlation is essential in interpreting the recordings.

One of the great benefits of intracranial electrodes is their precise spatial resolution of interictal and ictal activity. It is a common observation that epileptiform activity can be quite prominent at one electrode and be completely absent at adjacent electrodes. For this reason, the absence of epileptiform activity at electrodes that are near but not in a likely site of seizure initiation, does not exclude that site as a candidate of onset. The issue is that the electrical fields that are recorded from the electrodes are limited to what is essentially in direct contact with the conductor. Activity that is more than a few millimeters away is invisible to that electrode. As illustrated in Figure 1, from a patient with a malformation shows the
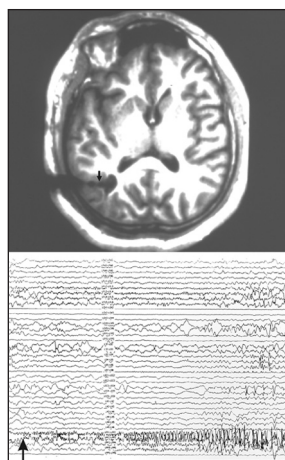
Table 2: Comparison between subdural (surface) and depth (intracerebral) electrodes

Subdural	Depth
Thin, flat	Thin Strands
Strips or grids	Single strand configuration, multiple contact
Size to match region, goals	Length and spacing varies
Strips through burr holes	Placed through burr holes
Grid requires craniotomy	Requires stereotactic frame and equipment
Free hand insertion	
Cortical surface recordings	Limited cortical coverage
Less well suited for medial targets	Better suited for medial and deep lateral targets

seizure onset is limited to a pair of electrodes in the depth of the malformation. Recording sites on the surface showed no evidence of involvement. This case illustrates how focal seizure onset can be and how recordings at the cortical surface can miss seizure onset just below. Of further interest, the seizure first spread to the ipsilateral mesial temporal structures, and not the overlying cortex. This case also emphasizes the importance of knowing exactly where the electrodes are positioned.

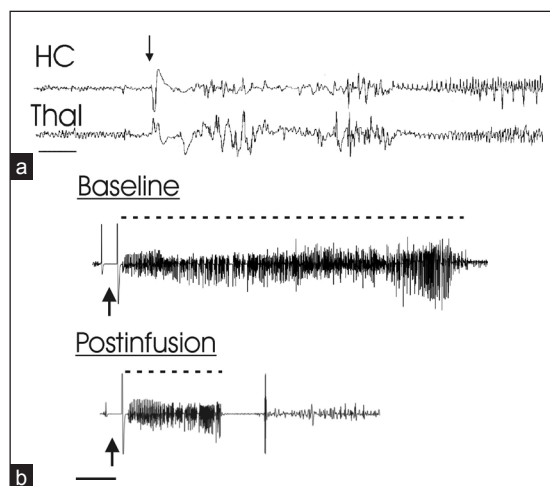## Electrophysiology in the Future: Defining Targets for Direct Focal Intervention

In recent years, there has been a growing interest in the potential of therapy that is delivered directly to the seizure focus, either with electrical stimulation or with infusion of a neuroactive compound which would suppress the development of seizures.[6] There have been several clinical trials of focal electrical stimulation that have shown marginal benefit, even though some preclinical studies had shown promise.[7-10] There have been a number of preclinical reports about the potential benefits of various focal drug infusions or recently,[11-13] focal transfection with a light-activated protein,[14] but no clinical trials have been reported with this approach. Animal stimulation studies have also had quite variable results.[15,16] Although, there is great belief and hope for the potential benefits of direct and focal therapy, the results have been underwhelming. However, this lack of major efficacy should not be an indication that the approach is ill considered. Rather, the failures to date may result from the lack of understanding the circuits of epilepsy and its manipulation. This problem is compounded by the many types and locations of epilepsy, each of which likely has a unique pathophysiology and circuitry. It is very likely that part of the problem arises from a "one size fits all" approach, such that either the right treatment is given to the wrong region or the wrong treatment is given to the right region. Moving this type of treatment forward requires that we have a greater understanding of seizure circuitry and the ways of altering the physiology of any particular circuit.[17]

Thalamic involvement in seizures has been recognized for many years, first for spike and wave seizures and recently, for focal seizures. The role of the thalamus is not clear, but some studies suggest that it is part of a divergent-convergent excitation amplification circuit that prolongs the duration of excitatory drive on target structures.[18,19] There is preclinical evidence that intervention in the thalamus, either by infusion or stimulation, can suppress seizures.[14,20] However, it is also clear that the site specificity for either stimulation or infusion may be highly restricted so that any slight misplacement of electrodes or cannulas may result in a therapeutic failure.[20,21] This issue is illustrated well in Figure 2, in which, placement shifts of one millimeter can bring about very different results.[22] This potential need for precise placement of electrode may be a reason for the modest benefit observed from thalamic stimulation in clinical trials. These observations suggest that a better understanding of the cortical-subcortical circuits is needed to guide therapy trials in the future, while we use intracranial electrodes to define seizure onset zones. It will be necessary to use that opportunity to define the circuits that may be targets for future therapies.

Figure 1: Magnetic resonance imaging (MRI) shows posterior temporal dysplasia leading to cyst not connected to ventricle. A depth electrode runs in the cleft between the two sides of the dysplasia. Electrode 1, is in the cyst and electrode 2 (arrow), is at the deepest point of the dysplasia. In the electroencephalography (EEG), seizure onset is electrode 2. Note that electrodes 3, 4, and 5, which are adjacent, but more superficial, are not involved. The next involved set of electrodes is a number of seconds later at the mesial temporal contacts (the electrodes labeled "EC"). Resection of the dysplasia resulted in seizure freedom. This case demonstrates how focal seizures can be in onset and how the spread is not always to adjacent structures. It also emphasizes that surface recordings (strips or grids) will not reveal seizure onset from underlying cortical abnormalities

Figure 2: Thalamic involvement in limbic seizures. (a) Spontaneous limbic seizure from a rat with limbic epilepsy. Onset is synchronized between the medial dorsal thalamic nucleus and the hippocampus (HC). Time bar is 2 sec. (b) Seizure induced in the HC with direct electrical stimulation. Top trace is baseline recording. Bottom trace follows infusion of inhibitory drug muscimol in medial dorsal nucleus of the thalamus, which results in a significant shortening of seizure duration and prevention of secondary generalization. Infusion adjacent to, but outside the medial dorsal nucleus has no effect on any seizure characteristic. These data demonstrate the involvement of a specific thalamic nucleus in limbic seizures and how precise the placement of the therapeutic intervention has to be. It also demonstrates the importance of the concept of circuit in epilepsy. Time bar is 5 sec

The preclinical data are clear that it is necessary to alter the physiology of the circuits to have a therapeutic effect and it is possible to measure that effect.[18,19] One of the problems with the clinical trials is that there is no evidence that the interventions do anything to the system. In designing future approaches to epilepsy treatment with intracerebral therapy, it may not only be necessary to have a more complete picture of the key seizure circuits and their modulations, but also demonstrate that the intervention also changes the physiology. Such a measure might be able to predict seizure suppression from the outset and if the physiology did not change, the measure would allow for an adjustment in the placement of the therapeutic device. Looking into the future, neurophysiology may allow us to identify the many components of the seizure circuits, to determine their roles in the seizure, and to test how our interventions affect circuit function and ideally lead to improved therapies.

Conclusions

After almost 80 years of modern epilepsy surgery, electrophysiology remains a central component for the identification of the seizure onset zone. How electrophysiology is used has continued to evolve, but what has remained unchanged is the need to have hypotheses about the focus, so that the results of the EEG can be appropriately interpreted. Intracranial EEG has clear limitations with regard to the identification of the three-dimensional (deep and surface) components and these limitations must always be kept in mind. The treatment of intractable epilepsy is also evolving, so that focal delivery of different types of intervention (electrical or pharmacological), are not at a too distant future. Physiology will be essential in defining the targets for these interventions, but also for predicting the success from treatment at one of the nodes of the circuit.

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