

Invasive Evaluations for Epilepsy Surgery: A Review of the Literature

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Abstract

Invasive evaluations play important roles in identifying epileptogenic zones and functional areas in patients with intractable focal epilepsy. This article reviews the usefulness, methods, and limitations of invasive evaluations for epilepsy surgery. Invasive evaluations include various types of intracranial electrodes such as stereotactically implanted intracranial depth electrodes (stereo-EEG), chronic subdural electrodes, and intraoperative electrocorticography. Scalp EEG is distorted by the skull, meninges, and skin. On the other hand, intracranial electrodes provide spatial information with higher resolution than scalp electrodes, thereby enabling further delineation of epileptogenic zones and mapping of functional areas with electrical stimulation. In addition, intracranial electrodes record a wide frequency range of electrical activity, which is not possible with scalp electrodes. The very slow potentials in ictal recordings, known as ictal direct current (DC) shifts and ictal/interictal high frequency oscillations, such as ripples (100–200 Hz) and fast ripples (200–500 Hz), have been correlated with the ictal onset zone and are a sensitive and specific marker for epileptogenicity. Furthermore, several studies reported that the electrical stimulation of epileptogenic zones elicited enhanced cortical evoked potentials, abnormal delayed or repetitive responses, and fast ripples. These responses may assist in the delineation of the epileptogenic cortex as a potential new marker. There are definite risks of complications associated with the use of intracranial electrodes. However, when an invasive evaluation is selected based on careful consideration of the risks and benefits, it provides useful information for establishing a strategy for epilepsy surgery.

Key words: intracranial electrodes, functional mapping, cortical stimulation, electrocorticography, focal epilepsy

Introduction

The electrical current recorded by scalp electroencephalography (EEG) is distorted by high-resistance tissues such as the skull, meninges, and skin. In addition, epileptiform discharges must involve the synchronized activity of a significant extension of the cortex (approximately 6 cm²) in order to be detected by scalp EEG.¹⁾ Therefore, scalp EEG is limited in its detection, precise localization, and determination of the extent of epileptogenic zones. Direct intracranial recordings from the brain are used to further delineate the regions of epileptogenicity in cases in which scalp EEG has failed to localize the epileptogenic zone. Intracranial electrodes are advantageous because they provide a markedly higher resolution than scalp electrodes and a clearer view of small loci of activity that are difficult to detect on the scalp.²⁾ In addition to the localization

of epileptogenic zones, intracranial electrodes aid in the mapping of eloquent brain areas in order to preserve brain function. The invasive electrodes used by institutions vary greatly in indications, techniques, types of electrodes, and number of implanted electrodes. These variabilities in the techniques used for invasive recording have led to different approaches to the treatment of epilepsy.³⁾ This article will review invasive evaluations for epilepsy surgery, including types of invasive electrodes, surgical procedures, monitoring of epileptic activity, methodology for electrical stimulation, complications, and new approaches to identify epileptogenic zones.

Types of Intracranial Electrodes

The implantation of an intracranial electrode is indicated when the precise localization of an epileptogenic zone and functional cortex is required in order to plan surgical resection with the preservation

of brain function. Intracranial electrodes include two types of electrodes, i.e., depth electrodes and subdural grids/strip electrodes (Fig. 1a, b).³⁾ The techniques and types of recordings used by institutions vary widely. Most major epilepsy centers in North America and Japan employ subdural electrodes or a combination of subdural and depth electrodes (Fig. 1c, d). European epilepsy centers rely primarily on stereotactically-inserted depth electrodes (stereoelectroencephalography, SEEG), which were introduced by Bancaud and Talairach in the 1950s (Fig. 1e, f).^{4,5)} Furthermore, the choice of electrodes depends on the areas that need to be explored. Invasive recordings with subdural electrodes are helpful in the precise description of seizure onset and spread in the cortical surface, and provide a more precise definition of the functional cortex and delineation of the interface between epileptogenic

zones and functional cortex. However, subdural electrodes cannot explore deeper generators such as the insula and amygdalo-hippocampal complex.^{3,6)} On the other hand, depth electrodes penetrate the brain and are indicated when recording is needed from these deep brain structures.³⁾ SEEG has a number of advantages including its ability to sample deep areas of the brain and anatomically distant regions and both hemispheres.⁷⁾ However, the main constraint of depth electrodes is limited spatial sampling and difficulties in precise anatomical delineation between contiguous cortical regions of the epileptogenic zone and functional cortex.^{3,6)} Careful consideration of their advantages and disadvantages needs to be coupled with a hypothesis about the epileptogenic zone derived from a non-invasive evaluation in order to decide the electrode, technique, and location for electrode implantation.

Surgical Procedure of Electrode Placement

Intracranial electrodes are implanted under general anesthesia. The placement of subdural electrodes is performed through burr holes for subdural strip electrodes and via craniotomy for grid electrodes. Most subdural grids are placed under direct visualization in order to avoid bridging veins or bony deformities and additional smaller grids or strips sliding over or under the brain without direct visualization, especially at orbito-frontal, inferior-temporal, and interhemispheric locations.²⁾ When intraoperative electrocorticography is recorded, the effects of anesthesia need to be considered.^{8,9)} A specific study on the effects of anesthesia reported that high-dose (1.5 MAC) sevoflurane anesthesia and isoflurane anesthesia provoked interictal spike frequency, whereas low-dose (0.3 MAC) isoflurane anesthesia suppressed interictal spikes.⁸⁾

The planning of SEEG electrode implantation requires a specific hypothesis of epileptic lesions based on non-invasive evaluation tests.⁷⁾ After the localizing hypothesis is formulated, the targets are reached using depth electrodes of various lengths and number of contacts, depending on the specific brain region to be explored. Electrodes are implanted using a conventional stereotactic technique through drill holes. These intracranial electrodes are typically left implanted for a period of 5–14 days.²⁾

Localization of Epileptogenic Zones

An epileptogenic zone is defined as the area of the brain that is necessary and sufficient for initiating seizures and whose removal or disconnection is needed for the abolition of seizures.^{10,11)} This area

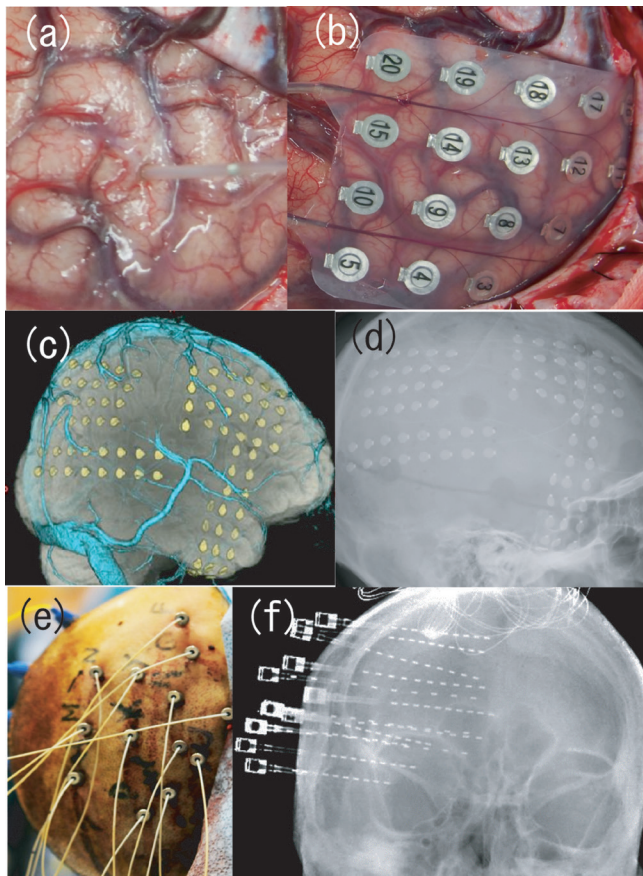


Fig. 1 Various types of intracranial electrodes. Intraoperative view of (a) the depth electrode and (b) the subdural grid electrode. Three-dimensional reconstructed computed tomography (c) and radiography of implanted subdural grid electrodes (d). Intraoperative view (e) and radiography of stereotactically inserted depth electrodes (f) (stereoelectroencephalography, SEEG).

is a theoretical concept and cannot be measured directly. Therefore, the location of the epileptogenic zone is considered to reside within an area defined by a concordance of findings from several investigations, including clinical seizure semiology, the scalp/intracranial EEG localization of epileptiform abnormalities, neuroimaging, and nuclear imaging. The identification of irritative zones and seizure onset zones detected with intracranial electrodes is the most concordant finding with the epileptogenic zone.^{10,11} Early ictal patterns recorded by intracranial electrodes may take various morphologies, including rhythmic sinusoidal waves, irregular spike discharges, spike and wave activity, and low voltage fast activity (Fig. 2a).¹² Familiarity with these patterns is crucial for identifying the epileptogenic zone. The interpretation of ictal patterns requires knowledge of not only pathological, but also physiological and artefactual patterns. Moreover, invasive recordings provide new information on wide frequency-band EEG data such as ictal direct current (DC) shifts and high-frequency oscillations (HFOs), which play important roles in the definition of the epileptogenic zone (Fig. 2b). Ictal DC shifts are slow negative shifts at the beginning of seizures, and were initially recorded in animal epilepsy experiments.^{13,14} In order to record these very slow potentials, electrocorticogram recordings must employ a very low setting for the high-pass filter; no higher than 0.016 Hz. It has been speculated that ictal DC shifts reflect passively depolarized glial activity following the

highly synchronized paroxysmal depolarization shifts (PDSs) of pyramidal cells, which occur in association with ictal activity. Therefore, ictal DC recordings may provide very important information on core epileptogenicity in patients with intractable partial epilepsy as surgical candidates. DC recordings are especially useful in cases of neocortical epilepsy in which conventionally filtered EEG shows only ill-defined broad electrodecremental patterns.² The recent development of technology has enabled us to record focal HFOs with intracranial electrodes over regions of primary epileptogenicity in patients with intractable focal epilepsy. (HFOs) between 100 Hz and 500 Hz (such as ripples for 100–200 Hz and fast ripples for 200–500 Hz) were identified in the epileptogenic area as interictal activity in animal experiments and human epilepsy patients.^{15,16} Previous studies reported that ictal HFOs were well-defined in the primary seizure focus of patients with mesial temporal lobe epilepsy and neocortical epilepsy, and thus, delineate core epileptogenicity and the common properties of epileptogenicity regardless of etiology.¹⁷ Kanazawa et al. reported that ictal DC shifts and ictal HFOs were observed in 75.0% and 50.0% of patients, and 71.3% and 46.3% of analyzed seizures, respectively.¹⁸ The onset of ictal DC shifts preceded that of ictal HFOs, and the spatial extent of ictal DC shifts or HFOs was smaller than that of the conventionally defined seizure onset zone. Therefore, ictal DC shifts and HFOs may both represent the core of tissue generating seizures.

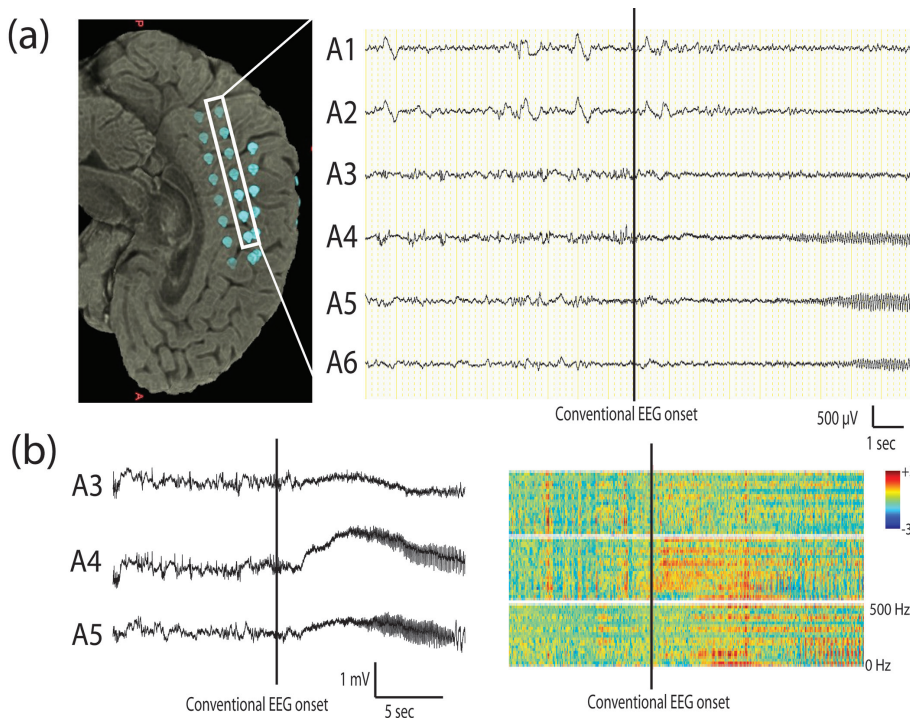


Fig. 2 Data from the implanted subdural grid electrodes. **a:** The ictal recordings, with conventional recording setting (time constant: 0.1 sec, low-pass filter: 600 Hz) showed electrographic seizure onset, consisting of low voltage fast activities on the several electrodes (A3–6). **b:** The same ictal recording with the setting for very slow potential (time constant: 10 sec) and the time-frequency analysis revealed the ictal direct current (DC) shift (left column) and the ictal high-frequency oscillations (HFOs) (right column), limited to A4 electrode, respectively. Both ictal DC shifts and HFOs might represent the core of tissue generating seizures. EEG: electroencephalography.

The opening of an analysis window to extremely slow and fast activities may be very important for the addition of clinically useful information to invasive presurgical recordings.

Function Brain Mapping

Electrical stimulation of the cerebral cortex has been used to localize the eloquent cortex, and mapping of these functional brain areas plays an important role in an invasive evaluation as well as the identification of the epileptogenic zone (Fig. 3).²⁾ Electrical cortical stimulation produces two effects: (a) a positive phenomenon, i.e., the activation of some function, such as tonic or clonic movements or (b) a negative phenomenon, i.e., interference with a function, such as speech arrest, the cessation of motor activity, or loss of muscle tone. The stimulation parameters used at our institution are 50 Hz, biphasic, constant current stimuli, a duration of 300 μ s, with intensity ranging from 1 mA to 15 mA. Stimulus intensity is increased stepwise at 1–2 mA while monitoring for neurological symptoms and afterdischarges. Since cortical stimulation may also induce seizures, continuous electrocorticographic monitoring is essential for checking afterdischarges induced by the electrical stimulation. Although patients are typically weaned from their anticonvulsants in order to better assure that seizures are captured, they need to be restarted on adequate doses of their anticonvulsants prior to the beginning of cortical stimulation. Surgical resection of eloquent

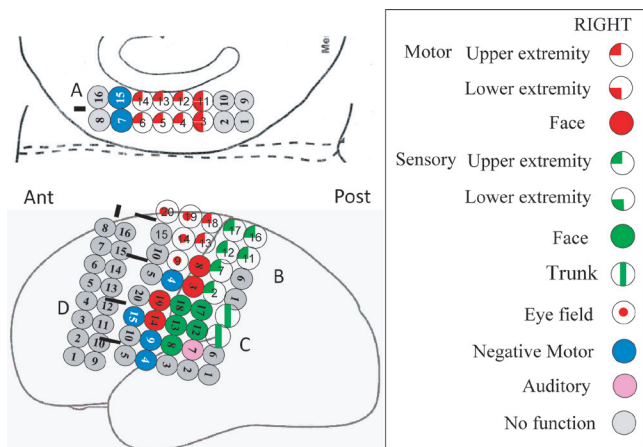


Fig. 3 Diagram of the functional brain areas defined by electrical stimulation in a patient with intractable left frontal lobe epilepsy. Red color indicates positive motor responses and green for sensory symptoms. Negative motor response is defined as the inability to continue voluntary movements or sustained muscle contraction without disturbance of consciousness.

cortical areas identified by cortical stimulation will generally lead to neurological deficits. However, there are exceptions and surgical removal of some cortical areas showing neurological symptoms during cortical stimulation (such as the anterior portion of the basal temporal language area, primary negative motor areas, and supplementary sensorimotor areas) leads only to temporary neurological deficits, with complete or almost complete neurological recovery.

Complications

There are definite medical risks associated with the use of intracranial electrodes. The complication rate of subdural electrodes has been reported to range between 6% and 26%.^{19–23)} Relatively common adverse events associated with subdural electrodes are fever, headache, and nausea.²⁴⁾ Another group reported transient cerebrospinal fluid (CSF) leakage (13–31%), infection (6–8%), intracranial bleeding (8%), and cerebral edema in addition to an intracranial mass effect.²⁵⁾ Nair et al. reported that complications included (in the order of their frequency) infection, transient neurological deficit, epidural hematoma, increased intracranial pressure, and infarction.²⁾ An increase in the complication rate was associated with (a) a greater number of grids/electrodes, (b) longer duration of monitoring, (c) older age of the patient, (d) left-sided grid insertion, (e) the use of burr holes in addition to craniotomy, and (f) an earlier year of monitoring (most likely a reflection of the aforementioned surgeon's experience).

On the other hand, the complication rate of SEEG has been reported to be 3–5.6%.^{7,26)} Previously reported complications of SEEG were intracranial bleeding and infection.^{4,20,26–28)} Subdural electrodes have been perceived to have lower permanent morbidity (0–3%) than that of depth electrodes (3–6%) because there is no intraparenchymal penetration.¹⁹⁾ Careful patient selection and consideration of the risk-benefit ratio of this modality are critically important, as is the case with all invasive techniques.

Cortical Stimulation for Epilepsy Evaluation

Adrian was the first to record the “spread of activity” of evoked cortical neuronal activity using a single-pulse electrical stimulation in animals.²⁹⁾ Several studies showed that direct electrical stimulation of the human cortex produced similar activities, forming an initial negative response (15–30 ms) followed by a slow positive response and then a slower negative response (lasting 250–300 ms).^{30,31)} These potentials were called direct cortical responses

(DCRs).^{30,32} Matsumoto et al. introduced an electrical stimulation technique termed cortical-cortical evoked potentials (CCEPs) in order to investigate the language network of the human brain.³³ CCEPs have been used to evaluate various brain networks.³⁴ CCEPs may provide information on pathological connectivity in the epileptic cortex as well as functional networks. Previous CCEP studies revealed that the stimulation of ictal onset zones elicited larger CCEP responses at the surrounding cortices than a normal cortex stimulation.³⁵ Other CCEP studies attempted to track seizure propagation pathways (Fig. 4).^{36,37} Furthermore, Lega et al. reported that CCEPs and post-stimulation changes in gamma band activity at early spread sites (ictal spread within 3 seconds) were enhanced more than late spread sites (spread later than 3 seconds).³⁷ These findings suggest that the size of CCEP responses reflect cortical excitability or dysfunctional inhibition.

Valentin et al. used a single-pulse electrical stimulation to study the epileptogenic cortex.^{38,39} This group also revealed that a favorable surgical outcome was associated with the removal of areas underlying electrodes showing a delayed and/or repetitive response to electrical stimulation.³⁹

A recent study revealed that fast ripples (250–520 Hz) induced by a single pulse electrical stimulation assisted in the delineation of the epileptogenic cortex.⁴⁰ The median sensitivity for the seizure onset zone was 100% for single pulse-evoked spikes and 67% for single pulse-evoked fast ripples, whereas

the median specificity was 17% for single pulse-evoked spikes to 79% for single pulse-evoked fast ripples. A median positive predictive value for the evoked responses in the seizure onset zone of 17% was found for spikes, 26% for ripples, and 37% for fast ripples. Single pulse-evoked fast ripples have potential as a new marker of epileptogenicity.

Conclusion

Invasive evaluations play important roles in the localization of epileptogenic zones in candidates indicated for epilepsy surgery. Subdural electrodes are useful for recordings in neocortical epilepsy in order to localize superficial epileptic foci and for mapping adjacent to the eloquent cortex. Depth electrodes are advantageous for recording epileptic activity arising from deep sources in the brain. Improvements in electrodes will allow the coverage of more extensive regions of the brain. Further advancements in intracranial electrodes, technology, and neurophysiological findings will lead to invasive evaluations that provide more precise information about not only the epileptogenic focus, but also brain functions and networks.

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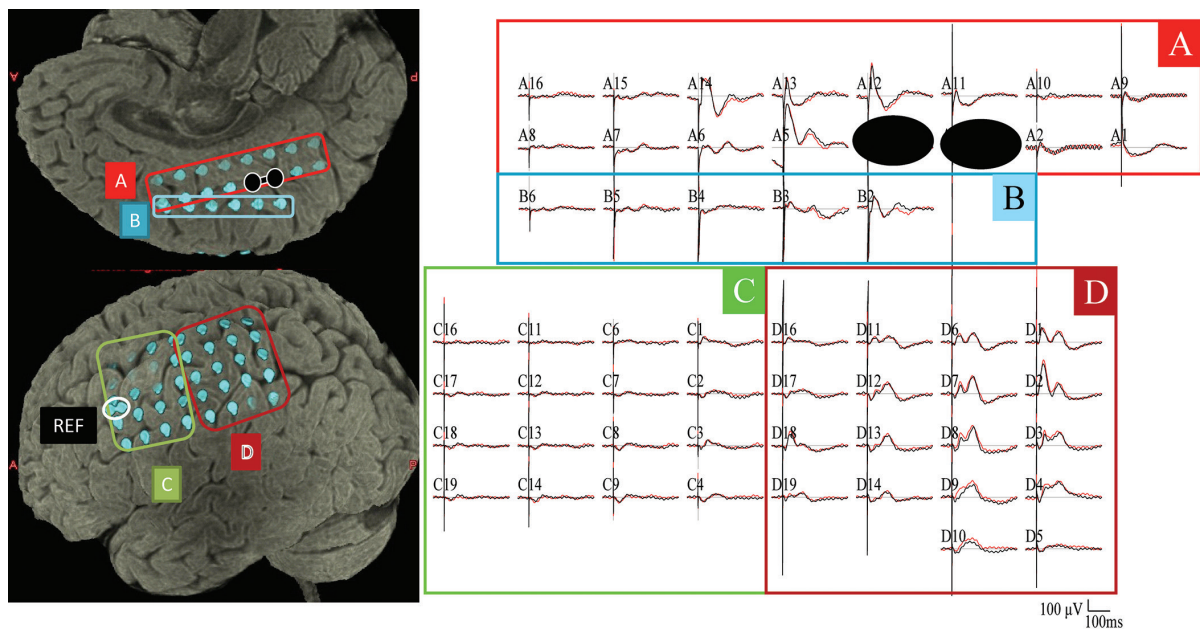


Fig. 4 Cortico-cortical evoked potential (CCEP) with ictal onset stimulation. CCEP distribution is correlated with seizure spread areas. *Black circle* indicates the stimulation sites.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in this article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI disclosure statement forms through the website for JNS members.

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