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Research Article


# Surgical Strategies for Epilepsy in Eloquent Areas

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**Abstract**

Patients with medically refractory epilepsy should be evaluated for potentially curative epilepsy surgery when feasible. However, if seizure foci occur in eloquent brain regions—regions where damage causes overt neurological deficits—alternative treatments must be considered. This review will discuss what defines eloquent cortex, and the various treatments of seizure foci in eloquent regions, including resective surgery, multiple subpial transections, electrical brain stimulation of the anterior nucleus of the thalamus, closed-loop responsive neurostimulation, and vagus nerve stimulation.

**Keywords:** Refractory epilepsy; Seizures; Eloquent; Palliative; Extratemporal lobe epilepsy

## Introduction

Medically refractory epilepsy is diagnosed after a patient fails two adequate trials of antiepileptic drugs [1]. Adding further drugs has a low likelihood of providing additional benefit (<5%), and patients should be referred to a comprehensive epilepsy center for surgical evaluation [2].

As part of their initial workup, patients typically undergo video-electroencephalography (video-EEG), magnetic resonance imaging (MRI) of the brain, and neuropsychological testing [3]. Depending on how well these tests localize the epileptic foci, additional studies might be indicated, such as positron emission tomography (PET), magnetoencephalography (MEG), and single photon-emission computed tomography (SPECT).

Extraoperative electrocorticography (ECoG), where electrodes are placed either cortically (with electrode grids and strips) or subcortically (with depth electrodes), is used to further refine the anatomic location of epileptic foci when prior studies are discordant or insufficiently detailed [4]. Bypassing the skull and scalp allows these electrodes to have greater spatial and temporal precision in detecting epileptic activity, since those tissues act as filters which degrade the normal EEG. In particular, if there is concern that seizure foci are localized within or near eloquent areas; ECoG can help identify safe margins of resection.

### What is eloquent brain?

Eloquent regions are loosely defined as anatomical brain areas where damage causes overt, disabling symptoms, such as language areas or primary motor cortex. Nevertheless, specific eloquent brain areas are often implicitly rather than explicitly defined. Robert Spetzler and Neil Martin proposed perhaps the most well-known delimited anatomical grouping of eloquent regions as part of their rating scale for evaluating arteriovenous malformations (AVMs) [5]. In their rating scale, eloquent regions were limited to "sensorimotor, language, and visual cortex; the hypothalamus and thalamus; the internal capsule; the brain stem; the cerebellar peduncles; and the deep cerebellar nuclei." All other regions were considered non-eloquent. The exclusion of the basal ganglia is an obvious omission, since damage to these structures can cause overt neurological deficits, and the inclusion of sensory cortex is somewhat conservative, given how patients will often tolerate sensory loss in return for treatment of tumors, vascular lesions, or epileptic foci. The Spetzler and Martin definition of eloquent cortex also disregards subtler neurological abilities of other cortical regions, such as memory, attention, and executive function. For example, while the hippocampus is not considered eloquent by Spetzler and Martin, indiscriminate hippocampal damage can be uniquely devastating (e.g., patient HM [6]), as can damage to the orbitofrontal cortex (Phineas Gage [7]) and amygdalae (patient SM [8]).

Ultimately, what constitutes eloquent cortex is best determined by detailed neuropsychological testing and discussions with the patient. For example, some patients are willing to risk visual field deficits for the chance of a cure, while others will find even the slightest risk of a quadrantanopia unacceptable. Other patients will draw similar "red lines" at memory, sensory, and language deficits.

### Surgical resection

Assuming both the seizure focus and eloquent cortex have been defined, surgical resection is a valid option if there is clear separation between the two regions. Close proximity of the epileptic focus and eloquent areas benefits from careful and detailed functional mapping. This will likely require extra-operative ECoG as a means to tightly define the seizure onset zone for resection [4]. ECoG will also permit preoperative motor, language, and sensory mapping, highlighting areas of the epileptic focus that are free of eloquent function.

Even if extra-operative mapping is used, intraoperative mapping is still indicated and can provide useful additional information. Motor mapping can be done with the patient under general or monitored (conscious) anesthesia, though language mapping always requires awake surgical techniques [9]. Awake motor mapping is generally considered better able to preserve function, though is sometimes impractical for young patients or patients otherwise unable to cooperate with detailed motor testing. Using a handheld stimulator (e.g., the Ojemann stimulator) will allow an unlimited number of test points for mapping, compared to the pre-specified points of the extraoperative ECoG grid, helping to maximize the area of safe resection.

Mapping of higher-level functions, like verbal memory, is less straight-forward and cannot currently be done with electrical

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stimulation intraoperatively. Determining the location of regions of higher-level eloquence is less anatomically precise and relies on preoperative techniques like the Wada test, functional MRI (fMRI), and transcranial magnetic stimulation (TMS) [10-13].

After detailed mapping, seizure foci are sometimes found directly within eloquent regions, or too close for safe resection. For these cases, a variety of non-destructive techniques have been devised, which will be described below (Table 1).

## Multiple subpial transections

Multiple subpial transection (MST) was first described by Frank Morrell and colleagues in 1989 [14]. The rationale was founded on the columnar organization of the cortex, as described by Vernon Mountcastle and others, which posits that vertical columns of neurons are the functional unit of the neocortex [15]. Severing the connections between these columns, but leaving the columns themselves intact, was hypothesized by Morrell to retain neurological function but prevent the spread of seizures by preventing aberrant synchronization between nearby areas.

The original technique used a thin stainless steel wire with the last 4 mm bent at a right angle [14]. The wire was inserted under a gyrus and the bent tip then raised orthogonally to the pial surface. The wire was then dragged across the gyrus, with the hook severing corticocortical connections within the cortical layers. Subcortical white matter was minimally affected.

Morrell et al. originally reported on 32 patients, where MST was used in primary motor cortex, primary sensory cortex, Broca's area, and Wernicke's area [14]. They had 5-year follow-up in 20 cases, and reported seizure freedom in 55%. No complications and no new neurological deficits were noted. Unfortunately, nearly all of these MST patients also underwent simultaneous surgical resection of non-eloquent epileptic areas. So there is no clear way to ascribe these benefits to MST vs. standard surgical resection. That is, we are unable to assess what additional benefit was conferred by MST over resection alone.

Numerous other studies went on to further investigate the risks and benefits of MST, along with disentangling the relative contributions of MST over unadorned surgical resection. The most recent meta-analysis by Spencer et al. showed excellent outcome (>95% reduction in seizure frequency) for isolated MST without resection in 62-71% of patients, depending on the seizure subtype [16]. When MST was combined with resection, the rates were better: 68-87%. New neurological deficits were observed in 19% of patients with isolated MST and 23% of patients with combined resection and MST [16].

| Treatment | Reversible/ Irreversible? | Advantages | Disadvantages |
|---|---|---|---|
| **Resection** | Irreversible | Potentially definitive cure if isolated focus identified | Highest risk of permanent neurologic deficit |
| **MST** | Irreversible | Potentially lower risk to neurological function than resection | Not as effective as resection when used alone; can still lead to permanent neurologic deficit |
| **Electrical stimulation (DBS or RNS)** | Reversible | Programmable with low likelihood of neurologic impairment | Requires periodic battery changes; newer and less-studied than surgical resection; very low chance of cure |
| **VNS** | Reversible | Entirely extra-cranial; no direct risk to brain tissue | Requires periodic battery changes; can achieve a reduction in seizures, but very low chance of cure |

**Table 1:** Comparison of treatments for eloquent seizure foci.

## Cortical and subcortical neurostimulation

Direct electrical stimulation of the brain, whether cortical or subcortical, is one of the most recently developed options for treating eloquent seizure foci. The two leading methods are deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) [17,18] and responsive neurostimulation (RNS) of epileptic foci [19]. ANT DBS is an open-loop stimulation paradigm, similar to DBS for movement disorders like Parkinson's disease, essential tremor, and dystonia. Briefly, a stimulation electrode with four contacts is stereotactically placed within the ANT and connected to an implanted pulse generator (IPG), which is typically placed in the patient's chest. The thalamic target is then stimulated continuously in an effort to modulate the epileptogenic network and reduce the frequency of seizures. The anterior nucleus was chosen based on its modulatory presence in the limbic circuit of Papez.

The RNS system, produced by the company NeuroPace (Mountain View, CA, USA), is a closed-loop system where recorded electrical ECoG activity is used to trigger stimulation in an effort to terminate seizures as they begin [20,21]. The completely implantable system is flexible in that either depth electrodes (like those used in DBS) or ECoG strips, or a combination of both, can be used for recording and stimulation. The stimulating electrodes are therefore cortical or subcortical depending on the patient's individual epileptic focus location. Seizure detection parameters and stimulation parameters are programmed over the course of several months (and sometimes years) following the device implant. Unlike DBS, the pulse generator is implanted in the skull itself, rather than distally in the chest.

Randomized clinical trials (RCTs) have been completed for both ANT DBS and RNS, and both showed positive results [21]. For RNS, seizures were reduced by 37.9% at the end of the 12-week blinded evaluation phase of the RCT [19], 44% at 1-year, and 53% at 2-years [22], showing a gradual increase in efficacy (though this follow-up data is unblinded). Similarly, ANT DBS showed a 40.4% decrease in seizure frequency at the end of the RCT's 3-month blinded phase [18], followed by a 69% decrease at 5-year, open-label follow-up [23]. Neither device has been examined for purely eloquent foci epilepsy, so results must be extrapolated for this indication. However, the reversibility—and thereby safety—of both procedures is an advantage compared to MST or resection.

## Vagus nerve stimulation

An alternative to the above modalities is vagus nerve stimulation (VNS), which is unique in being entirely extra-cranial, as compared to surgical resection, MST, or direct electrical stimulation of the brain [21]. In VNS, a stimulating electrode is coiled around the patient's vagus nerve within the neck (usually the left side) and connected to an IPG (typically placed within the chest, as in DBS). The device then stimulates the vagus nerve intermittently in an effort to modulate epileptogenic activity and reduce the frequency of seizures, similar to DBS of the ANT. The mechanisms are unknown, but presumed to act through neuromodulatory effects emanating from the brainstem [24].

Two large randomized clinical trials found a response of 23% [25] and 31% [26] of patients achieving a >50% reduction in seizures. Many other studies (though all retrospective or Class II-III) have shown better results, with a meta-analysis showing ~ 50% of patients experiencing a >50% reduction in seizures at long-term follow-up [27]. Of note, none of these studies specifically addresses VNS for use in seizures with eloquent foci, so the results in such patients must be extrapolated from the use of VNS in other indications.

Complications with VNS are common but usually mild. For example, hoarseness in 37-62% of patients, cough in 7-21%, and parasthesias in 6-25% [25-28].

## Discussion

For patients with refractory medical epilepsy, surgical resection offers the best hope for a potential cure. Unfortunately, if the seizure foci are located within eloquent cortex, resection might not be an option. In these cases, careful electrical stimulation mapping and neuropsychological studies are required to pinpoint the exact bounds of eloquent cortex and seizure foci. Safely resectable cortex should continue to be removed, leaving only truly eloquent cortex behind. For these remaining epileptogenic regions, options include MST, electrical stimulation of the brain, and VNS. MST has several studies showing its safety and utility in eloquent cortex, but is nevertheless higher risk than reversible procedures like DBS, RNS, or VNS [21]. No direct comparisons between these alternative treatments are available, so it is unknown if one is better than another. Moreover, none have been directly examined with regard specifically to eloquent cortex, while MST has. More research is clearly needed to address the comparative utility of these techniques for eloquent cortex. For patients, though, the choice will be an individual one, taking into account patient preferences for reversibility and risk tolerance.

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