Future of Neurology & Technology: Stereo-electroencephalography in Presurgical Epilepsy Evaluation

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Contributions:
Guillermo Delgado-Garcia: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Birgit Frauscher: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Abstract Word count: 244
Word count of main text: 1500
References: 12
Figures: 1
Tables: 0

Supplemental: Revised manuscript (highlighted)


Acknowledgements: The authors would like to thank Dr. Chifaou Abdallah (MNI), Dr. Andrea Bernasconi (MNI), and Dr. Neda Bernasconi (MNI) for sharing their images with us. These images are reproduced with authorization.

Study Funding: The authors report no targeted funding

Disclosures: G. Delgado-Garcia is an editorial team member of the Neurology Resident & Fellow Section. He also sits on the editorial boards of Neurology Clinical Practice and Brain & Life en Español. B. Frauscher received honoraria for speaking engagements and advisory board meetings from/with UCB Pharma and Eisai. These engagements are not related to the current work.
Abstract

Stereo-electroencephalography (SEEG) is not only a sophisticated and highly technological investigation but a new and better way to conceptualize the spatial and temporal dynamics of epileptic activity. The first intracranial investigations with SEEG were carried out in France in the mid-twentieth century; however, its use in North America is much more recent. Given its significantly lower risk of complications and its ability to sample both superficial and deep structures as well as both hemispheres simultaneously, SEEG has become the preferred method to conduct intracranial EEG monitoring in most comprehensive epilepsy centers in North America. SEEG is an invasive neurophysiological methodology used for advanced pre-surgical work-up in the 20% of drug-resistant patients with more complex focal epilepsy in whom non-invasive investigations do not allow to decide on surgical candidacy. SEEG uses stereotactically-implanted depth electrodes to map the origin and propagation of epileptic seizures by creating a three-dimensional representation of the abnormal electrical activity in the brain. SEEG analysis takes into account the background, interictal, and ictal activity, as well as the results of cortical electrical stimulation procedures, to reliably delineate the epileptogenic network. By means of a clinical vignette, this article will walk general neurologists, but especially neurology trainees through the immense potential of this methodology. In summary, SEEG enables to accurately identify the epileptogenic zone in patients with drug-resistant focal epilepsy who otherwise would be not amenable to surgical treatment, the best way to improve seizure control and achieve seizure-freedom in this patient population.
At least one in ten patients with epilepsy will fail two well-tolerated and appropriately chosen anti-seizure medications, and this is even more common in focal epilepsy.\textsuperscript{1} Surgery revolutionized the management of patients with drug-resistant focal epilepsy and, for them, represents the best way to improve seizure control and sometimes even result in seizure freedom (SF).\textsuperscript{2} These patients should be timely referred to epilepsy centers to determine surgical amenability. Pre-surgical evaluation has the goal of identifying the epileptogenic zone (EZ, i.e., the minimum cortical area whose removal is necessary for SF).

A phase 1 (non-invasive) work-up includes prolonged scalp video-electroencephalography (EEG) monitoring, structural and functional neuroimaging, as well as neuropsychological assessment. Magnetoencephalography, high-density EEG (HD-EEG), and combined EEG/magnetic resonance imaging (MRI) are additional auxiliary investigations. The exact combination of studies varies depending on the individual patient’s needs.

Some epilepsies are more complex than others and may therefore require invasive investigations (phase 2). This is the case in patients with inconclusive brain MRI, discordant findings in phase 1 work-up, or close vicinity of the assumed EZ to eloquent cortex. In patients with such features, a phase 2 evaluation is needed to determine surgical candidacy. Phase 2 investigations are defined by their invasiveness and include electrocorticography, subdural electrodes (SDE, i.e., strips and grids), and stereo-electroencephalography (SEEG). Nowadays, SEEG has become the principal method for intracranial EEG monitoring in most epilepsy centers in North America.\textsuperscript{3} This article will introduce general neurologists, but especially neurology trainees to the potential of SEEG.

**Clinical vignette**

A 25-year-old right-handed woman presented with sleep-related focal aware seizures characterized by an arousal due to a sensation involving her entire body, similar to a "wave starting in the middle of the stomach and going up and down", then "tactile hypersensitivity", restlessness, and anxiety. Sometimes this evolved into left arm stiffening and, more rarely, to left leg shaking and then impaired awareness. These seizures started at age 12.
risk factors were negative. She failed four anti-seizure medications and was having ten seizures per month. Her prolonged scalp video-EEG monitoring captured only late ictal EEG changes over the right central midline region. The interictal EEG was non-contributory. A 3-Tesla MRI showed a suspicious sulcus in the right posterior cingulate with subtle transmantle sign (Figure 1A). An unusual sulco-gyral morphology was also seen in the right anterior cingulate. The rest of phase 1 investigations (i.e., neuropsychology, functional neuroimaging, magnetoencephalography, and HD-EEG) were non-contributory.

SEEG was proposed. The main hypothesis was a right hemispheric, midline close, deep seated EZ in the parietal lobe in keeping with the potential MRI lesion. Alternatively, a mesiofrontal generator as well as an anterior insula generator with rapid mesiofrontal propagation were considered. To test these hypotheses, 16 depth electrodes were implanted over the right hemisphere (Figure 1B). Ictal recordings demonstrated that all seizures originated from the right midline parietal region (i.e., the presumed focal cortical dysplasia [FCD] seen on MRI) with rapid spread to the ipsilateral supplementary motor area (Figure 1, main panel and C). This patient underwent a selective right posterior cingulate cortical resection and histopathology revealed FCD type 2a. No seizure recurrence has occurred since surgery three years ago.

**SEEG: The ‘what’ and the ‘how’**

SEEG is an advanced invasive neurophysiological methodology that uses multi-contact intracerebral depth electrodes to record from superficial and deep brain structures in order to obtain three-dimensional representations of the seizure-onset zone (SOZ, i.e., the brain region where seizures are seen to start in the EEG) and epileptogenic network. This method has advanced considerably since its inception in the mid-twentieth century by Jean Talairach (1911–2007) and Jean Bancaud (1921–1993). It now also allows for not only tailoring resection to the minimum amount needed to achieve SF, but it also can be used to conduct (or guide) therapeutic procedures such as radiofrequency thermocoagulation, thermoablation, and responsive neurostimulation.
Interdisciplinary collaboration is a critical component of SEEG, and neurologists with subspecialization in epileptology or clinical neurophysiology play a key role during the entire process, including implantation planning, interpretation, and finally resection planning. Human SEEG recordings are already used in experimental neuroscience and, in the very near future, SEEG clinical applications will likely expand and impact on medical domains outside of epileptology such as neuropsychiatry and cognitive neurology.

SEEG uses stereotactically-implanted electrodes to map the epileptogenic network through the analysis of spatio-temporal dynamics of ictal and interictal discharges. SEEG relies on Bancaud’s analytical framework termed anatomo-electro-clinical correlation. This term refers to the way how we correlate the onset and evolution of abnormal electrical brain activity with brain anatomy and clinical manifestations. SEEG is a hypothesis-driven process and, to overcome the issue of a limited coverage—a limitation inherent to SEEG but also all other methods of intracranial EEG recording—, one main hypothesis with one or two alternative hypotheses are typically assessed. Seizure semiology is the driving force of hypothesis generation, that is then further complemented by results from phase 1 investigations. As the risk of complications increases with the number of implanted electrodes; the implantation should be planned to answer predefined hypotheses and therefore, no standard schemes are recommended.

SEEG signal data is then acquired using a system with capacity for at least 128 channels, preferably at a higher sampling rate. Synchronized video recording is essential for SEEG explorations to allow for a reliable anatomo-electro-clinical correlation. Background, interictal, and ictal activity, as well as data derived from cortical electrical stimulation (CES), is then assessed by a SEEG-trained neurologist or neurophysiologist. The main indications of CES are mapping of cortical functioning (e.g., language function) and reproducing habitual seizures, which has shown to add relevant information to the pre-surgical work-up.

After capturing enough intracranial data to postulate the anatomic location of the SOZ, surgical candidacy is determined by a multidisciplinary team that interprets SEEG findings in
consideration of the whole armamentarium obtained during the complete pre-surgical evaluation.

SEEG is considered to be the safest intracranial EEG recording modality with complication rates of 0.6-2%, including asymptomatic—and considerably less frequent symptomatic—intracerebral hemorrhages as well as transient postsurgical non-hemorrhagic neurological deficits. Admissions for SEEG exceeding four weeks are not recommended due to patient-related factors and a higher risk of infectious complications. In addition, SEEG is the only intracranial EEG option to sample deep regions, delineate epileptogenic networks, and also safely conduct bilateral explorations, as in suspected bitemporal epilepsy.

Until very recently, SDE was the mainstay of intracranial EEG monitoring in North America. Although SDE spatial coverage is often thought to be superior in the neocortex, this is only true for gyri, but not sulci. Regarding surgical outcomes, SEEG is at least non-inferior to SDE: slightly lower surgical resections (76.9 vs 81.6%) are outbalanced by better SF outcomes (61.0 vs 56.4%). In contrast to SDE, SEEG is better tolerated and also associated with lower morbidity (4.8 vs 15.5%) and mortality (0.2 vs 0.4%).

Training opportunities
SEEG training is recommended for the whole team involved in this procedure. For neurologists, some authors have suggested either a minimum of a 6-month training or participation in at least 10 SEEGs in a center with a minimum of five years of experience. At present, there are no clinical fellowship programs specifically focused on SEEG. However, this training is available at some epilepsy centers in North America as a part of epilepsy or clinical neurophysiology fellowships, especially for second-year or advanced fellows.

The Grenoble–Lyon–Milan alliance (https://seegcourse.com/) and Cleveland Clinic offer introductory courses on SEEG. While these courses do not intend to replace a formal training in an experienced center, they are a great starting point. An additional educational
initiative is the Montreal Neurological Institute (MNI) Open Intracranial EEG Atlas, a freely available online resource (https://mni-open-ieegatlas.research.mcgill.ca/) illustrating brain activity during both wakefulness and sleep across 38 different cortical regions.

**Research opportunities**

SEEG is a flourishing field for epilepsy research as well as research on experimental neurophysiology. Within epilepsy, new computerized approaches for EZ localization based on ictal or interictal data are currently in development. The aim of these algorithms is to improve localization accuracy, reduce functional deficits as well as the time needed for pre-surgical evaluation, and predict reliably the probability of SF after surgery. Hopefully, in the near future, these new techniques will inform clinical decisions during pre-surgical epilepsy work-up. Human SEEG-derived data is also increasingly used by neuroscientists. For instance, the Functional Brain Tractography international project aims to improve our knowledge on large-scale human brain connectivity using low-frequency CES in patients with epilepsy who are surgical candidates. SEEG-derived data has also contributed extensively to elucidate the local aspects of human sleep. These findings may soon have a clinical translation to different fields including neuropsychiatry, cognitive neurology, and sleep medicine.

**Conclusions**

In summary, SEEG is an invasive neurophysiological methodology originally proposed to map the SOZ and it is currently used for advanced pre-surgical work-up in patients with complex focal epilepsies. Research opportunities in this area are multiple and not only related to epilepsy. For neurologists, SEEG provides a unique possibility for subspecialization given the rise of SEEG procedures in North America.

**References**


Figure 1. Implantation scheme and SEEG ictal findings

A. Subtle transmantle sign in the right posterior cingulate gyrus. Courtesy of Neda Bernasconi, MD, PhD, and Andrea Bernasconi, MD (MNI).

B. Intracranial trajectories of two depth electrodes targeting the suspected focal cortical dysplasia (FCD). Courtesy of Chifaou Abdallah, MD (MNI). Dr. Abdallah authorized the reproduction of this image. **Main panel:** Spontaneous ictal SEEG recording showing a midline parietal onset with a build-up of polyspikes (red arrows) followed by low-voltage fast activity (red asterisks), and then spread to the ipsilateral supplementary motor area (yellow arrow). Postictal suppression was seen on the channels involved at seizure onset.

C. Sixteen depth electrodes implanted in the right hemisphere; they were chosen to answer the main hypothesis as well as two alternative hypotheses described in the text. For electrodes’ names, the main panel and panel C share the same color code. A written authorization was obtained from the patient to reproduce these images.
### Appendix 1. Authors

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Evaluation
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Neurology published online November 19, 2021
DOI 10.1212/WNL.0000000000013088

This information is current as of November 19, 2021

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