

Technical Aspects of SEEG and Its Interpretation in the Delineation of the Epileptogenic Zone

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Abstract

Stereo-electroencephalography (SEEG) has gained global popularity in recent years. In Japan, a country in which invasive studies using subdural electrodes (SDEs) have been the mainstream, SEEG has been approved for insurance coverage in 2020 and is expected to gain in popularity. Some concepts supporting SEEG methodology are fundamentally different from that of SDE studies. Clinicians interested in utilizing SEEG in their practice should be aware of those aspects in which they differ. Success in utilizing the SEEG methodology relies heavily on the construction of an *a priori* hypothesis regarding the putative seizure onset zone (SOZ) and propagation. This article covers the technical and theoretical aspects of SEEG, including the surgical techniques and precautions, hypothesis construction, and the interpretation of the recording, all with the aim of providing an introductory guide to SEEG.

Keywords: SEEG, epilepsy, epileptogenic zone, electrical stimulation, radiofrequency thermocoagulation

Introduction

Stereo-electroencephalography (SEEG) is a methodology to confirm or refute the hypothesis generated to delineate the epileptogenic zone (EZ) from the sum of non-invasive preoperative work-up in patients with pharmaco-resistant focal epilepsy. The term “SEEG” does not refer to the surgical technique of inserting intracerebral electrodes per se. Neither is depth electrode study a synonym because SEEG is not a method to record only from the depths, although it possesses a strength in recording from deep structures compared to other invasive studies. Indeed, SEEG is a methodology that allows three-dimensional recording of activity anywhere in the brain, and is utilized to delineate not only the EZ¹ but also the epileptic network that contributes to the clinical manifestations of a seizure. Moreover, SEEG electrodes can be used for (1) cortical electrical stimulation in

delimiting the EZ and defining the eloquent areas in relation to the EZ and (2) radiofrequency thermocoagulation (RF-TC) to treat a deep-seated EZ (or epileptogenic lesion) or EZ in the proximity to the eloquent cortex,² and to complement SEEG findings in delineating the EZ (details to be discussed later).

SEEG was first performed around 60 years ago in France, at the Sainte-Anne Hospital, by Jean Talairach and Jean Bancaud³ and has since been used in France, Italy, and Canada.^{4–6} SEEG was adopted in the United States around 2013, following the increase in surgeries of extratemporal and non-lesional epilepsies in major centers and the overall poor success rates for localization and surgery based on other intracranial approaches including subdural electrode (SDE) exploration.^{7,8} Its quick gain of popularity in a number of North American centers over a few years has contributed to the mounting recent evidence suggesting that SEEG is safer than SDE study. In contrast to the reported complication rates of SDE (5%–17%),^{9–13} a meta-analysis on 4000 patients has shown that the rate is much lower (<1%) for SEEG.¹⁴ A recent analysis of 239 patients that directly compared the two approaches has shown that implantation of SEEG electrodes is less

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time-consuming and less morbid, resulting in less postoperative pain and better seizure outcome in non-lesional cases.⁸⁾

The concept of SEEG methodology is fundamentally different from that of SDE placed on the cortical surface and also from depth electrodes used to lateralize temporal lobe epilepsy (a method developed by PH Crandall at UCLA in the early 60s).¹⁵⁾ Beyond obvious differences in the technical aspects of the procedure, stereotactic placement of intracerebral electrodes positioned through avascular trajectories, the success in utilizing this methodology relies heavily on a good hypothesis constructed before the implantation, and should be understood as a fundamental principle of SEEG. To succeed in utilizing this methodology, clinicians used to SDE should be aware of the characteristics in which they differ. In this review, we aim to share our experience in the technical aspect and highlight important points in the theoretical aspect of SEEG. We hope that it can serve as an introductory guide for using SEEG in the delineation of the EZ.

Indications of SEEG

The main purpose of SEEG is not different from other invasive EEG studies that is to complement the non-invasive studies to provide precise localization of the EZ and its relationship with the eloquent cortex or a lesion, to tailor a surgical resection. SEEG is indicated when non-invasive studies are inconclusive on the localization of the EZ, for instance, when non-invasive studies could lateralize but could not precisely localize the EZ or vice-versa (Table 1); or when they were not fully concordant in terms of the anatomico-electroclinical correlations, or early involvement of eloquent cortex is suggested.¹⁶⁾ Detailed indications of invasive EEG in general can be found in a summary by the ILAE task force and for SEEG specifically in the French SEEG guidelines and a review by Iida and Otsubo.¹⁶⁻¹⁸⁾ The idea that SEEG is indicated in cases not indicated for a classical SDE is a misconception. In fact, a fruitful SEEG study requires, as for any invasive approach, a clear hypothesis. Exploration without a strong hypothesis (AKA “fishing expedition”) is usually inconclusive and is strongly discouraged.¹⁷⁾

The modalities used for invasive studies vary among epilepsy centers. It is impossible to define a unified strategy that is acceptable to all centers and thus the ILAE task force recommended choosing invasive studies depending on each center’s ability or preference.¹⁷⁾ While some centers rely exclusively on a single modality (e.g., Montreal Neurological Institute [MNI] is using SEEG since the 1970s),

Table 1 Indications of SEEG

Based on non-invasive studies	Localized	Not precisely localized
Lateralized	A	B
Not lateralized	C	D

SEEG is best indicated for categories B and C. Invasive studies are not necessarily indicated for category A unless early involvement of the eloquent cortex is suggested. A good hypothesis is unlikely for category D and thus an invasive study is usually not indicated. SEEG: stereo-electroencephalography.

others prefer to adapt a modality or a combination of several modalities to each patient depending on their clinical needs. For the latter, SDE would be favored in cases with a seizure onset zone (SOZ) presumed to be in proximity to the skull and in those who need precise functional mapping of the eloquent cortex (especially speech). In contrast, SEEG would be favored for the following cases: a suspected SOZ in the depth of a sulcus and in deep structures including the mesial temporal, insula, cingulate, and all the parasagittal structures; deep-seated (heterotopic nodules) or multiple epileptic lesions (tuberous sclerosis); bilateral exploration; and prior surgery in which postoperative dura-brain adhesions usually hinder reopening for the placement of SDE. The indication of SEEG in young children is controversial because the skull is too thin for anchoring screw fixation and cranial immobilization. In general, most centers prefer to use SDE in younger and SEEG in older children, with a cutoff around 3- to 4-year old.^{12,19,20)}

Consensus on the Planning of SEEG Electrodes Placement

To serve its main purposes, SEEG electrodes need to be placed according to an exploration plan such that they can obtain sufficient electroclinical information during spontaneous seizures, based on the “anatomico-electroclinical correlations.” The plan has to be constructed so that it can answer the question: can the chronological occurrence of a seizure semiology be explained by the spatiotemporal organization of the epileptic discharges that involves a certain combination of anatomical regions (including an magnetic resonance imaging [MRI] lesion, if present) within the brain? Thus, it has to be based on a main working hypothesis in which most of the electrodes are invested. Alternative hypothesis(es) should also be considered and when necessary sentinel electrodes are placed to rule out alternative

hypotheses. The number of electrodes required is not fixed but usually between 6 and 15: fewer than 6 indicates that SEEG may not be necessary; more than 15 indicates possible fishing expedition.²¹ At least one electrode is usually placed in the presumed EZ and additional electrodes are placed around it to delimit three-dimensionally the resection margin. Electrodes are then placed in the immediate propagation zone and along the propagation pathway. Why would we need to place electrodes in areas other than the presumed EZ? Without these electrodes, the seizure would always appear like starting at the presumed EZ and it would be impossible to be sure that the apparent onset is not the result of propagation from a non-recorded region. This explains why more than five electrodes are necessary in SEEG. Moreover, more electrodes are often required if an RF-TC is planned at the end of recording because dense placement of electrodes at the potential coagulation sites may be needed.^{21,22}

The working hypothesis is based on the combination of seizure semiology, scalp EEG, and MRI findings. Other modalities are used to refine the implantation plan, if available. 18-fluorodeoxyglucose positron emission tomography (FDG-PET), single photon emission computerized tomography (SPECT), and magnetoencephalography (MEG) are common investigations in most epilepsy centers. High-density EEG has recently gained some popularity as an alternative to MEG. Our centers utilize simultaneous EEG-fMRI, as research tools and to guide SEEG planning.

Technical Considerations during SEEG Electrode Placement

SEEG electrodes are made to record *intracerebral* EEG, which means that they must be able to penetrate the brain safely. Commercially available SEEG electrodes are mostly flexible and semi rigid multi-contact electrodes with the rounded tip being a recording contact (Fig. 1a). An electrode usually contains 5–18 contacts, regularly spaced (2–5 mm or 10 mm apart) along the electrode, and can be customized according to the needs of the neurosurgeon and neurophysiologist.

SEEG electrodes are inserted under general anesthesia, using either a frame-based or a frameless technique. Following the introduction of neuronavigation in the 2000s, various frameless devices were developed or adapted for SEEG electrode implantation to take advantage of its versatility; a double-chuck articulated arm was developed at the MNI⁴ and others have adapted various commercially available devices, such as Varioguide (BrainLab AG, Feldkirchen, Germany),²³ Guide Frame DT (Minneapolis, MN,

USA),²⁴ Vertek arm (Medtronic),²⁵ and microTargeting Epilepsy Platform (FHC Inc., Bowdoin, ME, USA)²⁶ for the implantation using percutaneous drilling. The advance in robotics technology such as ROSA (Zimmer Biomet, Warsaw, IN, USA),^{27,28} NeuroMate (Renishaw, New Mills, UK),⁵ iSys1 miniature robotic device (Medtronic)²⁹ have further enhanced the development of the frameless technique. The main purpose of all these devices is to ensure a fast and yet precise insertion of the electrodes. The accuracy using a frameless technique (with or without robot-assistance) was not inferior to that of the frame-based technique. A recent meta-analysis reported an accuracy of 2.45 mm (95% confidence interval (CI): 0.39–4.51 at the entry and 2.89 mm (95% CI: 2.34–3.44) at the target using a frameless technique; 1.43 mm (95% CI: 1.35–1.51) at the entry and 1.93 mm (95% CI: 1.05–2.81) at the target using frame-based technique; and 1.17 mm (95% CI: 0.80–1.53) at the entry and 1.71 mm (95% CI: 1.66–1.75) at the target with robot-assistance.³⁰ Generally frame-based technique is more time-consuming. For instance, 26.5 min per electrode is required on average using a frame-based technique even in experienced hands²⁷ while only 15.7 min is required using Varioguide²³ and 10.4 min with robot-assistance.²⁷ Because not all hospitals have access to a robot in Japan, insertion using frame-based systems or currently available frameless systems such as Varioguide would be practical. We will describe below both the robot-assisted technique used at the MNI and the frame-based technique used at Osaka University.

At the MNI, we are using DIXI microdeep electrodes (intercontact interval 3.5 mm, 10–15 contacts, DIXI Microtechniques, France, Fig. 1a) and ROSA (Zimmer Biomet), for which the details of the technique have been published elsewhere.^{4,28} In brief, the ROSA software is used for planning the trajectories guided by a gadolinium enhanced T1-weighted MRI co-registered with a computed tomography (CT) angiogram, with care taken on the following: maximize sampling of gray matter while choosing avascular trajectories, avoid collision of the anchoring screw or cap between trajectories (see legend of Fig. 1e). Once the patient is positioned and head secured using a Mayfield head clamp attached to ROSA, registration is performed on the designated skin surface without additional fiducial. The robotic arm is driven to the preplanned trajectory and percutaneous craniostomy is performed with a 1.3-mm drill bit (DIXI) passed through a reducer held in the instrument guide of the robot arm (Fig. 1d). The hollow anchoring screw (Fig. 1a) is then screwed to the skull (Fig. 1e) using the long driver (DIXI), a stylet (Fig. 1c) passed through to make a path to the target,

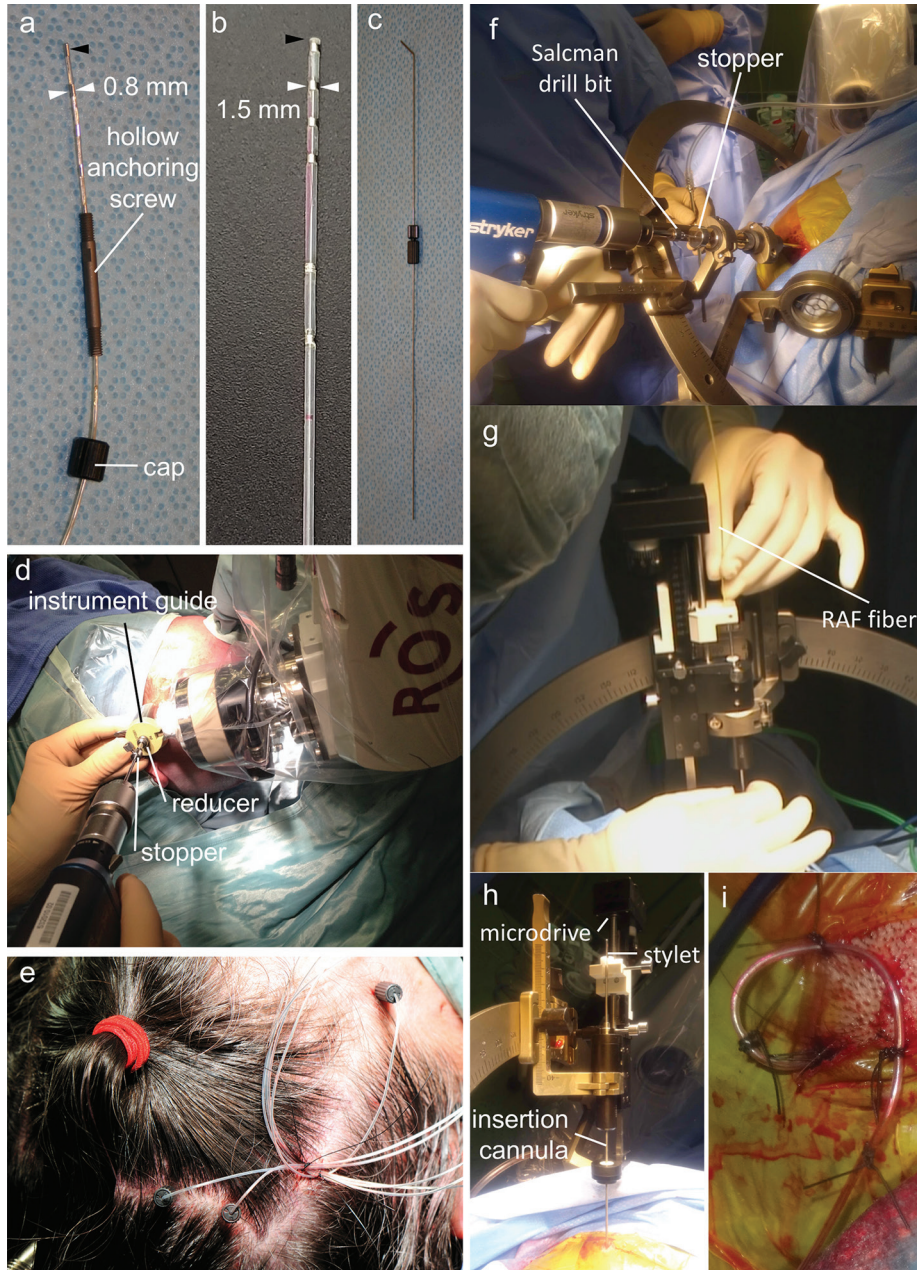


Fig. 1 Techniques of SEEG electrode placement and the instruments used at MNI and Hospital (MNI) (a, c–e) and Osaka University Hospital (b, f–i). An SEEG electrode (a) is different from a depth electrode (b): an SEEG electrode ends with an electrode contact at the tip while a depth electrode ends with its silicone tube (black arrowheads); the surface of an SEEG electrode is smooth while it is uneven at the boundary between the contacts and the silicon tube on a depth electrode. At the MNI, the robotic arm is driven to the preplanned trajectory and percutaneous craniostomy was performed with a 1.3 mm drill bit (DIXI) passed through a reducer held in the instrument guide of the robot arm (d). The hollow anchoring screw (a) was screwed to the skull and a stilet (c) was passed through to make a path to the target. The inserted electrode was then secured by screwing the cap onto the anchoring screw (e). Note that the cap is larger in diameter than the screw and this difference needs to be taken into account during trajectory planning to avoid collision. At Osaka University, we use a Leksell stereotactic frame combined with fluoroscopy (f) for guiding the trajectories, Salzman drill kit for craniostomy (f), RAF fiber for breaching the dura (g) and adapted instruments designed for DBS lead implantation (h) for inserting the SEEG electrodes. The implanted electrodes were first secured using a horizontal mattress suture at the skin outlet and then multiple interrupted sutures on the scalp (i). DBS: deep brain stimulation, MNI: Montreal Neurological Institute, SEEG: stereo-electroencephalography.

and the electrode inserted once the stylet is removed. The drilling process usually breach the dura. Otherwise, monopolar coagulation through the stylet held upon the dura can be applied for the breaching. Very little, if any, shaving of hair is necessary for SEEG.

At Osaka University, we use the Leksell stereotactic frame (Elekta, Stockholm, Sweden) (Fig. 1f) and the readily available instruments designed for implantation of deep brain stimulation (DBS) lead (insertion cannula, Microtargetting platform with attached microdrive, Medtronic). Because the anchoring screw and the SEEG electrodes are not yet approved in Japan, we used customized semi rigid depth electrodes (intercontact interval 5 mm, 10–12 contacts, Unique Medical, Komae, Tokyo, Japan, Fig. 1b) and secured them on the scalp with multiple sutures (Fig. 1i). BrainLab software (iPlan Stereotaxy version 3.0) is used for planning the trajectories guided by a gadolinium-enhanced T1-weighted MRI co-registered with a CT angiogram. A CT scan acquired after applying the frame to the patient's head is then co-registered to the preoperative imaging. A small incision (8 mm) is placed and a craniostomy is performed with a 2.1 mm drill bit (Salzman twist drill kit, Elekta, Fig. 1f) inserted through the reducer tube and sleeve held in the instrument guide and holder attached to the Leksell semicircular arc. The dura is breached using a monopolar radiofrequency coagulating fiber originally for use in neuroendoscopy (RAF fiber electrode, Aims, Osaka, Japan, Fig. 1g). The insertion cannula is then inserted up to 1 cm deeper than the inner table of the skull, a stylet is passed through to make a path to the target (Fig. 1h), and the electrode inserted once the stylet is removed. The insertion cannula serves to minimize potential deviation of the semi rigid electrode at the dura-cortex intersection and yet to minimize the damage to the brain tissue, as it is not inserted all the way down to the target. We utilized fluoroscopy to confirm the placement. Our preliminary experience showed a comparable precision with those reported in the literature³⁰ and no SEEG-related complication (data not shown).

Plenty of room is available for adaptation to the area(s) that need to be explored as the electrodes can be inserted orthogonally and obliquely (Fig. 2). The following should be kept in mind while planning the trajectories to minimize the risk of complications and to maximize the efficacy in sampling. To avoid skiving of the drill bit, the entry angles are kept preferably within 30° from the axis perpendicular to the skull surface.³¹ To reduce the risk of hemorrhagic complications, we avoid sulci and areas with a large subdural space (due to atrophy or previous surgical cavity) as the entry point; and

keep a distance of at least 5 mm especially from the superficial cortical vessels visible on gadolinium enhanced T1-weighted MRI, given that most SEEG-related bleeds are superficial^{27,28} likely because the superficial vessels are less mobile and thus prone to injury. To minimize deviation, the trajectories are kept short.³¹ Electrodes entering through the occipital convexity create pressure point when a patient is lying supine and thus are avoided. Entry anterior to hair line in the frontal region is avoided for cosmetic reason. In contrast to the principle in trajectory planning of DBS, a good trajectory for SEEG electrode crosses more sulci to maximize gray matter sampling, to be efficient for EEG recording. Eloquent cortices are avoided whenever possible although intentional insertion in these cortices can be performed if necessary (i.e., for delimiting the EZ from the eloquent areas).^{21,32} Theoretically, the general prevalence of hemorrhagic complication in SEEG (around 1%)³³ applies to these areas but with serious risks of significant functional deficits.

Post-implantation imaging is acquired to detect potential complication and to accurately locate each electrode contact for localizing the brain structure(s) sampled. Localization of the implanted electrode is crucial for the interpretation of SEEG recording (*where* a seizure starts and *where* it propagates) and electrical stimulation in defining the EZ and its network.

Intracerebral EEG Monitoring and the Interpretation of SEEG Data

The recording and monitoring procedures are similar to that of scalp EEG. At the MNI, two epidural electrodes are placed far from the epileptic field (usually over the parietal lobe opposite to the involved hemisphere) to serve as the referential and the ground electrode. The reference has the same surface area and constituent material as other recording contacts.³⁴ The electrocardiogram is also monitored. At the MNI, subdermal scalp electrodes (at positions F3-Fz-F4, C3-Cz-C4, and P3-Pz-P4) are also routinely placed for sleep staging.³⁵ A verification procedure is essential before recording to identify artefactual contacts in which instrumental, environmental or biological artifacts are seen. For example, the instrumental artifact caused by broken contacts is the most frequent and can be easily identified by the appearance of the signal or their high impedance. Biological artifacts are less likely in SEEG compared to subdural and scalp EEG. However, muscle artifact mostly seen in the superficial contacts of electrodes placed in the temporal regions and pulsation artifacts seen in contacts close to blood vessels are occasionally encountered.

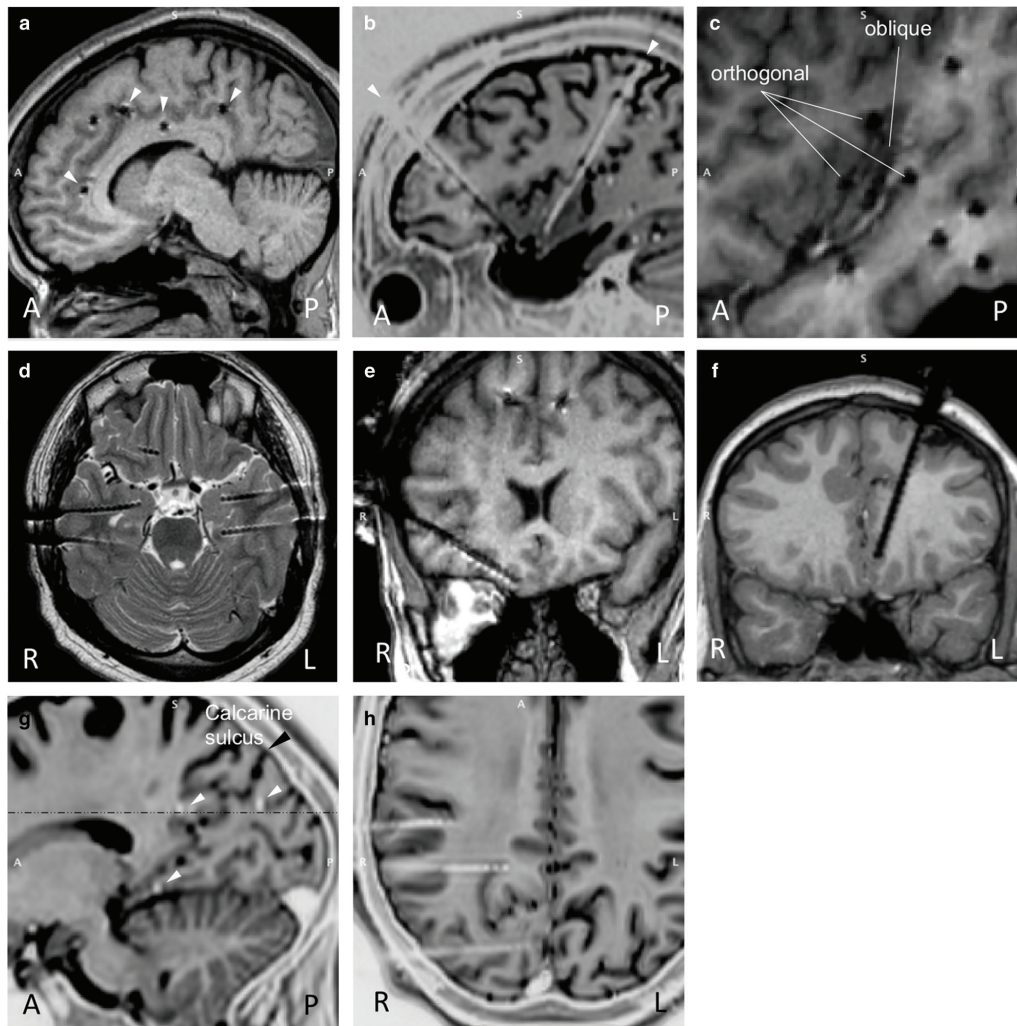


Fig. 2 Representative electrode insertion in structures or areas frequently explored in SEEG. **Cingulate gyrus** (a): Electrodes (white arrowheads) are typically implanted orthogonally (perpendicular to the sagittal plane) entering through the inferior frontal gyrus targeting the subgenual anterior cingulate; from the middle frontal gyrus targeting the pregenual anterior cingulate (usually the anterior insula can also be sampled with the same electrode) or anterior sector of mid cingulate; and from the inferior parietal lobule targeting the posterior sector of mid cingulate and posterior cingulate. **Insula** (b and c, sagittal images from different patients): Orthogonal and oblique implantations are utilized depending on the needs: orthogonal electrodes (c) are used when an operculo-insular seizure is suspected and oblique electrodes (can be placed anteriorly and/or posteriorly like in b) complement orthogonally implanted electrodes in covering the antero-inferior insula or as sentinel electrodes in temporal or frontal seizures with suspected insular involvement. Orthogonal electrodes (c) enter through the perisylvian sensorimotor cortices and oblique electrodes (c and white arrowheads in b) enter through the superior or middle frontal gyrus and the superior parietal lobule. **Mesial temporal structures** (d): electrodes are typically implanted orthogonally through the middle temporal gyrus targeting the amygdala and hippocampus; and through the inferior temporal gyrus targeting the fusiform gyrus. **Inferior frontal area** (e and f, coronal images from different patients): near-orthogonal electrodes (e) are typical although oblique electrodes (f) are sometimes utilized if needed. Orthogonal electrode entering through the inferior frontal gyrus and targeting the rectal gyrus covers the inferior frontal area along its trajectory. Oblique electrodes are used especially when seizures originated in the frontal pole are suspected. **Occipital lobe** (g and h): Electrodes are usually placed orthogonally, entering through the temporo-occipital junction targeting the lingual gyrus or the inferior calcarine, and through the parieto-occipital junction targeting the superior calcarine (g, white arrowheads). h is the axial slice of the same patient as g, traversing the plane where the two electrodes targeting supra- and infra-calcarine were placed (dotted black line). a, c, e, and f are T1-weighted and b T2-weighted MRI, in which electrodes are appreciated as black hallows; b, g, and h are T2-weighted images with the intensity inverted to highlight the electrodes in white. MRI: magnetic resonance imaging, SEEG: stereo-electroencephalography.

For review, we create bipolar and referential montages with electrodes grouped according to lobar location and displayed antero-posteriorly while the channels on each electrode are displayed from the depths to the surface. Because the number of channels on the recording can easily exceed 100 and thus difficult to be displayed on a computer screen, montages with limited channels grouped according to the area of interest are also created (e.g., montages limited to the spiking channels or channels of presumed SOZ). The montages are then switched back-and-forth between the overall montage and the limited montages with different timescales and sensitivity during the review process according to the needs of the reviewer.

Sufficient knowledge and experience are required for recognition of normal and abnormal activities. The characteristic of these activities varies depending on the structures explored. For instance, the EEG in the white matter is flatter and usually reflecting the propagated activity of adjacent gray matter channel (Fig. 3); the background activity in the motor cortex is distinct from the mesial temporal structures with the former predominated with beta, the latter alpha and delta rhythm during wakefulness.³⁶⁾ The activities also vary during different sleep stages.³⁷⁾ The atlas of human intracerebral EEG recently created at the MNI can be helpful in recognizing normal activities in different regions and during different vigilance stages (<https://mni-open-ieeg-atlas.research.mcgill.ca>).^{37,38)} Like with SDE, spikes, slow waves, and fast activities are typical interictal epileptic activities on an SEEG recording. Some interictal epileptic activities are pathology-specific: A continuous rhythmic epileptiform discharge is a signature of focal cortical dysplasia^{39,40)}; very frequent low-amplitude spikes with sharp morphology intermixed with low-voltage fast activity (LVFA) are pathognomonic of nodular heterotopia.⁴¹⁾ Gray matter with mainly non-layered structures such as amygdala and heterotopia are characterized by a lower amplitude activity compared to gray matter with layered structures such as the neocortex and hippocampus (Fig. 4). Increasing the sensitivity of channels located within non-layered structures for reviewing avoids missing important findings. Interictal high-frequency oscillations (HFOs) is another good biomarker of the EZ that can be recorded on SEEG if sampled at high rate (at least 2 kHz).^{42,43)} Resection of region generating high rates of HFOs is associated with good post-surgical outcome.⁴³⁻⁴⁵⁾

Knowledge on typical seizure onset patterns is important for the visual recognition and interpretation of ictal activities on SEEG. LVFA is the most common patterns on SEEG.^{46,47)} Some patterns are

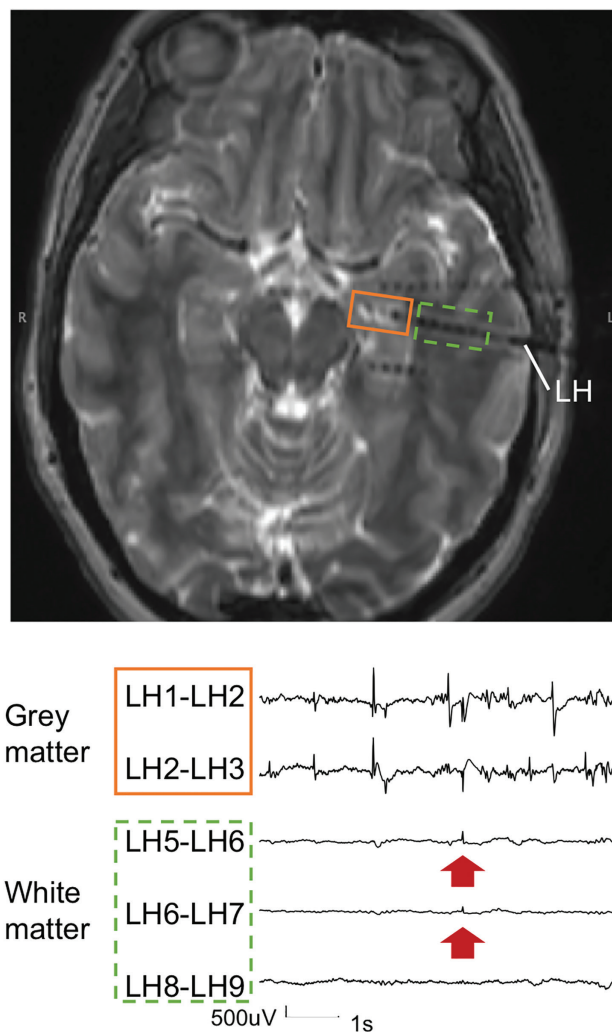


Fig. 3 An example illustrating the difference of EEG signal in the gray and white matter. (Top) The T2-weighted MRI image of the SEEG electrodes in situ. Electrode LH (DIXI electrode, 10 contacts, intercontact distance 3.5 mm) was targeting the hippocampus and entering from the left middle temporal gyrus. (Bottom) Interictal SEEG recording of electrode LH in bipolar montage with all the channels shown at the same scale (20 uV/mm). SEEG electrode contacts implanted within the gray matter of the hippocampus were indicated with an orange rectangle and contacts within the white matter in the temporal lobe were indicated with a green rectangle. The signals recorded within the white matter are flatter compared to those within the gray matter. Propagated signal of some spikes recorded on the gray matter channels can be seen on the white matter channels (red arrows). MRI: magnetic resonance imaging, SEEG: stereo-electroencephalography.

pathology-specific^{46,48,49)}: For instance, onset with low-frequency high amplitude periodic spikes is specific to mesial temporal sclerosis,⁴⁶⁾ and repetitive fast spikes burst specific to focal cortical dysplasia

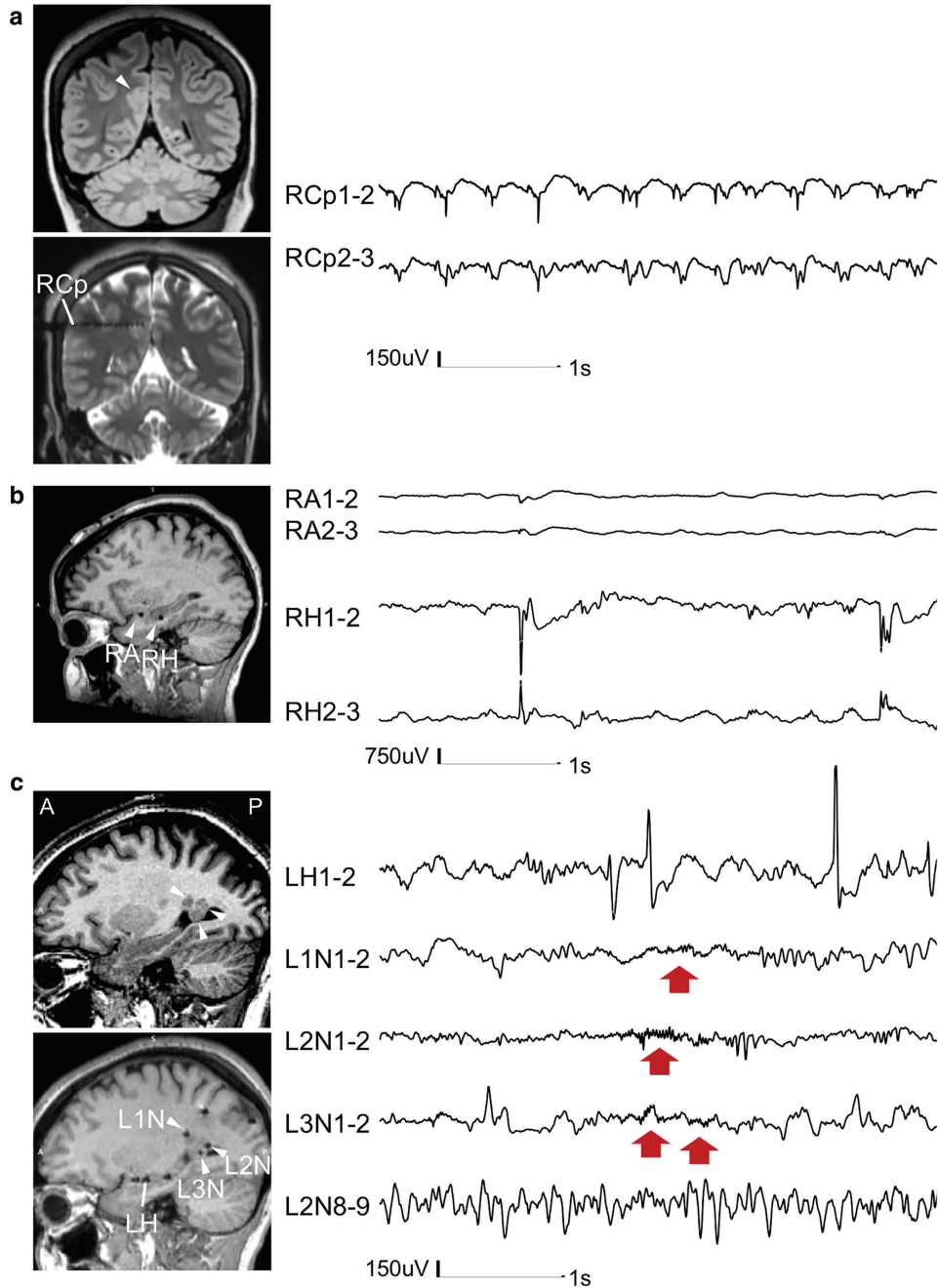


Fig. 4 Examples of SEEG signals recorded in different tissues. Pre- (only a and c, top image) and post-implantation MRI images are shown on the left and the SEEG recording in bipolar montage on the right. Each panel (a, b, and c) shows MRI images and the SEEG recording from different patients. Note that the sensitivity of all the SEEG channels shown are the same for each patient but may differ between patients. The post-implantation MRI images were acquired with the SEEG electrodes in situ and the electrodes are visible as a black hollow on the MRI images and appeared larger than the actual size of the electrodes (DIXI, $\phi = 0.8$ mm). (a) SEEG signals recorded in the FCD lesion as indicated with white arrow head on the FLAIR image (top MRI image) are characterized by continuous rhythmic epileptic discharges. (b) SEEG signals recorded in the amygdala (channels RA1-2, RA2-3) are much lower in amplitude compared to those in the hippocampus (channels RH1-2, RH2-3), and thus sensitivity adjustment for amygdala channels is necessary for review. (c) SEEG signals recorded in the periventricular heterotopic nodules (L1N1-2, L2N1-2, L3N1-2) are lower in amplitude compared to those in the hippocampus and the parietal cortical gray matter (L2N8-9). Low amplitude fast activities, a characteristic interictal epileptic discharge of heterotopia, are indicated with red arrows. MRI: magnetic resonance imaging, SEEG: stereo-electroencephalography.

IIa.⁴⁹⁾ Seizure onset pattern is also correlated with surgical outcome: post-surgical outcome was reported the best in patients with seizures starting with LVFA regardless of the presence of preceding spiking activities; LVFA preceded with a direct-current shift indicates widespread EZ and a less favorable surgical outcome; and slower activity in the absence of LVFA is usually associated with poor surgical outcome, likely because the actual EZ is missed. Nevertheless, the absence of LVFA is not necessarily a contradiction to resection because some patients without LVFA become seizure free.⁴⁷⁾ Indeed, it is almost impossible to be sure that what appears like an onset is not the result of propagation from a non-recorded region because intracranial EEG covers only a small fraction of brain volume (which is a common limitation of both SEEG and SDE).

Electrical Stimulation

Electrical stimulation through the implanted SEEG electrodes is used for functional mapping and for defining the cortical area responsible for seizure generation. Although SEEG is less well-adapted for functional mapping of the superficial structures (because of its limited access to superficial cortex) compared to SDE, it offers access to the deep structures and is better adapted for mapping the medial temporal structures, the insula, and entire cingulate gyrus.^{50,51)} Stimulation-evoked seizures were shown to be as reliable as spontaneous seizures in delineating the SOZ,⁵²⁾ defined by electrode contacts that evoked clinical findings mimicking the early manifestation of a typical seizure when stimulated. At the MNI, we perform stimulation before intense reduction or after re-introduction of antiepileptic medications to avoid evoking atypical seizures resulting from diffuse cortical hyper-excitability. Bipolar stimulation of two adjacent contacts is applied using biphasic square wave pulses at low frequency (1 Hz, pulse width per phase = 0.3 ms, at 1–3 mA, and train duration 20–30 s) and at high frequency (50 Hz, pulse width per phase = 0.5 ms, at 0.25–4 mA, and duration 3–5 s). The current intensity is increased stepwise until the appearance of an objective or a subjective symptom or after-discharges. To avoid an excessive electrical charge (Coulomb) at a given stimulation point, the current used is rarely over 4 mA in the mesial temporal structures or over 6 mA in the neocortices, lower than those in SDE due to the smaller surface area of SEEG electrode contacts. Stimulation of all the electrode contacts takes hours and thus the stimulation sessions are carried out over several days if necessary.

SEEG-guided RF-TC

RF-TC was first applied for epilepsy in 1965⁵³⁾ and has since developed as an alternative to resection. Among the lesioning techniques available, RF-TC is the only one that can be performed at the end of the study via the already-implanted SEEG electrodes. Therefore, it does not necessarily require an additional implantation. In contrast, the other lesioning techniques including laser ablation, focused ultrasound and gamma-knife, rely on separate procedures to determine the SOZ. Electrode contacts defined as SOZ are used in situ and thus RF-TC guarantees the ablation of the SEEG-defined SOZ. Nevertheless, the extent of the ablation depends on the number and configuration of the electrode array. The procedure is performed awake and thus monitoring for undesired neurological deficits is possible. The literature has shown that RF-TC is a safe and well-tolerated procedure if performed with caution.^{2,54–58)} We avoid vascular structures, functional area indicated by electrical stimulation, and proximity to the dura (to prevent inducing pain). We use bipolar RF-TC between two adjacent electrode contacts and deliver the current by increasing the voltage or intensity until an abrupt drop in these parameters (equivalent to an abrupt increase in the impedance) that self-terminates the coagulation, which is indicated by a crackling sound audible spontaneously by the patients and the neurosurgeon through a stethoscope placed on the patients' head. The patients are informed about this sound and requested to report it during the RF-TC. Typically, 6–8.32 W of current is delivered and coagulation is completed within 50 s.^{54,56)} The size of the generated lesion is usually relatively small but reproducible using this method, which, in turn, ensures the safety of RF-TC (because it is not possible to create lesions of excessive size unintentionally) (Fig. 5).²²⁾ RF-TC is mainly used for two purposes at the MNI: first, to predict the seizure outcome of resecting the SEEG-defined SOZ; second, as an alternative to surgical resection for SOZ deemed unresectable. Responders of RF-TC ($\geq 50\%$ reduction in seizure frequency at 2 months) are demonstrated very likely to have a good outcome with resection of the SEEG-defined SOZ (predictive value 93%).⁵⁴⁾ When an RF-TC is planned at the end of the SEEG study, electrodes are implanted densely within the presumed SOZ (see Fig. 5 and case 2 below) to allow optimal conformation of the RF-TC lesion. RF-TC is also possible between contacts on different electrodes that are less than 1 cm apart (Fig. 5, middle row). Although inferior to the success rate of conventional surgery, RF-TC alone can lead to seizure freedom (pooled rate 23%) despite being

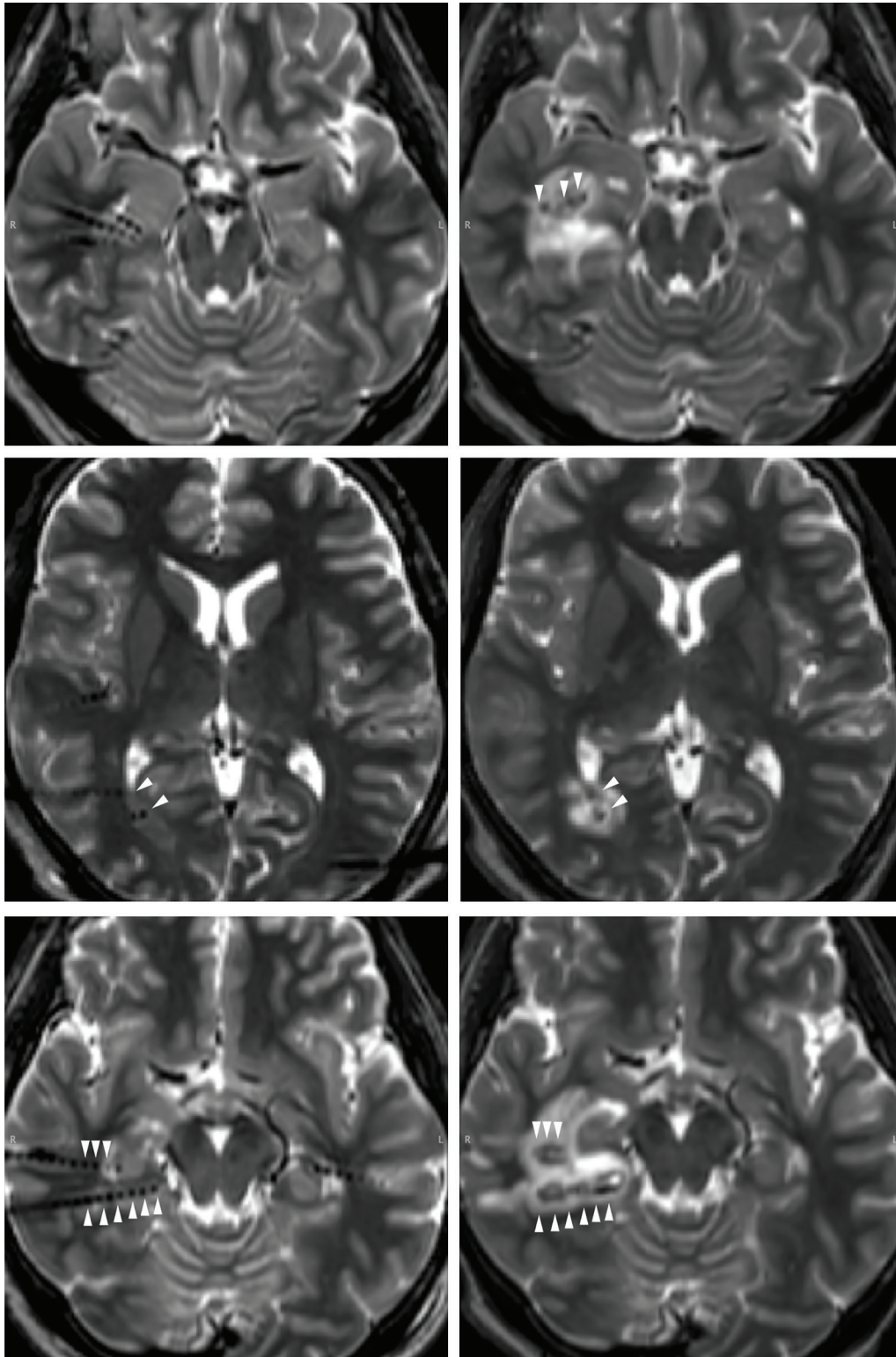


Fig. 5 An example showing coagulation using the electrode contacts of two adjacent electrodes that were placed within 1 cm in a patient with periventricular nodular heterotopia. T2-weighted MRI images acquired with the electrodes in situ (left) and a day after the radiofrequency thermocoagulation post-removal of the electrodes (right). The white arrowheads indicate the contacts used for thermocoagulation and the resulting lesions. MRI: magnetic resonance imaging.

indicated mainly in patients not eligible for a resection.²⁾ The efficacy of RF-TC varies among underlying etiology. The outcome is generally better in well-circumscribed small epileptogenic foci (up to 80% seizure-freedom for epilepsy related to periventricular nodular heterotopia)⁵⁶⁾ but less favorable in larger foci (around 25% seizure-freedom for hippocampal sclerosis),²⁾ likely because the generated lesion is small.²²⁾ A recent study suggested the possibility of generating a larger lesion by delivering lower power of current (<3 W), which may contribute to a better outcome in SEEG-guided RF-TC.⁵⁹⁾

Case Studies

Two cases are presented here to illustrate how we construct our hypothesis that has led to the implantation plan, which finally contributed to the surgical intervention. Case 1 demonstrates SEEG utilization when SEEG and SDE are both feasible and case 2 when the SOZ is less likely to be identified using SDE. Illustrative cases of periventricular heterotopia, a deep-seated lesion most suitable to be explored using SEEG, can be found in a book chapter from “A Practical Approach to Stereo EEG.”⁶⁰⁾

Case 1: frontal lobe epilepsy (Fig. 6)

26-year-old right-handed woman with a 12-year history of epilepsy. She had short stereotypical sleep-related seizures, characterized by a sudden awakening that was followed by a choking-like vocalization and slight agitation. She had daily seizures, each seizure lasted for 10–20 seconds and repeated more than 10 times per night. Scalp EEG indicated frequent low-amplitude interictal spike and wave over Fp2, F4, F8, and T4. The first ictal EEG change was seen over the same area followed by a spread bilaterally. MRI was normal; interictal FDG-PET showed a hypometabolism in the right fronto-opercular region. Simultaneous EEG-fMRI analysis of the interictal epileptic discharges delineated a clear activation in the same region. This case corresponds to category B of our scheme (Table 1). Her semiology was indicative of a frontal seizure that may have involved the anterior insula (her choking-like vocalization was due to throat constriction, a common sign when anterior insula is involved^{51,61)}); EEG indicative of a right fronto-temporal generator; and imaging studies suggested an involvement of the right frontal operculum. We hypothesized that the generator was located in the right fronto-operculum and the seizure likely propagated through the insulo-cingulate pathway. However, we could not completely rule out a temporal lobe seizure given the scalp EEG findings (and thus this became our secondary hypothesis). A third

hypothesis was that the generator was in the anterior insula. An SEEG study was undertaken to explore the right fronto-insular structures and the temporal structures. Nine SEEG electrodes were implanted (Fig. 6, middle left). A continuous 2–3 Hz interictal epileptiform anomaly was seen on the electrode contacts in the fronto-operculum but not on the electrodes superior or posterior to it. All typical seizures recorded had onset in the same electrode contacts. 50-Hz stimulation at 1 mA using the electrode contacts pair in the same region evoked her typical clinical and EEG seizures. Resecting the SOZ (without extending to the electrode superior and posterior to it) revealed a focal cortical dysplasia IIa and has rendered the patient seizure free at 10-year follow-up.

Case 2: temporal lobe epilepsy (Fig. 7)

32-year-old right-handed man with a 16-year history of epilepsy. He underwent an inconclusive SEEG study at another hospital 3 years earlier and thus surgery was not offered. He has two types of seizures, in which both started with the same aura, ringing in his left ear. The first type of seizure was characterized by terrified appearance, grabbing the bed rails with both hands, non-verbal vocalization, agitation, head and trunk version to the right, which led to a tonic-clonic seizure. The second type was characterized by staring, blinking, unresponsiveness, and bimanual automatisms and postictal nose wiping with his left hand and word finding difficulties. Some rare slow waves and sometimes rhythmic activity were seen over the left fronto-centro-temporal regions on interictal scalp EEG (not shown). The first ictal EEG change was seen over T3, T5, and P3. MRI was normal; interictal FDG-PET showed a diffuse hypometabolism in the left temporal lobe. MEG revealed a source localized in the left superior and middle temporal gyrus, adjacent to the transverse gyrus of Heschl. This case corresponds to category B of our scheme (Table 1). The semiology was indicative of a temporal neocortical seizure with likely two different propagation pathways. The EEG was indicative of a left temporal generator; imaging studies suggested left temporal lobe involvement, around the transverse gyri. We hypothesized that the generator was located in the left temporal lobe and likely propagated through either the parieto-frontal pathway or the temporal pathway. An SEEG study was undertaken to explore the left temporal structures and the propagation pathways. Ten SEEG electrodes were implanted (Fig. 7, middle left). Interictal epileptiform anomaly was seen on the electrode contacts in both the transverse gyri of Heschl and all electrographic seizures and aura

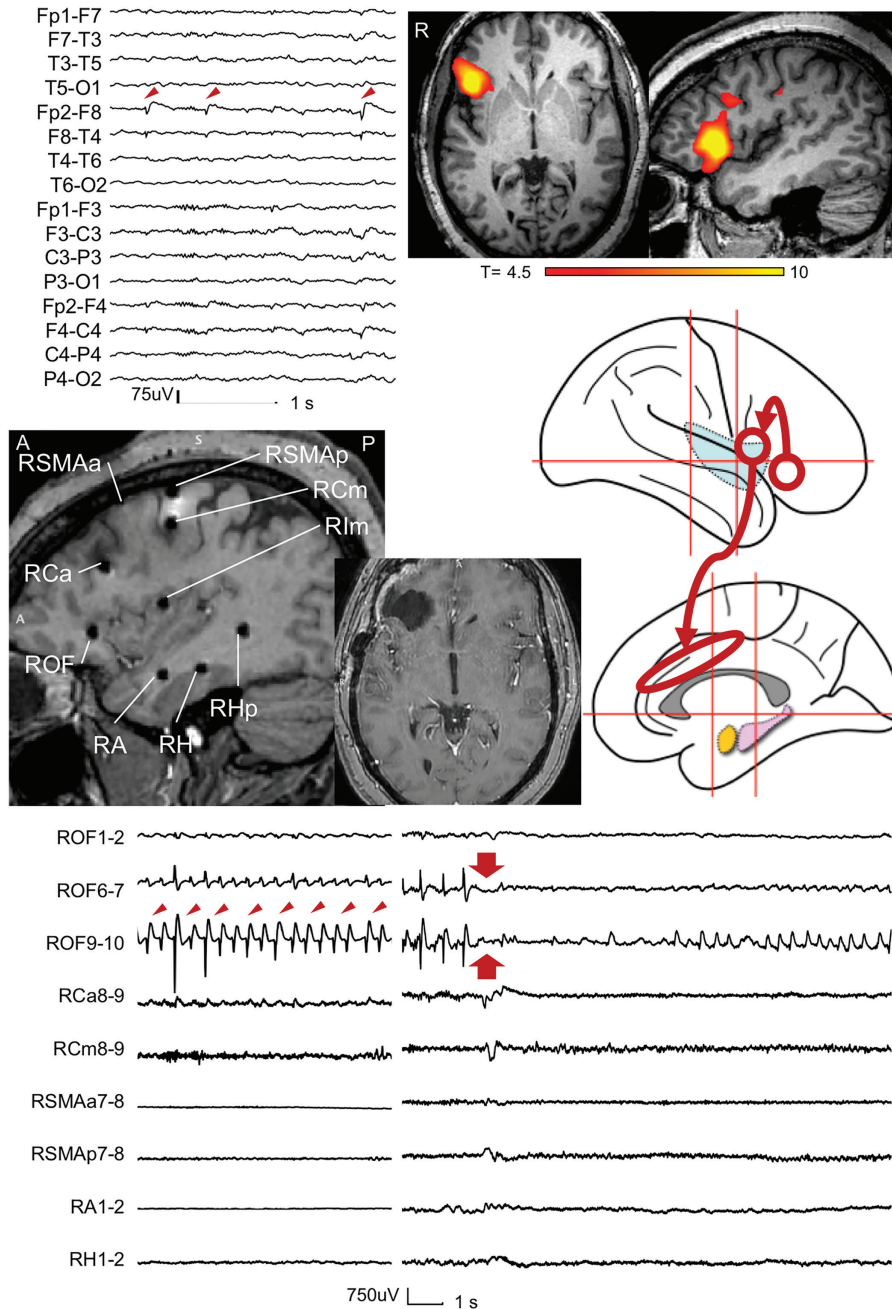


Fig. 6 A 26-year-old right-handed woman with frontal lobe epilepsy. Her scalp EEG (top left) indicated very frequent low amplitude interictal spike and wave over Fp2, F4, F8, T4 (red arrowhead). Simultaneous EEG-fMRI analysis of the interictal epileptic discharges delineated a clear activation in the right fronto-opercular region (top right). We hypothesized that the generator was located in the right fronto-operculum and the seizure likely propagated through the insulo-cingulate pathway (middle right). The nine SEEG electrodes implanted are visible as black circular artifacts on the T1-weighted MRI (middle left). Six were implanted in the right frontal lobe, one entering from the fronto-operculum aiming the anterior insula (ROF), one in the mid-insula (RIm), one entering from the middle frontal gyrus aiming the anterior cingulate (RCa), the middle cingulate gyrus (RCm), the anterior (RSMaA) and the posterior (RSMaP) supplementary motor area; and three in the right temporal lobe, aiming the amygdala (RA), anterior (RH) and posterior hippocampus (RHp). Her SEEG recording (only selected channels are shown) showed a continuous interictal 2–3 Hz spikes on channels ROF6-7 to ROF9-10 (bottom left, red arrowheads). The interictal activity was attenuated at seizure onset and was replaced by a LVFA on the same channels (bottom right, red arrow). These channels were resected as visible on the postoperative MRI (middle). MRI: magnetic resonance imaging, LVFA: low-voltage fast activity, SEEG: stereo-electroencephalography.

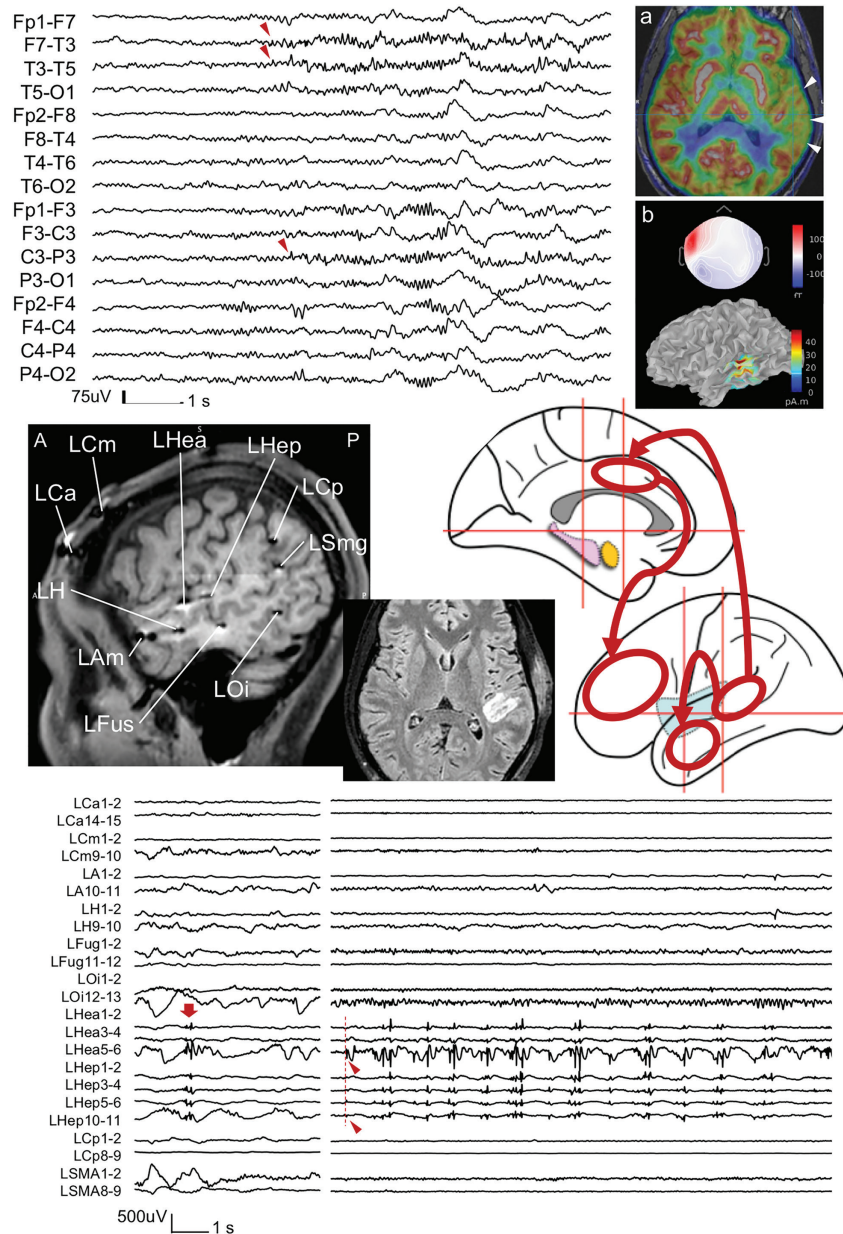


Fig. 7 A 32-year-old right-handed man with temporal lobe epilepsy. The first ictal EEG change was seen over T3, T5, P3 on his scalp EEG (top left). His interictal FDG-PET showed a diffuse hypometabolism (white arrowheads) in the left temporal lobe (top right, a). MEG analysis revealed a source localized in the left superior and middle temporal gyrus, adjacent to the transverse gyrus of Heschl (top right, b). We hypothesized that the generator was located in the left temporal lobe and likely propagated through either the parieto-frontal pathway or the temporal pathway (middle right). The ten SEEG electrodes implanted are visible as black circular artifacts on the T1-weighted MRI (middle left). Six were implanted in the temporal lobe, in which two were placed in the transverse gyri (one each in the anterior, LHea, and posterior transverse gyrus, LHep), one placed posteriorly in the superior temporal gyrus for determining the posterior margin (LSmg), four entering along the middle temporal gyrus targeting the amygdala (LA), the hippocampus (LH), the fusiform gyrus (LFus) and the lingual gyrus (LOi), for determining the inferior margin and for exploring the propagation pathway; one entering from the supramarginal gyrus targeting the posterior cingulate (LCp); two in the frontal lobe, entering from the middle frontal gyrus targeting the anterior (LCA) and mid-cingulate (LCm). His SEEG recording (only selected channels are shown) showed interictal spikes (bottom left) and electrographic seizures (bottom right, red arrowhead indicating the onset) on channels LHea1-2 to LHep5-6 and LHep10-11. The lesions resulted from the radiofrequency-thermocoagulation using the electrodes implanted in the transverse gyri are visible on FLAIR MRI image acquired a day after the procedure post-removal of the electrodes (middle). SEEG: stereo-electroencephalography

recorded had onset in the same electrode contacts. 50-Hz stimulation using these electrode contacts evoked the typical aura but did not induced speech deficits. Because no spontaneous full clinical seizure was recorded during the study that lasted 4 weeks, we finally performed RF-TC using the same contacts to confirm our hypothesis (Fig. 7, middle). The RF-TC alone has rendered the patient seizure free for 2 years; we are considering a resection of the transverse gyri of Heschl if the seizures recur.

Conclusion

We have briefly overviewed some surgical aspects and the interpretation of SEEG. For more details on SEEG, the readers are referred to the French guidelines on SEEG, the book “A Practical Approach to SEEG” and the book chapter on SEEG in “Current Practice of Clinical Electrophysiology” and “Techniques in Epilepsy Surgery, the MNI Approach.”^{4,18,21,22,34,62–66} The success of a SEEG study relies on the pre-implantation hypothesis. Without a clear and strong hypothesis, SEEG study can be misleading and would fail to lead to a correct localization of the EZ. Experienced teams are providing practical hands-on training on a yearly basis recently: For example, SEEG course by the European teams (www.seegcourse.com), SEEG workshop by the Cleveland clinic’s team (Cleveland clinic brain mapping workshop), and SEEG course by the Australian team (www.SEEGBrisbane2019.com). Clinicians who are interested in integrating this methodology in their practice are encouraged to participate in these courses to acquire prerequisite knowledge for constructing good hypotheses.

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Conflicts of Interest Disclosure

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All authors who are members of The Japan Neuro-surgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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