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Invasive EEG monitoring for Drug Resistant Epilepsy

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Introduction

Epilepsy was identified by the 75th World Health Assembly (2022) and WHO as one of the top priorities in prevention and control of non-communicable diseases. It is characterised conceptually by an enduring predisposition for seizure genesis. Epileptic seizures feature recurrent paroxysmal events with stereotyped behavioural alterations, due to abnormal, excessive or synchronous neuronal activity in the brain(1).

The ILAE definition of epilepsy (2014) describes it as a neurological dysfunction defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. Epilepsy poses risk to life due to sudden death (SUDEP), injuries, chronic cognitive decline, socioeconomic handicaps and more. This disease creates a significant psychosocial, economic, physical, and mental burden for nations' health systems, societies, people with epilepsy (PWE) and their families(2-4).

Epidemiological studies suggest that 51.7 million people with active epilepsy live in the world today (0.7 percent of the global population). The overall prevalence is about 658 per 1,00, 000 people with about 80% of the disease burden in LMICs. There are more than 10 million persons with epilepsy (PWE) in India with a population prevalence of 1 %.

Concept of Drug-Resistant Epilepsy (DRE)

Drug-resistant epilepsy (DRE) refers to a significant proportion of people with epilepsy who fail to achieve seizure control with antiseizure medications. Defined by Kwan *et al* (2010) as the failure of two appropriately chosen and administered antiseizure drug trials (1), drug-resistant epilepsy affects approximately 25-30% of people with epilepsy. Thus worldwide, among 50 million people with epilepsy, about 12-15 million people with drug resistant epilepsy exist (2,3). For these patients, surgical intervention offers the potential for seizure freedom or significant reduction in seizure burden. Approximately 50–60% of patients with newly diagnosed epilepsy become seizure-free on their first anti-seizure medication (ASM). If the first fails, the second medication offers a lower, but still reasonable, chance of success (about 10-15%). Adding a third drug adds a 1.6-4.4% success rate.

Hypotheses for DRE include the transporter hypothesis (efflux pumps limiting drug brain concentration), target hypothesis (altered drug targets), network reorganization, neuroinflammation, and genetic factors. De-novo, delayed and fluctuating patterns of anti seizure medication resistance are seen. A meticulous pre-surgical evaluation for surgical candidacy remains a critical prerequisite for successful outcomes (4,5). Although, there remains a widely accepted consensus on the pre-operative evaluation strategy, there are few studies of statistically significant controlled trials to consolidate the objective superiority of a single pre-surgical diagnostic panel. While non-invasive modalities provide the initial framework for hypothesis generation, the complexity of seizure networks often necessitates invasive monitoring to precisely delineate the epileptogenic zone, particularly in cases of non-lesional epilepsy or extratemporal localization where conventional imaging yields insufficient information (2,6). This review discusses the current accepted practice in pre-surgical work-up of DRE patients along with the fundamental principles, technical nuances, and clinical applications of SEEG, highlighting its role in defining the complex anatomo-electro-clinical relationships necessary for optimal surgical planning (4).

Surgically remediable Epilepsy Syndromes

A surgically remediable epilepsy syndrome refers to a type of epilepsy with a well-defined physical substrate that is highly likely to be cured or significantly improved by early surgical intervention. These syndromes are often resistant to antiseizure medications (ASMs) but have an excellent prognosis with surgically resection or disconnection of the underlying lesion. The term surgically remediable epilepsy syndrome was formally proposed and popularized in 1992 during the second Palm Desert Conference on Surgical Treatment of the Epilepsies by Jerome Engel Jr at el(1).

To be defined as a surgically remediable syndrome, a condition must meet four criteria:

1. Known Pathophysiology: There is a clear physical cause (substrate) identified.
2. Predictable Natural History: It is well-documented that the condition is unlikely to respond to medication once two appropriate drugs have failed.
3. Non invasive Identification: The problem can usually be located using non-invasive tests like MRI or scalp EEG.
4. Excellent Prognosis: Surgery offers a very high chance of complete seizure freedom.

Thus, surgical interventions could be offered early in surgically remediable epilepsy syndromes to prevent the morbidity of chronic seizures and multiple medications. Mesial temporal sclerosis is considered the prototype of Surgically remediable Epilepsy Syndromes (Figure 1 and Table1).

Surgical Candidacy- Overview of Presurgical Evaluation

- *Epileptogenic zone versus Epileptic Network hypothesis*

  The cornerstone of presurgical evaluation in drug resistant epilepsy rests on

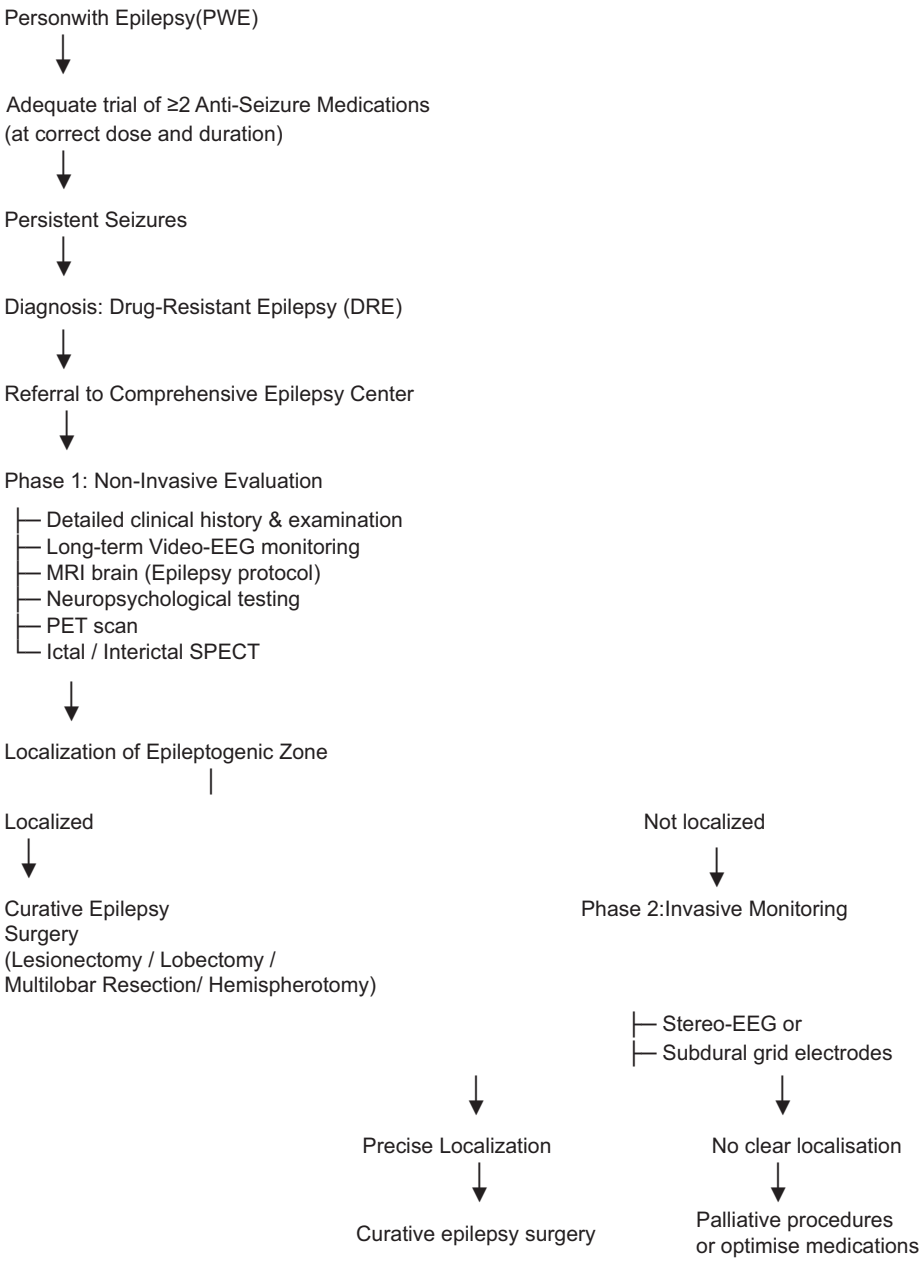

Figure 1: Flow chart for Pre-Surgical Evaluation of Drug Resistant Epilepsy

Table 1: Pathological Lesions Causing Surgically Remediable Epilepsy

Category	Lesion	Typical Age Group	Common Location	Features
Hippocampal Pathology	Mesial temporal (hippocampal) sclerosis	Adolescents & adults	Temporal lobe	Neuronal loss and gliosis in hippocampus; most common cause of drug-resistant focal epilepsy
Malformations of Cortical Development (MCD)	Focal cortical dysplasia (FCD)	Children & young adults	Frontal > temporal	Disorganized cortical lamination; most common pediatric surgical pathology
	Hemimegalencephaly	Infants	One cerebral hemisphere	Enlarged dysplastic hemisphere
	Polymicrogyria	Children	Perisylvian region	Abnormal cortical folding
Neoplastic Lesions (Low-grade tumors)	Dysembryoplastic neuroepithelial tumor (DNET)	Children & young adults	Temporal lobe	Benign, strongly epilepsy-associated
	Ganglioglioma	Children & young adults	Temporal lobe	Mixed neuronal-glial tumor
	Low-grade glioma	Variable	Cortical regions	Slow-growing epileptogenic tumors
Vascular Lesions	Cavernous malformation (cavernoma)	Any age	Cortical/ subcortical	Hemosiderin deposition → epileptogenic
	Arteriovenous malformation (AVM)	Young adults	Cortical	Seizures due to irritation or hemorrhage
Infectious/ Post-infectious	Neurocysticercosis	Endemic regions	Cortical	Calcified granulomas may cause focal seizures
	Post-encephalitic gliosis	Any age	Variable	Scar tissue after infection
Post-traumatic/ Scar Lesions	Post-traumatic cortical scar	Any age	Frontal/ temporal	Gliotic epileptogenic focus
Developmental/ Genetic Syndromes	Tuberous sclerosis complex (cortical tubers)	Children	Multiple cortical areas	Developmental lesions causing focal epilepsy
	Hypothalamic hamartoma	Children	Hypothalamus	
Inflammatory	Rasmussen encephalitis	Children	One hemisphere	Progressive unihemispheric inflammation; auto immune

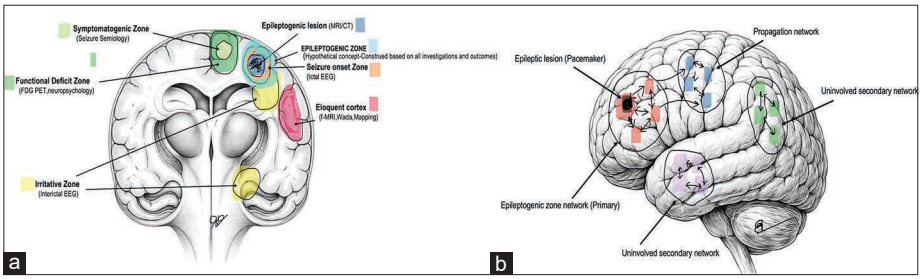

Figure 2: (a) Brain zones in Epilepsy (*Felix Rosenow and Hans Lüders, 2001*), (b) Epileptic Network Hypothesis

identification of the epileptogenic zone (EZ) and/or the epileptic network (Figure 2). In 2001, Felix Rosenow and Hans Lüders refined the classical Talairach–Bancaud framework and clearly defined five cortical zones involved in epilepsy(1-3)-

1. *Epileptogenic Zone (EZ)-*
   The EZ is the minimum amount of cortical tissue that must be resected to render the patient seizure-free. This is a theoretical concept, and a retrospective evaluation of surgical outcome helps to identify the EZ.
2. *Seizure Onset Zone (SOZ)*
   The SOZ refers to the area where seizures start electrically and is identified on scalp EEG or intracranial EEG. It may be smaller than the EZ.
3. *Irritative Zone*
   This refers to the area generating interictal epileptiform discharges and is usually larger than SOZ.
4. *Symptomatogenic Zone*-The area responsible for the clinical manifestation and

observable symptoms.For example the motor cortex causing clonic movement and the temporal lobe causing aura like fear, déjà vu.

5. *Functional Deficit Zone*
   This refers to the cortex involved in interictal dysfunction. It is identified by a neurological examination with neuropsychological testing and/or PET/SPECT hypometabolism

The alternate 'network hypothesis' (Spencer SS,2002) (7) suggests that epilepsy is not generated by a single focal point, but by an abnormal distributed neural network. Instead of one small cortical area causing seizures multiple interconnected brain regions maybe involved (7). They function together as a pathological network. Any critical node in the network can trigger seizure activity. This explains the occasional surgical failures despite aggressive and adequate surgical resections of the epileptogenic zone.

Tiers of Pre-Surgical Evaluation

The presurgical evaluation for drug-resistant epilepsy is a systematic, phased process designed to define the anatomo-electroclinical hypothesis necessary to localize the epileptogenic zone (EZ or epileptic network. It also aids to identify functional cortex and predict surgical outcomes(3). A collaborative multidisciplinary team approach through a patient management conference(PMC) remains a key element to corroborate the required patient specific intervention plan (Figure 1).

The broad classification of the structured framework divides it into non-invasive (Phase I) and invasive (Phase II) investigations. Standard noninvasive investigations (Phase I A) include high-resolution MRI, prolonged video-EEG monitoring, and neuropsychological assessment. Other ancillary tests (Phase I B) include positron emission tomography (inter ictal PET), ictal single-photon emission computed tomography, functional magnetic resonance imaging, and magnetoencephalography (MEG). There are wide variations in the practice of using these modalities in different nations, based on socioeconomic and infrastructural limitations. To address the lack of standardization, systematic reviews from the E-PILEPSY consortium have been developed using the GRADE methodology for selected diagnostic tools.

Those with complex pathology or diffuse epileptic network leading to difficulty in reaching at a concordant plan, will mandate the requirement of invasive tools in the pre-surgical evaluation. The standard invasive modalities in current practice include stereoelectroencephalography (SEEG) and subdural grid electrodes (SDG).

The spectrum of epilepsy surgery ranges from curative procedures to palliative ones and could also be classified as resective, disconnective and neuromodulatory procedures (Table 1)

- *Phase I-Non-Invasive Presurgical Evaluation*

The principal concept of Phase I involves applying the essential components of clinical history, examination, imaging and electrographic recordings to reach a conclusive evidence regarding the hypothesised epileptiform zone (EZ) and/or epileptic network localisation. A detailed clinical history with seizure semiology remains the cornerstone of initial assessment. Video EEG, a crucial first step to the pre surgical work up, aids to capture habitual seizures, localise the seizure onset zone, correlate semiology with EEG and assess inter ictal activity.

A 3-D volumetric MRI brain as per "HARNESS- (Harmonised neuroimaging of epilepsy structural sequence) protocol" is the other essential investigation. It utilizes thin-cut slices perpendicular to the hippocampus in 3-D T2-FLAIR, T1- weighted sequence and 2- dimensional coronal T2 -weighted sequence. The contrast enhanced as well as Diffusion weighted sequence are often required when the pathology is a tumor, vascular lesion or any infective lesion. Other MR adjuncts include volumetry (hippocampal asymmetry), DTI (tract mapping), Functional MRI (language, sensorimotor localisation), post-processing morphometry, arterial spin labelling (ASL), etc.

Functional neuroimaging techniques such as fluorodeoxyglucose-positron emission tomography (PET) and ictal single-photon emission computed tomography (SPECT) are useful when MRI & EEG are discordant or MRI is negative. SISCOM (Subtraction

Ictal SPECT Co-registered to MRI) improves accuracy of the work up. Other functional assessments like functional MRI and intracarotid amobarbital testing (Wada) to map language and memory dominance and sensorimotor lateralisation are also significant in eloquent cortex lesions. Wada in the current f-MRI era has a role in children and when f-MRI is ambiguous or inconclusive.

Magnetoencephalography (MEG) records magnetic fields generated by neuronal activity and helps localize interictal spike sources in drug-resistant epilepsy. It is particularly useful in MRI-negative and extratemporal epilepsy and guides intracranial electrode placement.Nearly 65–70% of patients can be directly considered for surgery based on concordant Video-EEG and MRI findings alone, without needing invasive monitoring.

- *Phase II - Invasive EEG Monitoring*

Approximately 12-20% of patients with drug-resistant epilepsy lack conclusive non-invasive data from scalp EEG, imaging, and other Phase 1investigations to identify the epileptogenic zone, thereby necessitating invasive monitoring to complement the non-invasive workup. The key indications for chronic invasive EEG monitoring are inconclusive or discordant evidence from non-invasive tests, proximity to eloquent regions, imaging negative focal epilepsy, multiple lesions, insufficient data to localize or lateralize the EZ.

Intracranial EEG is a diagnostic modality that entails the implantation of intracerebral and/or subdural macro electrodes directly placed in candidate sites of the brain and monitoring brain activities over days to weeks. Invasive EEG includes chronic invasive EEG monitoring using sub dural electrodes (SDE) or stereoelectroencephalography (SEEG) electrodes and acute intra operative elecectrocorticography (acute ECoG). For chronic EEG monitoring, the choice of the appropriate invasive monitoring modality, whether stereoelectroencephalography or subdural grids, is guided by the specific clinical hypothesis derived from the non-invasive evaluation. SEEG offers particular advantage for sampling deep or sulcal structures that are inaccessible to subdural electrodes. On the other hand, subdural electrodes (SDE) are often favored when the epileptogenic zone involves the cortical surface and requires extensive mapping of functional areas through cortical stimulation. This functional mapping capability is critical for minimizing postoperative neurological deficits, as it allows the surgical team to delineate the boundaries of the epileptogenic zone relative to essential language, motor, and cognitive regions before resectionThis prolonged recording period allows clinicians to capture multiple habitual seizures, which is essential for accurately delineating the seizure onset zone and understanding the network dynamics of seizure propagation . Recognizing and describing ictal and interictal patterns with intracranial electroencephalography recordings is important in order to most efficiently leverage advantages of this technique to accurately delineate the seizure-onset zone, its propagation and network before surgery.

The International League Against Epilepsy (ILAE) has defined specific indications for intracranial EEG, primarily to delineate the epileptogenic zone when prior non-invasive workup was inconclusive, to resolve divergence of non-invasive data in multiple epileptogenic lesions and to mitigate surgical damage to eloquent areas. The interpretation of intracranial stereoelectroencephalography signals remains a complex endeavor, as decision-making in SEEG-guided epilepsy surgery relies heavily on the accurate analysis of these recordings, despite persistent challenges related to signal interpretation. To address these limitations, there is a pressing need for objective, standardized methods to guide surgical decision-making and enable large-scale data analysis across centers and prospective clinical trials . Consequently, the establishment of standardized protocols for data acquisition, processing, and interpretation is essential to facilitate multicenter collaboration and improve the reproducibility of SEEG findings. Such standardization efforts are particularly vital given the variability in current practices across centers, where the absence of uniform guidelines for presurgical evaluation has led to significant heterogeneity in the selection of invasive monitoring modalities and technical standards (8). General indications for intracranial EEG encompass the definition of the epileptogenic zone and the determination of the location of eloquent cortex relative to the epileptogenic zone, typically achieved through cortical stimulation mapping.

Conversely, subdural electroencephalography(SDE) provides a two-dimensional image of the brain structures, whereas SEEG provides a three-dimensional network-oriented view (9). This volumetric sampling capability allows for the precise exploration of deep-seated and sulcal structures, such as the insula or mesial temporal regions, which are often inaccessible to surface grid recordings.

A brief overview of surgical technique, adverse events, choice of procedure and outcomes of SDE and SEEG are detailed below along with a comparative table (Tables 2,3,4 and 5)

A. Subdural Electrodes – Surgical Technique Overview

Types:

- Grid electrodes – rectangular arrays for cortical mapping (2x2,2x4,4x4,4x8,2x8,8x8, etc)
- Strip electrodes – narrow linear arrays (1x4,1x6, etc)
- Depth electrodes (1.1 mm thick,4,6,8 contacts)
- Combination placements for large cortical coverage

Electrode contacts are made of platinum or platinum-iridium (PtIr) alloys and earlier of stainless steel (Figure 3)

Surgical Steps:

1. Pre-operative Planning
   Using the High-resolution MRI, Video-EEG monitoring, functional imaging (PET/SPECT if needed), an ictal onset and propagation hypothesis is generated,

Table 2: Surgical Treatment of Epilepsy-Spectrum of procedures

Category	Procedure	Surgical Target	Rationale
Resective Surgery	Anterior temporal lobectomy with amygdalohippocampectomy	Mesial temporal lobe epilepsy	Resection of epileptogenic mesial temporal lobe and neocortex
	Selective amygdalohippocampectomy	Mesial temporal epilepsy	Removal of amygdala & hippocampus while sparing neocortex
	Lesionectomy	Tumor, cortical dysplasia, cavernoma	Removal of structural epileptogenic lesion
	Extratemporal cortical resection	Frontal, parietal, occipital epilepsy	Removal of identified epileptogenic cortex
Disconnective Surgery	Hemispherotomy/ Hemispherectomy	Hemispheric epilepsys (e.g., Rasmussen syndrome, hemimegalencephaly, porencephalic cysts, Sturge Weber syndrome)	Functional disconnectionof one hemisphere
	Corpus callosotomy	Drop attacks, generalized seizures (Lennox Gastaut syndrome)	Callosal disconnection to prevent synchronisation an seizure spread
	Multiple subpial transections (MST)	Epileptogenic cortex in eloquent area	Interrupt horizontal fibers while preserving function
Neuromodulation (Palliative/ Functional)	Vagus nerve stimulation (VNS)	Drug-resistant primary generalised epilepsy not suitable for focal resection	Intermittent vagal stimulation
	Deep brain stimulation (DBS – anterior thalamus, centromedian nucleus)	Refractory focal epilepsy	Thalamic modulation to reduce seizure frequency
	Responsive neurostimulation (RNS)	Focal epilepsy with identifiable focus	Closed-loop stimulation at seizure onset
Ablative	Laser interstitial thermal therapy (LITT)	Mesial temporal epilepsy, small lesions	MRI-guided thermal ablation
	Radiofrequency thermocoagulation	Focal cortical epilepsy	Localized tissue destruction via electrode
	Stereotactic radiosurgery (Gamma Knife)	Selected focal epilepsies	Focused radiation to epileptogenic zone

Table 3: Choice of Invasive EEG Technique

	SDE	SEEG
Advantages	• Functional mapping • Resection during electrode removal	• Deeper targets • Bi hemispheric targets • Smaller access • Delayed future resections
Limitations	• Limited deep coverage • Larger incisions • More Morbidity	Restricted functional mapping
Ideal candidate	Cortical eloquent lesions	• Deep lesions • Failed surgery • MR negative

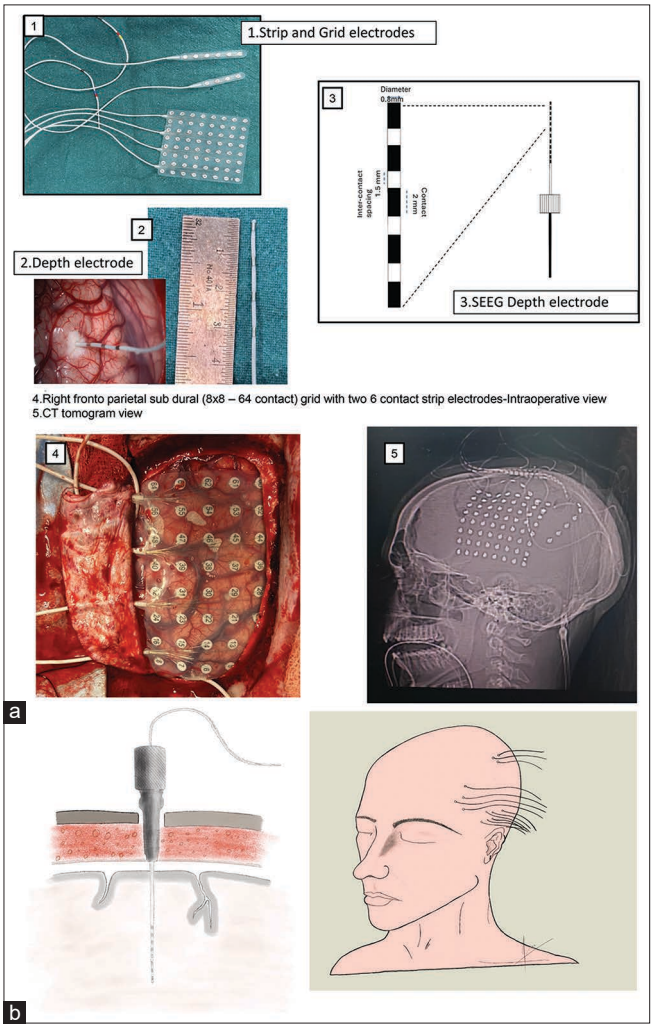

Figure 3: (a) Sub dural grid strip,depth and SEEG electrodes. (b) SEEG overview (schematic)

electrode coverage and surgical exposure by a suitable craniotomy/burr hole are planned.

2. Positioning & Exposure
   Procedure done under general anaesthesia with the head fixed in Mayfield head holder. Targeted craniotomy or burr hole (for depth electrodes or strip electrodes) and dura opened in a curvilinear fashion.
3. Electrode Placement
   Gentle placement of grid electrode directly on cortical surface
   Strips inserted carefully under dura to extend coverage. Depth electrodes maybe placed using anatomical landmarks or neuronavigation.

Table 4: Chronic Invasive EEG scenarios

Clinical scenario	Method of choice	Second choice
MRI Positive lesion	SEEG	Sub dural grids/depth
	Deep subcortical (Insular)	SEEG
	Sub dural grids/depth	
	Superficial location	
	'Eloquent' proximity	
MRI Negative	SEEG	Sub dural grids/depth
	Deep subcortical (Insular)	SEEG
	Sub dural grids/depth	
	'Eloquent' proximity	
Bilateral explorations needed	SEEG	Sub dural grids/depth
Failed sub dural grids	SEEG	Extended SEEG/SDG
Multilobar network	SEEG	Sub dural grids/depth
Failed resective surgery	SEEG-Multilobar	Sub dural grids/depth
		'Eloquent' proximity

Table 5: Surgical Outcomes after invasive EEG

Year	Author	Total Patient SEEG	Outcome	Conclusion
2024	Murray-Douglass *et al.* (21)	66	63 (95%) Cases EZ localized 39 (59%) operated -23 achieved Engel's class i	SEEG implantation and evaluation can achieve high rates of epilepsy localisation with minimal complications.
2023	S. Maesawa *et al.* (37)	12 (out of 32)- rest 16 underwent SDG , 4 mixed evaluation	7 (58.3%) operated; 85.7 achieved Engel's class 1	The comparison with SDG and mixed evaluation showed SEEG to have superior outcome; with Mixed cases having 87.1% Engel's class 1 and those in SDG group having 0%
2022	Remick *et al.* (40)	134 SEEG, 42 SDG	Resection (75.4% SDE vs 21.4% sEEG, *P*<0.01) Seizure freedom 60.2% in SEEG; 75% in SDG	SEEG cases had a lower complication rate vs SDG case
2021	Kim *et al.* (41)	Total 66 patients – 47 SEEG; 19 SDG	1.EZ localization: SEEG 91.5%, SDG 88.2% 2. Engel class I (SEEG 29.3%, SDE 35.3%)	SEEG and SDE monitoring yield similar outcomes in seizure control; however, SEEG offers notable benefits including enhanced pain management, reduced reliance on narcotics, and generally eliminates the necessity for routine intensive care unit admission.
2021	Tsuboyama *et al.* (42)	104 SEEG	65.7% post resection seizure freedom	Good outcomes with SEEG
2020	Joswig *et al.* (43)	145 SEEG, 355 SDG	Surgical outcome was similar in both	Comparable outcomes with SEEG and SDE
2014	Serletis *et al.* (44)	200	87% patients were operated; 68% achieved seizure freedom	Good outcomes with SEEG
2005	Cossu (45)	211	82% patients were operated off whom 56% achieved seizure freedom	Good outcomes with SEEG

Care is taken to ensure that no cortical vessel is compressed especially large cortical veins. If needed the grid can be split without damaging the microelectrodes, good cortical contact with no folding of grid is to be ensured.
Leads tunneled percutaneously through separate stab incision or using a Tuohy needle.

4. Closure
   Dura loosely approximated
   Bone flap replaced
   Scalp closed in layers
   Patient is then transferred for continuous intracranial EEG monitoring (usually 5–14 days till adequate habitual events are recorded to generate a hypothesis).
5. Second Stage (Explantation of electrodes with/without resection)
   After seizure localization: Re-open craniotomy, remove electrodes, perform cortical resection as per ictal onset zone and functional map plan.

B. Stereoelectroencephalography (SEEG)

Concept and Rationale:

Stereoelectroencephalography(SEEG) is a hypothesis-driven, minimally invasive method that uses depth electrodes in the brain parenchyma to map the three-dimensional anatomical, electrical, and clinical structure of the epileptogenic zone and epileptic network. This helps to test thehypothesis about seizure onset and spread (9–11). The basic technique of SEEG comprises of precisely placing depth electrodes into deep cortical structures and thereby recording directly from these locations. The earliest SEEG concept and technique was developed by Talairach and Bancaud in the 1960s.It's basic concept was independent of structural neuroimaging findings, thereby making it particularly effective for the investigation of nonlesional focal epilepsy cases where the epileptogenic zone is not visibly apparent on radiographic studies (12,13). In contrast to prior stereotactic techniques confined to superficial cortical evaluation, the proportional grid system facilitated comprehensive analysis of the entire brain volume—including deep gray nuclei—relative to discernible anatomical landmarks, thereby enabling the investigation of 3-D seizure propagation patterns and their associations with clinical manifestations via extended serial recordings. Following its initial development in France, the dissemination of SEEG remained limited to specialized European centers for several decades before experiencing a rapid global expansion during the last 15 years (9). This resurgence in adoption has been driven by technological advancements in neuroimaging and stereotactic navigation, as well as the growing recognition of SEEG's utility in evaluating epileptic networks that are poorly assessed by subdural techniques (4,15,16). The evolution of SEEG from its origins in stereotactic neurosurgery to its current status as a cornerstone of presurgical evaluation reflects a paradigm shift towards the precise 3-D analysis of epileptic networks (4,9). This conceptual evolution has progressed from the original notion of a discrete seizure onset zone to a comprehensive network theory of epilepsy, wherein SEEG permits the clinician and surgeon to understand the complex interactions between pathologic epileptogenic networks and physiologic pathways (9,17). This framework contested the prior "irritative zone" hypothesis by revealing that areas of interictal spiking may differ from the true seizure onset zone, thereby solidifying the contemporary view of epilepsy as a network disorder rather than isolated focal cortical pathology (18,19). The network model of epilepsy has been backed by recent advances in neuroradiology and neurophysiology. Modern SEEG applications have been enhanced by incorporating advanced neuroimaging and robotic assistance, improving electrode placement accuracy and procedural safety (4). Recent studies show that SEEG safety and accuracy depend on vascular imaging choices and stereotactic methods. Robotic guidance with frameless systems offers the best balance of precision and minimal invasiveness (20). These technological improvements have streamlined the implantation process, shortened operative duration and facilitated the exploration of deep cortical structures and bilateral networks that were previously difficult to access with traditional methods (9,21).

Physiological Basis of SEEG Recordings

SEEG directly records electrical activity from cortical and subcortical structures via intracerebral depth electrodes, enabling 3D exploration of epileptogenic networks with high spatial and temporal resolution (22). Unlike scalp EEG—limited by electrode distance to generators and skull/scalp filtering—SEEG captures epileptogenic zone signals with minimal attenuation (22). This direct intracranial access enables the detection of low-amplitude fast activity (LVFA), high-frequency oscillations (HFO), and distinct ictal onset patterns that are often obscured on surface recordings, thereby providing a more precise delineation of the epileptogenic zone and its functional networks (22,23). To precisely record these high-frequency oscillations and low-

voltage fast activities, the EEG system requires at least 128 channels and a sampling rate of 256 Hz or higher, although most centers employ rates of 1,280 Hz or more to optimally assess high-frequency oscillations (9). In clinical practice, monitoring is typically conducted over a period of 5 to 21 days using a 128-channel video-SEEG system, with acquisition parameters often set to a sampling rate of 2,000 Hz and a 500-Hz low-pass hardware filter to ensure high-fidelity signal capture (24). A setting of 1-kHz sampling rate and a greater than or equal to 16-bit analog-to-digital conversion is required to obtain the appropriate quality intracranial sEEG signal for diagnostic purposes (25). The referential montage, which calculates the potential difference between a specific contact and a common reference such as a white matter contact or linked ears, is frequently employed to visualize these signals, though an average reference montage may also be utilized to estimate the potential at infinity. Alternatively, bipolar montages are often employed to maximize local precision by referencing each recording site to its nearest neighbour, which reduces the contamination from distant electrical sources and enhances the spatial resolution of the recorded activity (26).

Stereo-EEG (SEEG) Insertion – Surgical Technique Overview

Stereo-electroencephalography (SEEG) is a minimally invasive method used to localize epileptogenic zones and networks in patients with drug-resistant epilepsy. It allows three-dimensional recording from deep cortical and subcortical structures.

Can be done using any of the following,

- Frame-based stereotaxy (e.g., Leksell frame)
- Frameless stereotaxy/image guidance (Brain Lab/Stealth)
- Robotic guidance (e.g., ROSA,Renishaw)

1. Pre-operative Planning

- Define anatomo-electro-clinical hypothesis
- Choose entry and target points
- Avoid: Sulci (reduce haemorrhage risk), Vessels (arteries & veins), Ventricles (if possible)
- Maintain safe electrode trajectories
- Ensure orthogonal sampling of suspected epileptogenic networks

Trajectory planning

Trajectory planning is typically done using stereotactic planning software integrated with neuronavigation or robotic platforms.

The trajectory of implantation can be either orthogonal or oblique. However, there remains no universal consensus on the maximum number of electrodes to implant, necessitating a careful assessment of the benefit-risk ratio for each patient (25). While surgeon training and experience often guide the choice between orthogonal and oblique trajectories, evidence favors orthogonal (or quasi-orthogonal) approaches for most SEEG targets. These optimize coverage volume, as many functional networks align orthogonal to the mid-sagittal plane (27). The orthogonal approach works well for exploring mesial temporal areas like the amygdala and hippocampus, while also allowing shallower paths to capture signals from the temporal neocortex. This front-to-back and top-to-bottom setup helps rebuild a full 3D map of brain activity (27). However, oblique trajectories are appropriate in accessing the deep-seated or perisylvian structures (the insular cortex or opercular regions), where orthogonal approaches may be limited by skull anatomy or vascular constraints (9,20). Therefore, the judicious choice of trajectory configurations is critical for optimizing the diagnostic efficacy of SEEG implantation while minimizing the risks of intracranial haemorrhage and electrode deflection inherent in prolonged oblique trajectories (27–29).

2. Patient Positioning & Setup

- General anaesthesia
- Supine or lateral depending on targets
- Head fixation as per technique Frame-based stereotaxy or Frameless stereotaxy or neuronavigation with/without robotic guidance

- Registration with Surface matching and bone fiducials

3. Twist drill craniostomy access

Technique:

- Small stab incision (~5 mm)
- Twist drill craniostomy (~2–3 mm)
- Dura coagulated and pierced with stylet
- Haemostasis ensured

A bolt or anchor system is inserted to secure the electrode (Figure 2).

4. Electrode Insertion
   - Use rigid stylet or guide
   - Advance electrode to pre-measured depth
   - Verify depth using mechanical stop and navigation confirmation
   - Lock electrode into cranial bolt

Electrode characteristics:

- Diameter: ~0.8–1.3 mm
- Multiple contacts (5–18 contacts)
- Contact spacing: 2–5 mm

5. Intraoperative & Postoperative Verification
   - Immediate postoperative CT
   - Fuse CT with preoperative MRI
   - Confirm: Correct target location, no hemorrhage, no significant trajectory deviation

Comparison of SEEG with Other Invasive Monitoring Techniques

The identification of the ictal onset zone relies on the analysis of the earliest electrographic changes, which are frequently characterized by rapid discharges or low-voltage fast activity that define the seizure onset zone within the three-dimensional SEEG framework (30). While visual inspection remains the cornerstone of identifying the ictal onset zone, quantitative methods such as the epileptogenicity index have been developed to objectively assess the degree of epileptogenicity by calculating the energy ratio between fast activity and slow activity during the early seizure phase (13,31). These computational approaches utilize statistical measures such as variance, skewness, and kurtosis to differentiate the seizure onset zone from the early propagation zone, as the latter typically exhibits simpler waveform morphology and greater normality (23). Furthermore, the concept of the "early spread network" is utilized in SEEG interpretation to characterize the propagation of ictal activity to connected regions, distinguishing this secondary involvement from the primary epileptogenic zone (9,32). The correlation of spatial ictal spread to clinical semiology constitutes the cornerstone of seizure comprehension, as the evolving subjective and objective symptoms reflect the recruitment of anatomically and functionally interconnected cortical and subcortical regions that form the epileptic network (25). This spatiotemporal propagation is particularly rapid in neocortical epilepsy, facilitated by short intralobar and interhemispheric connections that can be estimated using diffusion tensor imaging tractography (33). In contrast, mesial temporal seizures typically exhibit slower propagation patterns, allowing for more distinct delineation of the epileptogenic network through quantitative signal analysis (33,34). The neural network of epilepsy patients is subdivided into seizure-onset regions, propagation regions, and onward propagation regions, necessitating the use of quantitative methodologies to identify these distinct areas within the epileptogenic network (35-49).

Choosing SEEG versus Sub dural electrodes (SDE)

In the current era of minimally invasive surgery, SEEG explorations are preferred over SDE in MRI negative focal epilepsy, bilateral explorations, deep cortical explorations like the insula, mesial temporal, cingulate cortex etc. While SDE are preferred in eloquent cortex mapping with extra operative stimulation. Both SEEG and SDE could be used for inducing habitual seizures but stimulation, but rarely used. SEEG also offers the scope for therapeutic interventions like SEEG guided radiofrequency thermocoagulation (Table 2,3).

Complications and Safety Profile of Invasive EEG

1. Haemorrhage is the most commonly reported complication of SEEG electrode implantation, with incidence rates ranging from 0.075% to 0.45% per electrode—generally lower than the 4% risk associated with subdural grid placement (13). A

recent meta-analysis by Mullin *et al*. confirmed this safety benefit, reporting an overall complication rate of 1.3% for SEEG versus 4.0% for subdural recordings, alongside a statistically significant higher risk of haemorrhagic and infectious complications with subdural electrodes (36).

2. Infection rates after SEEG implantation are markedly lower than those associated with subdural grid and strip procedures (37,38). In a systematic review of 2,624 patients undergoing 22,085 electrode implantations, the most common complications were identified as haemorrhagic or infectious events, with a total of 121 surgical complications and 5 mortalities reported (39). More recent comparative studies involving 1,468 patients from multiple centers have found that the risk of symptomatic haemorrhage ranges between 1.4% and 2.8% with SEEG, compared to 1.4% and 3.7% with subdural electrodes, while infection rates vary from 0% to 0.9% for SEEG versus 2.2% to 7% for subdural grids (21).
3. Neurological Deficits: Though uncommon, permanent neurological deficits have been documented in a limited number of cases, with intracerebral hematoma identified as the nearly exclusive cause in instances of mortality. A review of 2,624 patients showed a 0.6% rate of both transient and permanent neurological deficits, but it's unclear if permanent ones are directly caused by the procedure (2). Transient neurological deficits, such as aphasia or hemiparesis, are usually temporary and resolve without permanent effects. They occur more often in patients with prior brain issues or many implanted electrodes (37).
4. Technical Malfunctions: Such issues may encompass electrode fractures, dislodgement, or signal deterioration, which—although not directly threatening patient safety—can impair the diagnostic effectiveness of the SEEG evaluation (6). Although electrode fractures and dislodgements remain uncommon owing to precise surgical planning and durable electrode construction, signal loss may occasionally result from tissue responses or subtle movements, requiring thorough assessment of recording integrity.

Outcomes of Epilepsy Surgery Guided by SEEG

The cases of DRE, operated and treated after invasive EEG explorations show a favourable outcome measured by seizure freedom, withdrawal of anti-epileptic medications and overall quality of life indices (Table 4). For example, extended follow-up investigations have repeatedly demonstrated seizure-free rates of 60% to 80% among meticulously selected patients, emphasizing SEEG's critical contribution to favorable surgical results (37). These statistics highlight the transformative potential of SEEG in ameliorating drug-resistant epilepsy, thereby significantly improving patient prognosis and functional independence. Furthermore, comparative assessment of outcomes proves SEEG guided interventions to perform better than those of sub dural grid electrodes, offering superior diagnostic accuracy and lower morbidity (9).

Predictors of Surgical Success

Key predictors of favorable surgical outcomes often include the complete resection of the epileptogenic zone as defined by SEEG, a shorter duration of epilepsy, MRI positive lesions and the absence of secondary generalization. The extent of resection, particularly the complete removal of the ictal onset zone, also emerges as a significant prognostic factor for long-term seizure control, further emphasizing the precision offered by SEEG in surgical planning.

Acute intra operative Electrocorticography (I-ECoG)

Acute intraoperative electrocorticography (ECoG) is used during epilepsy surgery to record electrical activity directly from the surface of the cerebral cortex(50-58).It is used to ascertain the epileptogenic zone based on inter ictal intraoperative 'spikes'.It is used for 'tailoring' resection margins and helps to identify potentially epileptogenic tissue that is often morphologically unremarkable as in focal cortical dysplasias.Preservation of eloquent cortex function is also aided by acute ECoG.A large series from our centre concluded that acute ECoG is not of much value in mesial temporal sclerosis(58).In long term epilepsy associated tumors(LEAT),additional ECoG tailored resections do not add to better seizure outcomes(52).However,in focal cortical dysplasias, I-ECoG may add value.The fallacies include the inter ictal nature of the recording and the influence of anaesthetic agents.

Future Directions and Emerging Technologies

The field of epilepsy surgery is currently undergoing a significant technological transformation, driven by the integration of advanced robotics, sophisticated neuroimaging techniques, and novel electrophysiological biomarkers that promise to enhance the precision and safety of SEEG procedures. With the increasing use of these newer technologies there has been a remarkable decline in measurement error, improved post-operative outcome and fewer complications associated with the procedure.

1. *Robot-assisted SEEG:*
   Robot-assisted stereotaxy enables precise placement along orthogonal and oblique trajectories, which was previously challenging with frame-based methods (18,37). A key advantage is the seamless transition between trajectory types using a single technique (18), with improved accuracy and reduced operative times compared to frame-based or frameless manual approaches (39). ROSA platform studies report fewer complications—one per 129 electrodes on average—and lower haemorrhage and infection rates than craniotomy-based subdural placement (18,46). Overall, the haemorrhage rates are comparable to frame-based techniques, but vascular imaging (e.g., CT angiography) prevents vessel injury (46). Robotic use features a learning curve, with operative times peaking at ~75 cases and plateauing at 150, enhancing accuracy and reducing haemorrhages (29,41). Modern software and robotics ensure reliable, reproducible, safe, accurate, and efficient insertions (9,29). Commercial systems like ROSA and Renishaw™ integrate with frame- or frameless techniques and are standard in major centers (9,23,39); Renishaw™ uses a 2.5 mm cannula for 2 mm burr holes and bolt insertion (9). Robotics yield superior accuracy—entry errors of 1.17 mm and target errors of 1.71 mm—versus frame-based systems (1.43 mm and 1.93 mm) (21,23). Meta-analyses confirm reduced target errors by automating tasks and minimizing human error (29). Robotic platforms such as ROSA and NeuroArm provide enhanced dexterity and precision through the integration of real-time imaging and haptic feedback, which facilitates minimally invasive interventions that would be technically challenging to perform manually (47,48).
2. *Computer-assisted planning/ Artificial Intelligence:*
   The increasing incorporation of artificial intelligence and advanced planning software standardizes the trajectories and limits manual adjustments (22). These automated systems utilize advanced algorithms to optimize electrode placement while minimizing the risk of vascular injury, thereby enhancing the overall safety and efficiency of the implantation process (9,49). Artificial intelligence has emerged as a promising tool for identifying the seizure-onset zone and the epileptogenic zone, leveraging hidden EEG features associated with epileptogenic regions through methods such as wavelet transformations and support vector machines (21).
3. *High-frequency oscillations (HFO)* represent another emerging frontier in SEEG analysis, serving as potential biomarkers for the epileptogenic zone that may provide greater spatial specificity than conventional ictal-onset patterns (23). Systematic reviews of high-frequency oscillations have confirmed the potential utility of fast ripples in delineating the epileptogenic zone, with a pooled sensitivity of 0.8, specificity of 0.72, and an area under the curve of 0.82, whereas ripples demonstrated lower sensitivity and specificity metrics (21). Despite the theoretical promise of HFOs, a randomized controlled trial failed to demonstrate their diagnostic superiority over conventional spike activity in defining the epileptogenic zone (21).
4. *Other electrophysiological biomarkers*
   Furthermore, other interictal biomarkers, including spike-gamma and spike-ripples, have shown stronger correlations with the epileptogenic zone than HFO rates, while ictal biomarkers such as the chirp and epileptogenic zone fingerprint are also under investigation (21).

Illustrative cases-Invasive EEG scenarios

1. *Wasted Hippocampal syndrome*

A 28-year-old male presented with a 10 year duration of complex partial seizures with right limb automatisms. The MRI showed right hippocampal sclerosis with temporal atrophy(Figure 4 A-E). The video EEG was not clearly lateralising, with bitemporal seizure onset (70% right and 30% left). Invasive EEG (bilateral hippocampal depth electrodes were placed using neuronavigation through an occipital oblique trajectory).Clear right temporal seizure onset was recorded in the invasive EEG and a hypothesis of 'burnt out hippocampus''/wasted hippocampus' was made. The patient underwent a right temporal cortico-amygdalo-hippocampectomy with Engel Class 1 outcome at 4 years follow up.

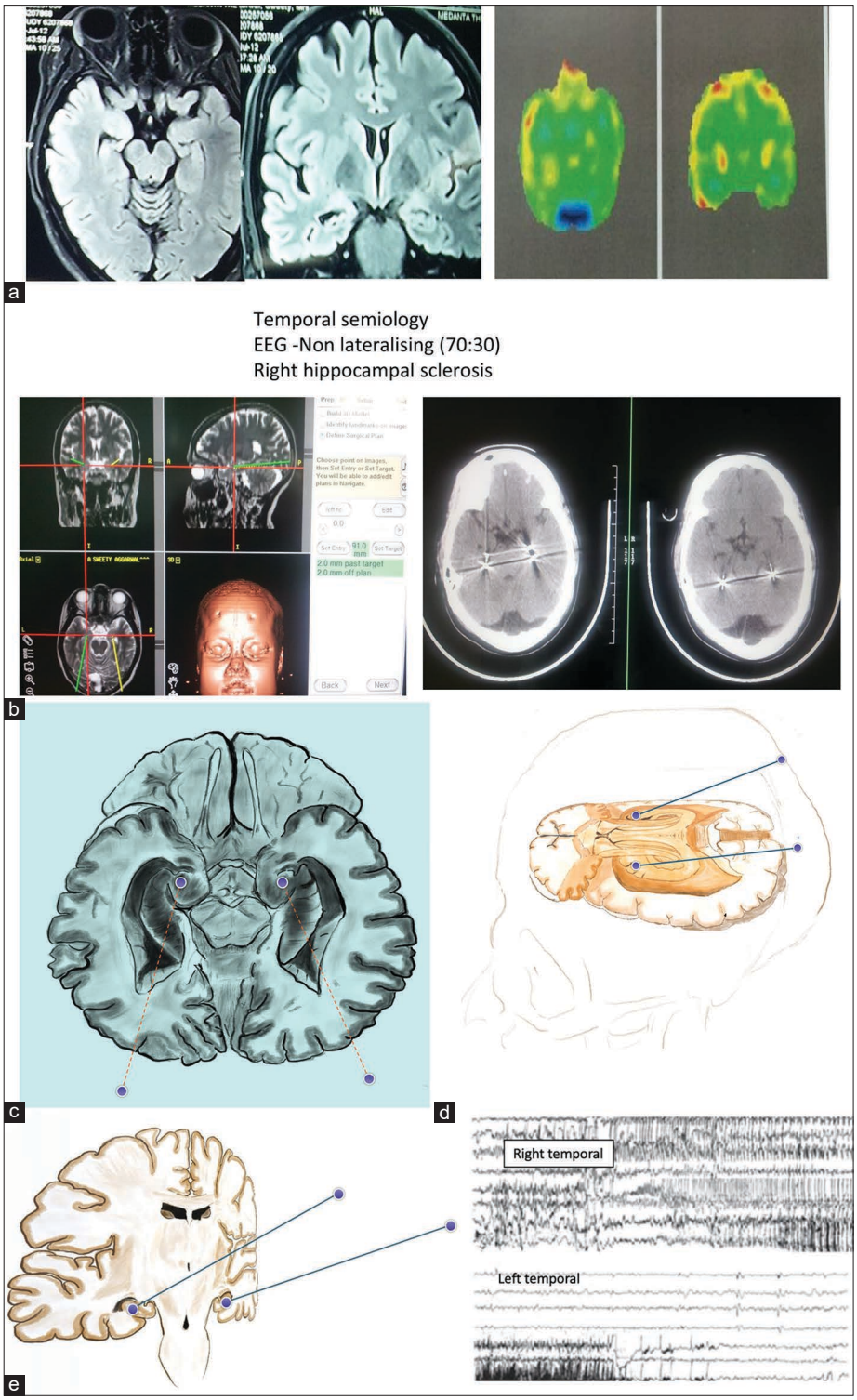

Figure 4: (a) Illustrative case 1-Right hippocampal sclerosis with right temporal ASL hypoperfusion. (b) Illustrative case Bilateral hippocampal depth electrodes-Frameless navigation guided. (c) Illustrative case 1-Bilateral hippocampal depth electrodes(oblique)-Schematic. (d) Illustrative case 1-Bilateral hippocampal depth electrodes(oblique)-Schematic. (e) Illustrative case 1-Bilateral hippocampal depth electrodes with right hippocampal ictal onset

2. MRI Negative fronto insular epilepsy

14-Year-old boy, pre-term, born by Ceaserean section presented with seizures of 5 years duration. The seizure semiology included behavioural arrest, stare, chewing automatisms with left hand automatisms. He did not respond to 3 anticonvulsants. The video EEG helped form a hypothesis of fronto-insular epilepsy with no clear lateralization. SEEG exploration with

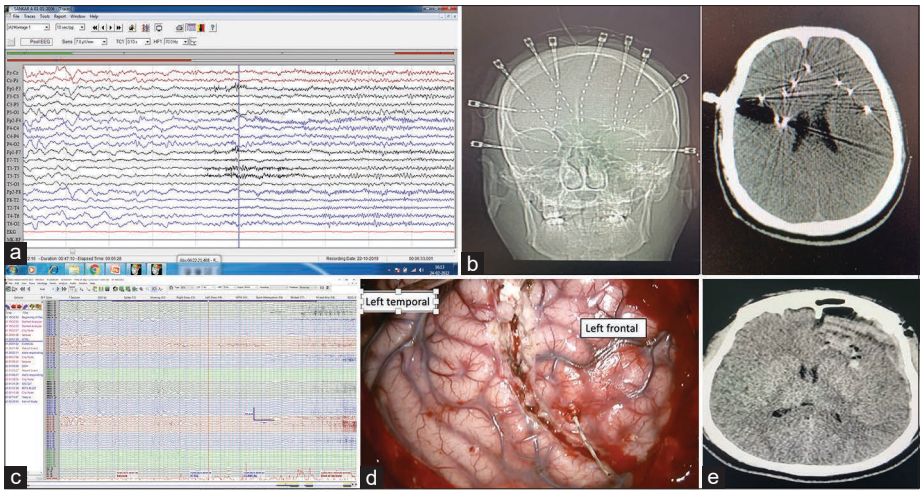

Figure 5: (A) Illustrative case 2-MRI negative and VEEG showing frontoinsular seizure onset. (B)Illustrative case 2-Bilateral frontoinsular SEEG exploration with 10 electrodes. (C) Illustrative case 2-Bilateral frontoinsular SEEG exploration showing left anterior insular onset with temporalspread. (D) Illustrative case 2-Left Anterior Quadrant(fronto temporo insular) resection. (E) Illustrative case 2-Left Anterior Quadrant Resection (Post Operative CT)

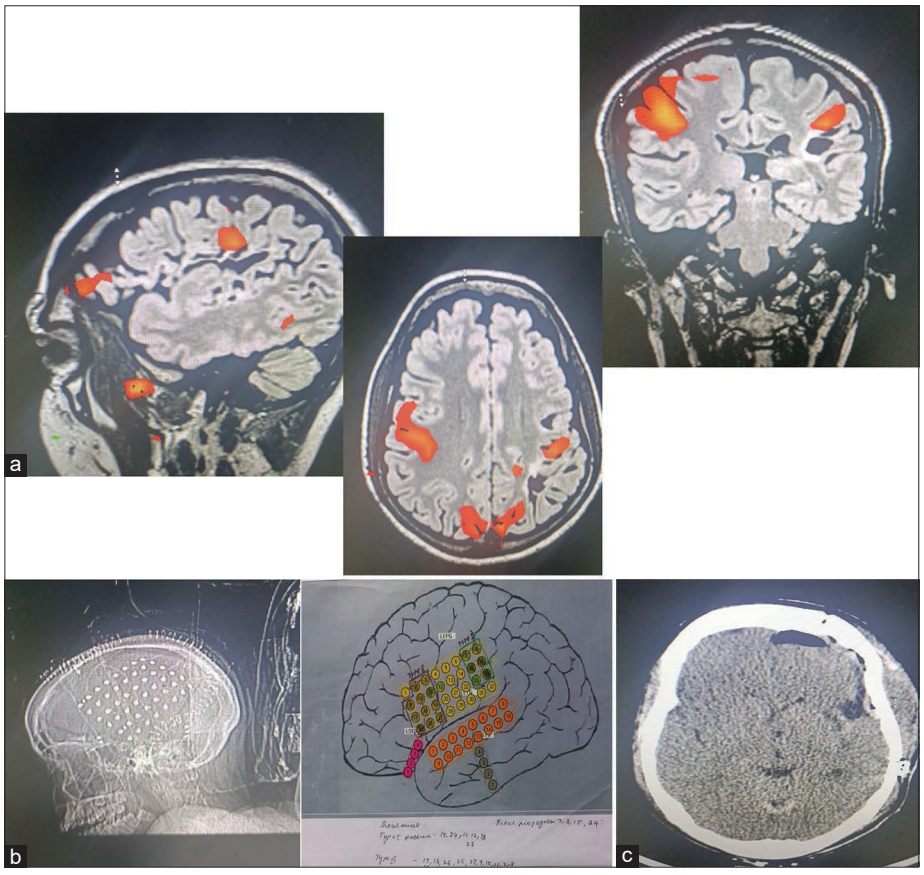

Figure 6: (a) Illustrative case 3- Left operculoinsular gliosis with language area functional overlap. (b) Illustrative case 3- Left operculoinsular gliosis with sub dural electrodes and schematic figure showing speech area overlap on extra operative speech mapping. (c) Illustrative case 3- Left operculoinsular resection post operative CT

bilateral frontal, insular and temporal coverage was done (Figure 5 A-E). A clear right fronto-insular ictal onset and bihemispheric spread was seen, A fronto-temporoinsular resection was done with excellent seizure outcome(Engel Class 1at 3 years). Histology suggested a type 1 focal cortical dysplasia.

3. Eloquent cortex epilepsy

15-year-old girl presented with a 12 years duration of complex partial seizures with head drops and posturing (2 different semiologies). MRI showed extensive left perisylvian and insular gliosis with f-MRI suggestive of overlap of language areas.

(Figure 6 A-C). Video-EEG suggested left insular and temporoparietal ictal onset. Invasive EEG with sub dural grids was done for ictal onset identification and functional mapping with extraoperative stimulation. After ictal onset zone and functional language area mapping a left temporoparieto-insular resection was done sparing the functional areas. Engel class 1 seizure outcome was noted at 3 years follow up.

Conclusion

Invasive EEG has an indispensible and evolving role in the presurgical evaluation of drug resistant epilepsy.Though useful in eloquent cortex invasive EEG ,the traditional sub dural electrodes have given way to the contemporary SEEG based evaluations. SEEG has fundamentally transformed the presurgical evaluation of drug-resistant epilepsy by providing a minimally invasive, three-dimensional approach to delineating the epileptogenic zone with high spatiotemporal resolution. This allows for a more nuanced understanding of the epileptic network, moving beyond the traditional localization of a single seizure onset zone to a systems-level perspective that enhances both diagnostic accuracy and prognostic reliability. Its routine use in the pre-operative workup has remarkable potential at improving patient's outcome. Meanwhile, rapidly developing technological advancements with artificial intelligence and robotics will certainly prove instrumental in shaping the future guidelines and treatment paradigms for epilepsy surgery.

Abbreviations

ILAE - International League against epilepsy
DRE - Drug Resistant Epilepsy
VEEG - Video Encephalography
SEEG - Stereo Encephalography
SDE - Sub Dural Electrodes
LMIC - Low and Middle income countries
HFO - High Frequency Oscillations

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