Invasive epilepsy surgery evaluation

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Abstract:

Intracranial EEG (iEEG) recordings are widely used for the work up of pharmacoresistant epilepsy. Different iEEG recording techniques namely subdural grids, strips, depth electrodes and stereoencephalography (SEEG) are available with distinct limitations and advantages. Epilepsy centres mastering multiple techniques apply them in an individualised patient approach. These tools are used to map the seizure onset zone which is pivotal in approximating the epileptogenic zone, i.e. the zone which is indispensable for the generation of seizures and when resected will render the patient seizure free. Besides, the implanted electrodes can be used to define eloquent cortex through direct cortical stimulation.

Different clinical scenarios exist which favour one iEEG recording technique over the other. Proximity of the presumed epileptogenic zone to eloquent cortex, for example, is a clinical scenario which may favour grid electrodes over SEEG.

We here review the indication for iEEG for the work-up of patients suffering from pharmacoresistant epilepsy. In addition, we provide a description of the recording techniques focussing on the main techniques used: grid electrodes, depth electrodes and stereoencephalography. We then outline different clinical scenarios and the preferred technical approach for intracranial recordings in these scenarios. Finally, we highlight which advances have been made in the field of iEEG and which advances are in the pipeline waiting to be established for clinical use.

This review provides the clinician with an update on the diagnostic use of intracranial EEG for epilepsy surgery and thus aids in understanding patient selection for this technique which may ultimately improve referral patterns.

1 Introduction

Intracranial EEG recordings (iEEG) date back to the days of Berger, who recorded electrical activity from the cortex using silver-chlorided needle electrodes [1]. Förster and Altenburger extended Berger´s work and performed intracranial recordings in the operating theatre showing focal slowing in EEG produced by tumours [2,3]. Subsequently many attempts at recording brain activity have been made, most notably by Delgado, who showed that recordings could be performed over an extended period of time with electrodes implanted in various animal species and subsequently also in humans [4,5]. Delgado's work in humans however was aimed at treating psychotic patients. The first approach at continuously recording iEEG in patients with epilepsy was made by Penfield and Jasper at the Montreal Neurological Institute. Besides their seminal study of human brain function through cortical stimulation, which led to the description of somatotopic organization of the cortex and the first schematic drawings of the homunculus, they also instigated the first iEEG recording in 1938 [6]. In this first recording Penfield's goal was to lateralize seizure onset by implanting bilateral electrodes on the dura overlying the temporal lobes. Further advance in iEEG recording came from the Mayo clinic advocating the use of depth recordings and discussing the interpretation of data derived by intracerebral electrography [7]. Around the same time in France, Bancaud and Talairach proposed the technique of stereoencephalography in the work-up of pharmacoresistant epilepsy which since has been widely used [8] (for a review about the history of invasive EEG see [3]). Nowadays iEEG recordings are performed in epilepsy centres all over the world. These recordings are aimed at approximating the epileptogenic zone (EZ) which is the region of cortex that needs to be removed to render the patient seizure free [9]. In addition direct cortical stimulation (CSM)

through the same electrodes provides information on eloquent cortex which needs to be spared during resection.

The percentage of patients considered for epilepsy surgery in need for iEEG ranges approximately between 30 and 40% in tertiary epilepsy centres. Certain clinical scenarios which necessitate iEEG recordings are common and recurring. Different iEEG recording techniques, namely subdural grids, strips and depth electrodes and stereoencephalography (SEEG) are in use, each with different limitations and advantages. Large epilepsy centres with experience in both approaches employ these techniques in an individualized patient approach, drawing on strengths and weaknesses of both methodologies.

Here we provide a comprehensive review of the indication for intracranial recordings in patients suffering from pharmacoresistant epilepsy, defined as having failed two or more antiepileptic drugs [10]. Intracranial recordings are performed to establish surgical candidacy by delineating cortical areas presumably necessary to generate the seizures and eloquent cortex using CSM. We focus on the different recording techniques using subdural grids, strips, depth recordings, combinations of all the former, and stereoencephalography (SEEG), including strategies underlying the planning of such investigations. We will highlight how subdural grid recordings, combination recordings of grids, strips and depth and SEEG recordings differ, and how individual cases can be approached. This will also illustrate limitations, advantages and disadvantages of subdural grid recordings and SEEG and inform clinicians on patient selection for iEEG recordings and the different types of recording.

Intraoperative EEG recording (ECoG) to capture interictal activity, through subdural strip/grid and depth electrodes, is also widely used. Continuous epileptiform discharges are considered a reliable marker of the epileptogenic zone and those discharges are often seen in focal cortical dysplasias, where ECoG has been shown to be beneficial in tailoring the extent of resection [11,12]. However, continuous epileptiform discharges are not always present on recordings and many centres rely more on ictal recordings and thus chronically implanted electrodes are needed. Although of some interest in iEEG evaluation in selected cases, acute intraoperative ECoG recordings are not in the scope of this review. Foramen ovale electrodes and epidural electrodes will also not be covered in this review due to their more limited use.

2 Who should undergo iEEG monitoring?

2.1 The definition of the epileptogenic zone

The overall aims of iEEG are 1. To aid defining the epileptogenic zone (EZ) and 2. To determine the location and extent of eloquent cortex in relation to the EZ to define safety margins for epilepsy surgery via CSM. The EZ has been defined as the minimum cortical area that needs to be removed to render the patient seizure free [9]. The definition of the EZ hence is a theoretical concept, and no single test or combination of tests describes it accurately. In fact, even after resection we can only conclude that the EZ was included in the area of resection if the patient became seizure free, but it is not known whether a smaller resection may also have achieved the same result. To propose surgical margins however, the EZ is approximated from all presurgical information delineating all zones described in table 1, including iEEG, if performed. The diagnostic modalities available and knowledge of and criteria for

interpretation of advanced tests have of course changed over the years, with our ability of identifying underlying lesions majorly benefiting from the wide availability of MRI from the 80s. Refinement of video EEG recording equipment allows the analysis of EEG both at very low and very high frequency spectra, constantly giving rise to new insights in the dynamics of seizures, even at single cell level. Analysis of structural, functional and effective connectivity measures using neurophysiological and imaging modalities have only begun recently to add to the armamentarium.

The concept of the epileptogenic zone underlying the planning and implementation of SEEG studies was proposed during the sixties by Talairach and Bancaud [13,14], with a slightly different emphasis. Its starting point derived primarily from a working hypothesis to establish the region of cortex generating the epileptic seizures that had to be determined electrophysiologically, and then translated into anatomical terms [14]. This has been phrased as “the ictal electroencephalographic changes must be recorded at the very point where they occur (anatomo-electrical relationships), and that their initial or secondary reverberations on the clinical picture (electro-clinical relationships) must be evaluated as the discharge spreads” [15]. It is important to note that the EZ in this definition does not equate to the region of cortex that needs to be removed [14]. These two approaches have shaped the strategies for implantation in many centres, with the latter being virtually universally adapted in centres traditionally only performing SEEG, the former in centres performing traditionally exclusively or more commonly subdural grids or combinations of depths, strips and grids.

2.2 Practical considerations for the implementation of iEEG

IEEG is considered a further diagnostic step necessary in a number of patients to establish surgical candidacy and delineate surgical margins. It is often needed to complement or resolve contradictory findings obtained by non-invasive tests. It adds cost and risk to epilepsy surgery and outcome studies consistently find that surgical outcome is inferior if iEEG was necessary [16]. Therefore, physicians may be reluctant to offer the procedure, and decide that patients are not a surgical candidate. However, a recent study showed that intracranial monitoring is favoured over VNS and medical management as it is a strategy which increases quality-adjusted life years over a broad range of variables such as the chance to localize the seizure focus and surgical morbidity [17]. In this challenging group, good outcomes in the range of 61% at one and 47% at 3 years can be achieved in a substantial number of well selected patients [18].

Decision on surgical candidacy and whether iEEG recordings are needed is typically made in a multidisciplinary team meeting after patients have undergone a number of non-invasive investigations, which typically include careful history and analysis of seizure semiology, scalp video EEG, neuropsychological and neuropsychiatric testing, structural and often also functional imaging such as PET and ictal SPECT. The latter is mostly only needed if MRI is normal or if other confounding factors exist regarding the formulation of a clear hypothesis of the EZ. Advanced neurophysiological options include MEG or high density EEG. Recent surveys have highlighted the variability of use of diagnostic modalities [19]. For paediatric candidates of epilepsy surgery, guidelines and recommendations regarding diagnostic test utilization have recently been made [20,21]; no such clear guidance

exists for the adult population although health technology assessments have been published [22].

Over time, most epilepsy centres report fluctuations in volume of iEEG recordings, and many experience more recently a resurgence in iEEG recording numbers. No study has specifically looked into the reasons for this, but changing trends in referral patterns, definitions of pharmaco-resistance, improved understanding of outcomes following epilepsy surgery as well as better understanding of risks of ongoing seizures such as SUDEP most certainly play a role. In addition, improved non-invasive diagnostics such as structural MR imaging and functional imaging techniques, advanced neurophysiological methods have all contributed to allow more complex epilepsies to be brought forward to establish surgical candidacy. Other considered classic surgical substrates such as temporal lobe epilepsy due to hippocampal sclerosis are in decline [23]. Furthermore, centres have inherent biases towards iEEG modalities, often due to varied availability of equipment and training background of the teams in question.

In the early days of iEEG recordings, iEEG recordings were performed in the operating theatre and due to time constrains these were aimed at recording interictal activity. However, the ultimate goal of epilepsy surgery is to remove the EZ, which is an area that is indispensable for generating seizure activity. Nowadays it is well accepted that the seizure onset zone is contained in the EZ and thus is a better approximate of the EZ than interictal activity. Interictal activity represents the irritative zone and can extend beyond the EZ [24]. There are, however, certain pathologies such as focal cortical dysplasia Type II where the presence of continuous or frequent

rhythmic epileptogenic discharges may be a very good approximation of the seizure onset zone [12], and some centres may rely solely on intraoperative ECoG in these cases. IEEG recordings with chronically implanted electrodes are performed to record seizures to define the seizure onset zone. Not every patient undergoing presurgical investigations for epilepsy surgery needs to undergo invasive recordings. If there is a clear lesion on imaging such as in hippocampal sclerosis with EEG scalp recordings of seizures and interictal findings together with other non-invasive tests supporting epilepsy arising from this lesion, then epilepsy surgery can be performed without further invasive recordings, given that the lesion is remote from eloquent cortex. Using closely spaced electrodes according to the international 10-10 system, in contrast to the conventional 10-20 system of electrode placement during video EEG monitoring may improve localization of the ictal onset zone and thus obviate the need for iEEG monitoring [25]. High density scalp EG coverage may also be used for advanced EEG reviewing tools such as source localization where additional electrodes may improve localization of the irritative and seizure onset zones [26,27].

Relative indications for iEEG recordings have been defined as normal imaging, presumably extratemporal epileptogenic zone, discordant findings in non-invasive tests, proximity of the presumed epileptogenic zone to eloquent cortex and certain imaging findings and syndromes with a tendency to multiple lesions such as tuberous sclerosis or lesions that may only be partially visible and where the epileptogenic zone may involve areas surrounding the lesion as well, as may be the case in focal cortical dysplasia [20] or some developmental tumours associated with dysplasia [28]. Table 2 outlines typical clinical scenarios with and without the need for iEEG recording. Invasive EEG recording may also be needed in patients with a

lesion on MRI, if data obtained from EEG and/or semiology are discordant to the site of the lesion.

Particularly difficult to localise or lateralize seizure patterns on scalp EEG are a challenge in the work up of patients suffering from pharmacoresistant epilepsy. Such EEG patterns are often seen in frontal lobe epilepsy where in addition scalp EEG is often obscured by artefacts [29]. If non-invasive data allows to formulate a hypothesis about the epileptogenic zone, iEEG monitoring might confirm this and aid in delineating extent of resection and to proceed to successful surgery. The major advantage of all iEEG recording is the high spatial resolution compared to scalp EEG. This is due to the fact that the recording electrodes in iEEG are very close to the generator thus obtaining more precise information. Spikes in scalp EEG are detected if a considerable area of cortex is excited synchronously. Simultaneous recordings of scalp EEG and iEEG showed that an area of $10cm^2$ needs to be excited in order to be recorded by scalp EEG and discharges which were confined to an area of less than $6cm^2$, as determined by intracranial recordings, were not detected on scalp EEG [30,31]. It is important to understand that some seizures occur in deep structures of the brain or in the depth of sulci. Such seizures might not be recorded on the gyral surface as they may behave as closed current circuits and thus may only be picked up with depth recording. These issues highlight the importance of a clear hypothesis prior to implanting iEEG. In the case of subdural EEG, implantation is usually limited to one hemisphere, although some centres perform bihemispheric strip implantations. In SEEG, implantations can be made bilaterally. Regardless, a clear hypothesis of the EZ is needed to inform the implantation strategy, as otherwise the iEEG is likely to fail due to the limited

sampling volume of the iEEG electrodes, not allowing to go forward to resection, or worse, iEEG results may be misleading and inappropriate resections are performed. Another important advantage of iEEG compared to scalp EEG is that the frequency range of brain signals which can be detected by iEEG is much larger than that recorded by scalp EEG. In addition, iEEG is devoid of muscle artefacts and baseline drift due to impedance changes of the skin, and does not suffer from the signal attenuation by skull [32]. Focal high frequency activity is often observed at the seizure onset recorded by intracranial EEG and is a reliable sign of the seizure onset zone. Removal of the cortex overlying contacts with high frequency activity at seizure onset correlates with a good outcome [33]. In addition, removal of cortex underlying electrodes which display high frequency oscillations (HFOs) has been shown to be an independent predictor for a good outcome after epilepsy surgery [34–36].

Another reason to perform iEEG recording is the need for cortical mapping of eloquent areas via direct CSM prior to epilepsy surgery [37,38]. Many eloquent areas are contained in the frontal, parietal or parieto-temporal lobes, thus epilepsy surgery in proximity to eloquent cortex in those areas can only be performed after these eloquent areas have been defined to allow for safe resection margins. Non-invasive tools such as motor and language fMRI, diffusion MRI and tractography are all techniques which allow mapping of eloquent cortex [39], but direct CSM still remains the gold standard. In particular, fMRI highlights networks involved in a task, allowing lateralisation of language for example, but does not allow inferences on the result of resection of a cortical area and how essential this area may be for function. Thus it does not allow decisions on safe resection margins for epilepsy surgery by itself, particularly not when mapping complex functions. When localisation of complex

functions such as language is needed, most centres still rely on CSM, although this remains a matter of debate [40].

3 Methods used to record iEEG

3.1 Subdural electrodes

Subdural electrodes are 4-5 mm disc shaped contacts usually made of nickel-chromium or platinum-iridium composite, a material which is nonmagnetic and thus compatible with MRI scanning after local safety measures have been carried out. The electrodes are arranged in several rows on a piece of silicone, typically with an inter-electrode distance of 1 cm, although higher density grids with typically 5 mm centre to centre inter-electrode distance are also available. Subdural electrodes are usually inserted through a large craniotomy. Often depth electrodes are inserted in addition to the subdural grids or strips through small holes which can be made in the silicone bedding. This allows sampling of deep brain structures in addition to gaining a more three dimensional representation of the seizure onset and early propagation paths. Compared to SEEG, a volume is sampled with a greater density of cortical electrode contact points. This may theoretically allow for smaller resection volumes compared to SEEG, although this has never been researched, and will be difficult to ascertain in the absence of a carefully designed prospective trial. Relatively less information is known of more remote propagation pathways when compared to SEEG.

The advantage of subdural electrodes is that it can cover large continuous cortical areas, sampling from the crown of the gyrus, thus allowing to trace seizure spread across the cortex, and to delineate extent of resection based on the distribution of

onset and the rapidly engaging network on the cortical surface. Subdural grids are advantageous when eloquent cortex is close to the presumed EZ to allow for extra-operative direct CSM, as well as evoked potentials to delineate central sulcus for example. In addition compared to depth electrodes, subdural grids and strip electrodes usually cover cortical surfaces and do not have contact with white matter. Areas which are not directly exposed after a craniotomy, such as the basal frontal area, the basal temporal area and the mesial frontal cortices are more difficult to implant with subdural grid electrodes, and may carry a higher risk of bleeding due to the presence of draining veins, which may be difficult to directly visualise intraoperatively. However, with careful inspection the surgeon can slide strips in place, allowing for excellent sampling from areas like the SMA, basal temporal regions and temporo-occipital junction, orbitofrontal cortex. Unlike with SEEG, subdural grids are difficult to implant bilaterally, thus largely restricting use to unilateral implantations, although some centres use them to sample bilaterally with a multiple burr hole technique.

Figure 1 shows a case of a histologically proven left inferior frontal focal cortical dysplasia Type IIB, which was visible on MR imaging in the left posterior middle and inferior frontal gyri, with an area of cortical thickening and FLAIR signal hyperintensity extending towards the ventricle. Language fMRI using word fluency and verb generation paradigms revealed left> right language dominance, with activation clusters surrounding and inferior and anterior to the lesion. Careful mapping of the ictal onset zone and language and motor mapping using a combined grid and depth electrode approach allowed for separation of the anterior language area and the seizure onset zone. The resection led to seizure freedom. The figure demonstrates how this approach allows for definition of resection margins, with

meticulous language mapping by electrical CSM showing reorganisation of Broca's area into the posterior inferior aspect of the frontal operculum (contact GA56), where extraoperative CSM revealed speech arrest in the absence of negative or positive mouth motor findings. This location is distinct from areas highlighted by fMRI language mapping, revealing the limitations of fMRI for precise language localisation. The resection was guided by ictal onset mapping taking into account interictal spiking, and limited to a region in middle and inferior frontal gyri, just anterior to precentral sulcus. Absence of language function in the resection area was verified using cortical stimulation intraoperatively. The patient did not suffer any speech difficulties after resection, and has remained seizure free for 4 years. Figure 2 allows for comparison of this technique to the results of an exploration of the right frontal lobe using SEEG. In this patient the pathological substrate was MRI negative cortical dysplasia; the EZ was felt to be more anterior in the frontal lobe based on semiology, scalp EEG and non-invasive functional imaging data.

A recent meta-analysis reviewed complication rates and types of complications in patients undergoing subdural grid implantation for seizure mapping [41]. The most common complication which was reported was intracranial haemorrhage with a mean rate of 4% closely followed by other complications such as neurologic infections, superficial infections and elevated intracranial pressure. They also found that an increased number of electrodes (>67 electrodes) was independently associated with complications.

Recent data from the prospective Swedish National Epilepsy Surgery Register examining complication rates of patients undergoing subdural strips or grids, intracerebral depth electrodes, foramen ovale electrodes or epidural electrodes reported similar rates of haematomas, whereas infection rates were much lower. The

authors hypothesized that this is due to shorter surgical times due to the practice of implanting fewer electrodes when compared to other series. In addition patients who had valproate in their treatment regimen had higher odds to suffer from haematoma during invasive monitoring when compared to patients who were not treated with valproate [42]. Large numbers of electrodes and bilateral implantations - if performed - also raise the concern regarding risk of elevated intracranial pressure.

3.2 Stereoelectroencephalography (SEEG)

Stereoelectroencephalography uses depth electrodes which typically have 4-18 contacts arranged 2-10 mm apart. The electrodes are either semi-rigid or flexible with a rigid stylet which can be removed upon insertion. The implantation strategy for the multiple depth electrodes used in the SEEG approach is different from the above described depth electrode sampling in addition to grids. The few depth electrodes inserted through the grid into the cortex and beyond in a subdural EEG study are meant to supplement the information by obtaining a more 3 dimensional volumetric view of the seizure onset zone and not to miss deep onsets for example from dysplasias at the bottom of a sulcus or deep within a dysplasia. In SEEG the depth electrodes are the only electrodes used and supply all information, giving typically less volumetric information of the seizure onset, as the next depth electrode with multiple contacts will be typically several cm away. However, seizure propagation along known anatomico-functional connections can be much better studied, as typically a hypothesis of the seizure onset zones is supplemented by exploring the most likely spread pathways. This strategy estimates the EZ according to the “anatomical-electrical-clinical correlation”, as conceptualised by Bancaud and Talairach. The method relies on interpreting a seizure network by looking at both

semiology and intracranial SEEG recordings [14]. Seizures which are stimulated by CSM are also taken into account if certain criteria are met and are used to define the epileptogenic network [43].

Compared to subdural grid studies, more detailed imaging of the cerebral vasculature is required to make the procedure safe, and this includes digital subtraction angiography in most centres. The planning of individual electrode trajectories requires a multidisciplinary approach keeping in mind the targets for best sampling of the anatomo-clinical hypothesis brought forward ahead of the study.

After stereotactic insertion of the electrodes, the position of the electrodes needs to be confirmed via CT superimposed on MRI or in MRI compatible electrodes with MRI only. SEEG recordings were traditionally performed in France, Italy and Canada, whereas in the USA mainly subdural grids, strips or a mix with depth electrodes were used as iEEG tools. Given these preferences and geographic separation of practices in iEEG, it is not surprising that the concept and approach of interpreting SEEG studies has been different (see above), although most recently many centres using grids mainly now have gained experience with both techniques.

The main advantage of SEEG over subdural grid recording is that there is no need for a large craniotomy which adds to the patient´s morbidity. The SEEG electrodes can be inserted via burr holes and do not require a second operation for removal of the electrode as is the case in subdural EEG. In subdural EEG recordings, the removal of the electrodes is sometimes combined with the resection of the presumed epileptogenic zone. This approach necessitates quick interpretation of the iEEG data, which is sometimes difficult in epilepsies presenting with frequent seizures and

different seizure types. SEEG approaches are difficult if there is a need for detailed extraoperative CSM. Due to the nature of the techniques, there will be only limited often non-contiguous contacts with gray matter; many electrode contacts will have only contact with white matter. This in turn can be used to track corticospinal tracts via white matter stimulation.

A particular strength of SEEG is the ability to sample from deep cortex, such as insular cortex, cingulate gyrus, medial temporal structures or the medial frontal or parietal walls. The insula in particular is not possible to access safely with grids or strips, and most experience has been gained using a traditional SEEG approach, although some centres also use a mix of depth electrodes to cover the insular depth and strips to cover the perisylvian cortex following craniotomy [44]. On the other hand, certain locations such as basal temporal regions are more difficult to sample extensively using SEEG compared to strips or subdural grids.

Reoperations requiring implantations are safer with SEEG methodology, and SEEG is clearly favoured if bilateral explorations are necessary.

It is noted that a large number of EEG electrode contacts are not in contact with cortex, but come to lie in white matter. Considering the average number of SEEG electrodes implanted [45], there may be only 30-40 electrode contacts in cortex. This is significantly less than the typical sampling using grids. At the end of the study, SEEG electrodes are removed, and resections are performed typically several months later.

Figure 2 shows a patient with MRI negative histology proven focal cortical dysplasia Type IIB. Scalp EEG findings, semiology, PET and ictal SPECT (shown co-registered into the T1 MRI-based 3 dimensional representation in Figure 2)

supported a hypothesis of a mid to anterior medial or orbitofrontal focal epilepsy, and an SEEG approach was chosen to delineate electroclinical correlation with EEG and clinical seizure onset. The demarcation line to the SMA was successfully drawn; SMA was functionally confirmed in the single contact pairs in this region, although precise mapping of extent of the SMA particularly anteriorly was not possible due to the more limited coverage. Based on ictal onset patterns, SMA was spared and resection limits laterally and anteriorly had to be chosen using anatomical criteria due to the sparser sampling. This patient has remained seizure free for one year to date.

A recent meta-analysis summarizing 30 studies about the safety of SEEG, concluded that complications occurred with a pooled prevalence of 1.3%. This is a much lower overall complication rate when compared to subdural EEG. The main complications in SEEG were haemorrhages (pooled prevalence 1.0%) and infections (pooled prevalence 0.8%) [46].

4 Direct cortical stimulation

IEEG electrodes can both record cortical activity, but can also be used to stimulate the cortex underlying the electrode in subdural EEG recording or surrounding the electrode in depth electrode recording or SEEG. Direct CSM dates back to the pioneering work of Penfield and Jasper who elicited clinical signs via intraoperative cortical electrical stimulation [47]. In iEEG CSM is used to map eloquent cortex [38,48]. The advantage of extraoperative compared to intraoperative, CSM is that there are less time constraints outside the operating theatre. CSM is used to map language, motor and sensory function. Particularly language function can be difficult

to map and extraoperative CSM is the preferred choice, although intraoperative CSM can complement extraoperative CSM in difficult cases [49]. Cortical stimulation for mapping is typically performed using up to 5s trains of 50-Hz unipolar bi-phasic square wave pulses of an AC-current with a pulse width of 500µs [48]. Either two adjacent electrodes are stimulated in bipolar stimulation mode or an electrode remote from eloquent cortex is referenced to an electrode overlying presumed eloquent cortex in so called ‘monopolar stimulation mode’. Both methods yield similar results with regards to mapping of eloquent function, but monopolar stimulation is associated with less afterdischarges which can evolve into stimulation induced seizures [48]. CSM overall, although considered the best standard for functional mapping, is not standardised, and a large variability exists across centers. Primary motor cortex and anterior and posterior language areas are most widely investigated; other cortical regions are much less studied, and little is known which active tasks should be performed for various brain regions to yield best insight in the underlying function, allowing for deficit prediction.

Stimulation induced seizures can have habitual or non-habitual semiology. Seizures with a non-habitual semiology are an unwanted side-effect of CSM [50].

Habitual seizures induced via CSM, in contrast, have been used to define the epileptogenic network. The value of such stimulation induced seizures in defining the epileptogenic zone and network has been highlighted some investigators who traditionally have performed SEEG investigations where this technique is routinely used for the work-up of patients undergoing invasive recordings [43,51], although the evidence supporting such practice is sparse.

5 Future directions of iEEG

Although iEEG recordings have been utilised for a long time and the technical aspects have been improved over the years, there are still areas that warrant further improvement. The goal of epilepsy surgery is to achieve seizure freedom with minimal surgical morbidity. This can only be achieved by optimising all aspects of the process: 1. The candidate selection for intracranial EEG, with a clear hypothesis of the presumed EZ and choice of the best approach to the investigation based on the criteria listed in table 1; 2. Optimized implementation of the invasive investigation of choice with maximum safety and precision; 3. Analysis of data obtained including advanced neurophysiological analysis; 4. Optimised mapping of eloquent cortex and lastly 5. Clear communication with the Neurosurgeon regarding margins of resection.

Innovation and novel health technologies have influenced points 1-3. Computational power has fuelled more sophisticated techniques such as multimodal image integration which allows more detailed planning of the implantation strategy and particularly more precise placement of depth electrodes [52,53]. Multimodal image integration allows reconstruction of vessel, gyral and sulcal anatomy and thus aids to improve the safety of the implantation procedure. Robot-assisted stereotactic placement of depth electrodes is another means of implementing safety measures in the implantation process [54]. Taken together, this means that exploration of more complex epilepsies has become possible, requiring more extensive sampling and implantation of riskier structures such as insular cortex.

Whilst safety and feasibility of various iEEG sampling procedures and strategies have been widely demonstrated, and their strengths and weaknesses have become clearer, the efficacy to delineate the EZ and cure epilepsy has been less systematically investigated, and a prospective study has not been conducted

comparing different approaches. It is currently not understood how various sampling strategies affect size of the resection and seizure and cognitive outcome. Both may be related to each other in a complex manner; larger resections may increase odds of seizure freedom, at the expense of poorer cognitive outcomes, depending on premorbid functioning, anatomical location of the resection, presence, extent and nature of a lesion and its pathological substrate. Such data should ideally be acquired as part of a prospective trial, although it will be very difficult to account for the significant biological variability. In the meantime, thoughtful multicentre retrospective analysis of such data could perhaps start to shed some light on those issues.

Not only does the implantation of electrodes feature new methods, but analysis of iEEG data has been expanded to include more objective measures of EEG review when compared to standard visual EEG analysis. Tools like the epileptogenicity index and other semi-quantitative iEEG analysis tools have been explored [55–58]. Even if such tools are not able to replace traditional EEG review, these tools help to formulate a hypothesis about the EZ. Similarly, high frequency oscillations (HFOs) have been found to help in defining the EZ and thus may in the future be used routinely alongside traditional EEG review [34,36]. Another exciting field of research is automated seizure detection. Compared to scalp EEG, iEEG is less prone to artefacts and thus seizure detection algorithms are likely to be more successful. Several studies have proposed different seizure detections systems in iEEG. Some of these systems could be used in a therapeutic approach via close loop systems, which detect seizures and then stimulate the cortex to prevent seizure spread [59–61]. The type of implantation most certainly influences our appreciation of the

localised onset of seizures and their spread behaviour. SEEG may be biased towards distant spread, due to its ability to sample from widely dispersed regions. On the other end of spectrum, sampling via micro- electrodes increasingly allows to gain insights at the neuronal level. Improved understanding of the epileptic networks may hold promise to better therapeutic surgical strategies to cure focal epilepsy. This will in some selected cases include very focal interventions via laser lesioning for example.

6 Conclusion

With the beginnings of iEEG dating back to the pioneering work of Penfield and Jasper, iEEG has now evolved into a tool which is used in many epilepsy centres all over the world. Subdural grids and strips with depth electrodes are used as are SEEG electrodes. The advantages and disadvantages of both modalities has prompted many epilepsy centres to use both approaches in an individualized patient approach. Often the advantages of both techniques can be combined with the combination of subdural strips and depth electrodes through burr holes employing a hybrid (HEEG) of fluoroscopy and stereotaxy [62]. Particularly the low morbidity of the SEEG procedure has led to its dissemination outside of countries who have traditionally chosen this approach.

LEGENDS OF TABLES/FIGURES:

Table 1: *Definition of different zones in Epilepsy*

Table 2: *Clinical constellations in the presurgical work-up for pharmacoresistant seizures and the need for iEEG recordings.*

Fig.1: *Case study with subdural and depth electrodes:*

A 27 year old, left handed man with seizure onset at 14 years, presented with pharmacoresistant multiple daily seizures with vocalisations, automatisms and right arm posturing.

His MRI showed a lesion in the left inferior frontal gyrus suggestive of focal cortical dysplasia. (A) Coronal FLAIR MRI images show a hyperintensity in the crown of the left inferior frontal gyrus extending towards the ventricle. (B) 3 –D MRI reconstruction image with the lesion (red), veins (blue), fMRI of verb fluency and verb generation (yellow and orange) and lip/hand motor activation (green) paradigms. Non-invasive EEG monitoring recorded multiple seizures which were in keeping with seizures arising from the left dorsolateral aspect of the frontal lobe. Due to the proximity of eloquent cortex and in order to delineate the area of cortex that needs to be resected, an invasive study with subdural electrodes and depth electrodes was planned. (C) 3-D MRI reconstruction image showing the lesion (red) and the grid electrodes (yellow dots) and site of depth electrode insertion (orange and blue dots). The electrodes involved in the seizure onset zone are within the red circle. (D) Intraoperative photograph showing the electrodes embedded in silicone (electrode grid) overlying frontal lobe cortex. The white arrow highlights Broca's area (electrode GA56) based on extraoperative electrical stimulation mapping, and central sulcus. (E) Habitual seizure recorded with intracranial electrodes (F) Visualization of the Epileptogenicity index (EI; [63]). The normalised EI ranges from 0 to1 (1 indicating highest epileptogenicity), colour coded according to the colour coding legend. Note: not all channels are displayed. (G and H) Intraoperative photographs: (G) craniotomy with the cortex exposed. (H) Cortex after resection of the presumed epileptogenic zone. The dotted line outlines the central sulcus and the asterisk marks the hand knob, the primary motor hand representation (D, G and H).

Fig.2: *Streoelectroencephalgraphy (SEEG) case study:*

A 19 year old right handed man with seizure onset at age 5 presented with pharmacoresistant epilepsy with daily seizures with hypermotor phenomena including whole body turning, screaming and rhythmic upper and lower limb movements. His MRI was non-lesional. Scalp video-EEG telemetry recorded multiple habitual seizures with a frontocentral seizure pattern, but failed to lateralize the seizure onset. (A,B,D) Ictal SPECT highlighted the right frontal lobe as a focus of hyperperfusion (crosshairs reveal the maximum hyperperfusion determined by ISAS, Interictal Ictal SPECT analysed by Statstical Parametric Mapping; [64]; the same area is marked in rose colour in C and F). Interictal PET showed hypometabolism in the right antero-medial frontal lobe (area highlighted in dark purple in C and F). He underwent SEEG implantation targeting right orbitofrontal and mesial frontal regions and cingulum. MRI (E) and 3-D MRI reconstruction images (C,F) visualizing the SEEG implantation and the integrated SPECT and PET findings. The seizure onset was focal and mapped to electrode contacts MF 3 and 4 (white arrow). (E) coronal T1 MRI image showing the electrode contacts involved at seizure onset. The area highlighted in red represents the seizure onset. (G) Habitual seizure as recorded by intracranial EEG. (H and I) 3-D MRI reconstruction showing the electrode positions and the area which was resected (highlighted in green). The anterior and lateral borders of resection were informed by interpolation of most involved EEG electrodes and anatomical borders. He has remained seizure free for over 1 year and pathology showed focal cortical dysplasia Type IIB.

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Zone	*Definition*	Tools to define the area
Epileptogenic zone (EZ)	*Area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures* [1,2]	The area can only be approximated post hoc after successful epilepsy surgery
Seizure onset zone (SOZ)	*Cortical area that initiates clinical seizures* [1,2]	• EEG (non-invasive, invasive) • Ictal SPECT
Irritative zone	*Cortical area which generates interictal spikes* [1,2]	• EEG (non-invasive, invasive) • Magnetoencephalography (MEG)
Functional deficit zone	*Area of cortex that has no normal function interictally* [1,2]	• Neurologic examination • Neuropsychiatry • PET • Interictal SPECT • EEG (slowing)
Epileptogenic lesion	*Macroscopic lesion causing the seizures:* • *epileptogenic lesion* • *secondary hyperexcitability of adjacent cortex* [1,2]	MRI
Symptomatogenic zone	*Cortical area which produces the initial ictal symptoms or signs, when activated* [1,2]	Analysis of seizure semiology and correlation with functional neuroanatomy
Eloquent cortex (EC)	*Area of cortex that if removed will result in loss of motor, sensory or language function* [1,2]	• fMRI • Neuropsychiatry

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Clinical scenario (Lesion/EEG/semiology)	**Additional information:** **Neuropsychometry **; functional imaging such as PET, ictal SPECT, EEG fMRI, fMRI, ESI*****	**Location of the presumed epileptogenic zone**	**Invasive EEG**	**Subdural grid electrodes**	**Added depth electrodes**	**SEEG**
A1 Clear Lesion **EEG and semiology concordant**	Rarely indicated to perform all (except Neuropsychometry). If performed and all or mostly concordant	Away from eloquent cortex	Invasive recording almost never needed	N/A	N/A	N/A
		Away from eloquent cortex, deep structures involved	Invasive recording often not needed	N/A	N/A	++
		Close to eloquent cortex, deep structures not involved	May require invasive recordings	++	-	-
		Close to eloquent cortex, deep structures involved	May require invasive recordings	++	++	+
	If performed, and most information is discordant	Away from eloquent cortex, deep structures not involved	Likely requires invasive recordings	++	+	++
		Away from eloquent cortex, deep structures involved	Likely requires invasive recordings	+	+	++
		Close to eloquent cortex, deep structures not involved	Will require invasive recordings	++	-	-
		Close to eloquent cortex, deep structures involved	Will require invasive recordings	++	++	+
A2 Clear Lesion **EEG and/or semiology discordant**	All or mostly concordant	Away from eloquent cortex, deep structures not involved	May require invasive recordings	+	+	++
		Away from eloquent cortex, deep structures involved	May require invasive recordings	+	+	++

		Close to eloquent cortex, deep structures not involved	Likely requires invasive recordings	++	-	+
		Close to eloquent cortex, deep structures involved	Likely requires invasive recordings	++	++	+
	Mostly discordant	Away from eloquent cortex, deep structures not involved	Invasive recordings almost always needed	+	+	++
		Away from eloquent cortex, deep structures involved	Invasive recordings almost always needed	+	+	++
		Close to eloquent cortex, deep structures not involved	Will require invasive recordings	++	-	+
		Close to eloquent cortex, deep structures involved	Will require invasive recordings	++	++	+
B1 No Lesion **EEG and semiology concordant**	All or mostly concordant	Away from eloquent cortex, deep structures not involved	Invasive recordings almost always needed	+	-	++
		Away from eloquent cortex, deep structures involved	Invasive recordings almost always needed	+	+	++
		Close to eloquent cortex,	Invasive recordings almost always	++	-	(+)

		deep structures not involved	needed			
		Close to eloquent cortex, deep structures involved	Invasive recordings almost always needed	++	++	(+)
	Mostly discordant	Away from eloquent cortex, deep structures not involved	Invasive recordings may still be appropriate and will be needed	+	-	++
		Away from eloquent cortex, deep structures involved	Invasive recordings may still be appropriate and will be needed	-	-	++
		Close to eloquent cortex, deep structures not involved	Invasive recordings may still be appropriate and will be needed	++	-	++
		Close to eloquent cortex, deep structures involved	Invasive recordings may still be appropriate and will be needed	++	++	++
B2 No Lesion EEG and semiology discordant	All or mostly concordant	Away from eloquent cortex, deep structures not involved	Invasive recordings may still be appropriate and will be needed	-	-	++
		Away from eloquent cortex, deep structures involved	Invasive recordings may still be appropriate and will be needed	-	-	++
		Close to eloquent cortex, deep structures not involved	Invasive recordings may still be appropriate and will be needed	+	-	++

		Close to eloquent cortex, deep structures involved	Invasive recordings may still be appropriate and will be needed	+	++	++
	Mostly discordant	Away or close to eloquent cortex, with or without involvement of deep structures	Patients likely are not candidates for epilepsy surgery	N/A	N/A	N/A
C1 Two lesions/ subtle or large lesions **EEG and semiology concordant**	All or mostly concordant with a single likely epileptogenic lesion	Away from eloquent cortex, deep structures not involved	Invasive recordings almost always needed	+ (subtle small lesions)	-	++ (large lesions, two lesions)
		Away from eloquent cortex, deep structures involved	Invasive recordings almost always needed	+	+	++
		Close to eloquent cortex, deep structures not involved	Invasive recordings almost always needed	++	-	(+)
		Close to eloquent cortex, deep structures involved	Invasive recordings almost always needed	++	++	(+)
	Mostly discordant, concern of multiple epileptogenic lesions remote from each other or inability to resect entire lesion	Close to or away from eloquent cortex, with or without involvement of deep structures	Patient may not be a surgical candidate. In selected cases, invasive recordings may still be worth while pursuing, according to strategy algorithm above			
C2 Two lesions/	All or many data	Often difficult to	Invasive	N/A	N/A	N/A

subtle or large lesions **EEG and/or semiology discordant**	points discordant or uninformative	define, multifocal	recordings are likely not indicated due to poor hypothesis about presumed epileptogenic zone			
D Failed invasive recordings with subdural grid electrodes	All or mostly concordant,	Any location	Invasive recordings almost always needed	-	-	++
	Mostly discordant	Any location	Likely not a surgical candidate	-	-	-
E Multilobar epilepsy or presumed bilateral epileptogenic zones	All or mostly concordant, favouring a contiguous epileptogenic zone which could be resectable	Any location	Invasive recordings may occasionally still be appropriate and will be needed. May be leading to a palliative procedure.	-	-	++

N/A: not applicable; ** needed in all cases; *** not always needed, ++: likely method of choice; + can be used as additional/alternative method; (+) possibly used as an alternative method; - likely not used method

Definitions for purpose of this table:

Deep structures: insula, mesial temporal lobes, cingulate gyrus, interhemispheric regions, posterior orbitofrontal gyrus and depth of a sulcus. Please note: if deep structures are only the medial temporal structures, insertion of depth electrodes is technically feasible and may be a good choice.

Eloquent cortex: anatomically delineated cortex considered indispensable for a function (for example motor cortex, primary visual cortex, anterior or posterior language areas) , resection of which leads to significant largely irreversible impairment or potentially causing a significant deficit in short to median term with potential to good recovery (SSMA, basal temporal language cortex)

Figure 1

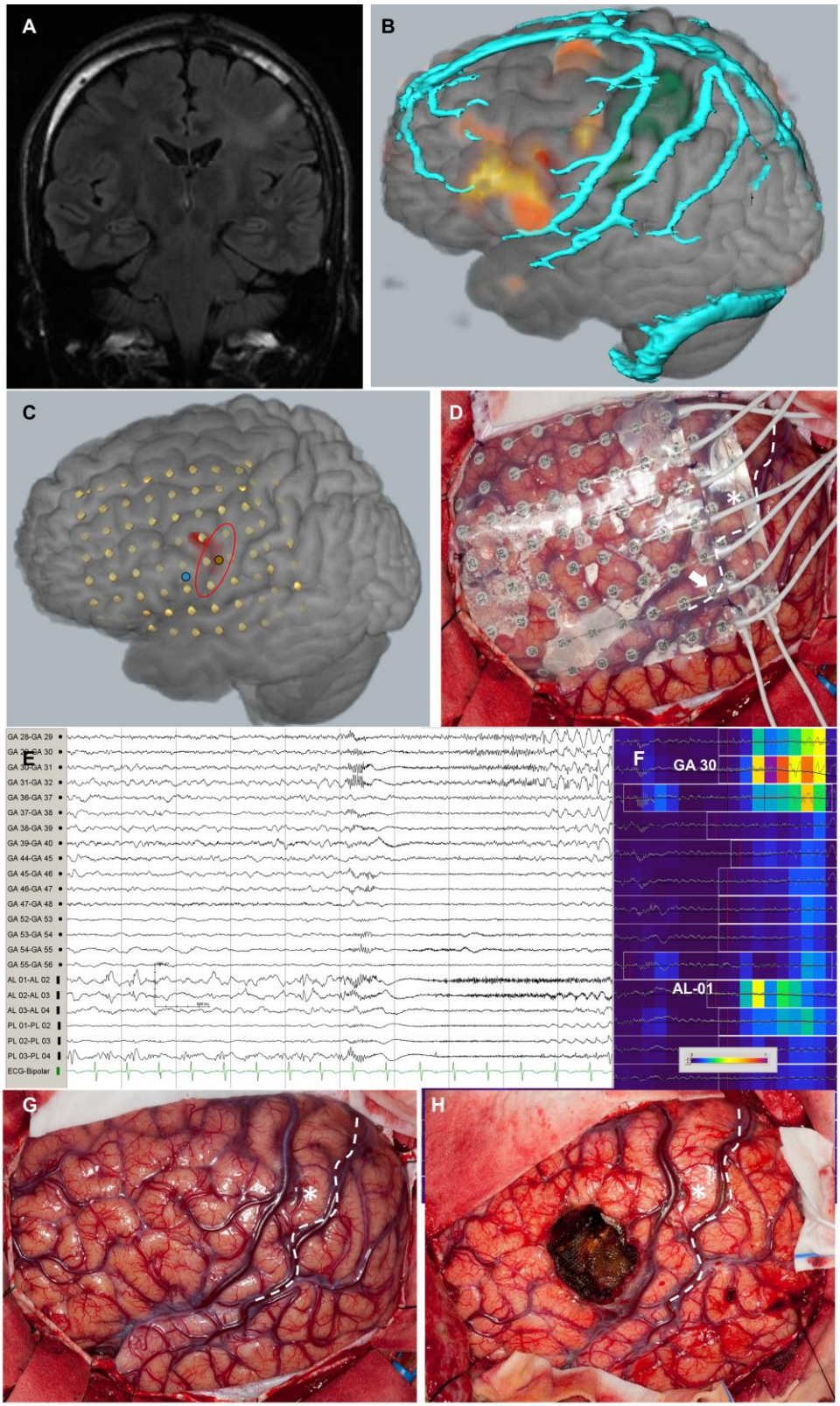

Figure 2