Towards precision medicine in epilepsy surgery

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Abstract: Up to a third of all patients with epilepsy are refractory to medical therapy even in the context of the introduction of new antiepileptic drugs (AEDs) with considerable advantages in safety and tolerability over the last two decades. It has been widely accepted that epilepsy surgery is a highly effective therapeutic option in a selected subset of patients with refractory focal seizure. There is no doubt that accurate localization of the epileptogenic zone (EZ) is crucial to the success of resection surgery for intractable epilepsy. The pre-surgical evaluation requires a multimodality approach wherein each modality provides unique and complimentary information. Accurate localization of EZ still remains challenging, especially in patients with normal features on MRI. Whereas substantial progress has been made in the methods of pre-surgical assessment in recent years, which widened the applicability of surgical treatment for children and adults with refractory seizure. Advances in neuroimaging including voxel-based morphometric MRI analysis, multimodality techniques and computer-aided subtraction ictal SPECT co-registered to MRI have improved our ability to identify subtle structural and metabolic lesions causing focal seizure. Considerable observations from animal model with epilepsy and pre-surgical patients have consistently found a strong correlation between high frequency oscillations (HFOs) and epileptogenic brain tissue that suggest HFOs could be a potential biomarker of EZ. Since SEEG emphasizes the importance to study the spatiotemporal dynamics of seizure discharges, accounting for the dynamic, multidirectional spatiotemporal organization of the ictal discharges, it has greatly deep our understanding of the anatomo-electro-clinical profile of seizure. In this review, we focus on some state-of-the-art pre-surgical investigations that contribute to the precision medicine. Furthermore, advances also provide opportunity to achieve the minimal side effects and maximal benefit individually, which meets the need for the current concept of precision medicine in epilepsy surgery.

Keywords: Refractory epilepsy; epilepsy surgery; pre-surgical evaluation; precision medicine

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Introduction

Epilepsy is the second most common neurological disease worldwide, affecting people of all ages. Despite it has been recognized since antiquity, we continue to struggle to understand and treat this kind of paroxysmal brain disorder. In principle, the management of epilepsy requires comprehensive care to address the efficacy, side effects and quality of life issues. The mainstay of epilepsy management is drug therapy with antiepileptic drugs (AEDs). There are almost two-thirds of patients responding to mono-therapy or rational poly-therapy and achieve complete seizure control without major side effects. Whereas, up to a third of all patients with epilepsy are still refractory to medical therapy even in the context of the introduction of new drugs with considerable advantages in safety and tolerability over the last two decades (1,2). Currently, intensity studies are focused on improving the treatment of patients with drug-resistant or pharmaco-resistant epilepsy, which is associated with higher rates of physical and psychiatric comorbidities, cognitive decline and sudden death (3,4).

It has been widely accepted that epilepsy surgery is a highly effective therapeutic option in a selected subset of patients with refractory focal seizure (5,6). For instance, grade 1 evidences from prospective randomized controlled trials (RCT) showed the superiority of epilepsy surgery to pharmacotherapy for patients with medial temporal lobe epilepsy (MTLE) not responding to treatment with two AEDs (7,8). In addition to seizure, cognition, behavior, and quality of life also improved substantially after epilepsy surgery (9,10). Epilepsy surgery roots in the hypothesis of epileptogenic zone (EZ), which is typically defined as the area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for complete abolition of seizures (11,12). The risk and benefit assessment prior to epilepsy surgery needs to be considered carefully. The process of the pre-surgical evaluation requires a multimodality approach wherein each modality provides unique and complimentary information, consisting of clinical history, detailed analysis of semiology, long-term video-EEG recording, inter-ictal and ictal EEG analysis, neuroimaging, and neuropsychological assessment (13). Surgical resection of the EZ is the preferred procedure including antero-medial temporal lobectomy, tailed neocortical resection, lesional resection, and hemispherectomy. Nevertheless, disconnection (corpus callosotomy, multiple subpial transections) and neuro-modification procedures (vagal nerve stimulation, responsive neuro-stimulation, and transcranial stimulation) are most applicable to patients who are currently not candidates for resection epilepsy surgery, because their seizures arise from eloquent cortex, are multifocal/generalized or EZ cannot be identified with available approaches (14).

The influence of epilepsy surgical outcome is multifactorial, depending on epilepsy type, underlying pathology, and accurate localization of EZ by various clinical, neuroimaging, and neurophysiological investigations (15). The purposes of the pre-surgical evaluation are twofold: accurate delineation of the extent of the EZ and precise description about the relationship of EZ with eloquent cortex for complete and safe resection. Stepwise pre-surgical procedure starts from the basic and non-invasive investigations and progressing to more complicated and invasive approaches. However, since no single current available method can identify EZ reliably and each modality has its own limitation, comprehensive investigations had to be needed to assess the different dimensions of the EZ.

Admittedly, accurate localization of EZ still remains challenging, especially in patients with normal features on MRI (16), whereas substantial progress has been made in the methods of pre-surgical assessment in recent years, which widened the applicability of surgical treatment for children and adults with refractory seizure (17). Furthermore, advances also provide opportunity to achieve the minimal side effects and maximal benefit individually, which meets the need for the current concept of precision medicine in epilepsy surgery. In this review, we focus on some state-of-the-art pre-surgical investigations that contribute to the precision medicine.

Advances in neuroimaging have improved our ability to identify lesions causing focal seizure

Identification of structural lesion is one of the best prognostic factors for post-operative seizure freedom. MRI is an essential method for identifying an epileptogenic lesions underlying focal epilepsy (18). The sensitivity of MRI for detecting a structural abnormality is varied, relying on the pathological substrates, applied techniques, and the experience of the interpreting physician. Some types of epileptogenic lesion such as tumors, vascular malformations, infarcts, or post-traumatic defects are easily to be detected. Meanwhile, advances in MRI have improved our ability to identify subtle structural lesions causing focal seizure (18). For example, thin sections perpendicular to the longitudinal

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axis of the hippocampus are indispensable for detailed evaluation of hippocampal sclerosis, and three-dimensional (3D) MRI with voxels smaller than 1 mm is needed in order to detect subtle structural brain abnormalities. However, there are still epileptic lesions escaping visual detection even with specific, high-resolution imaging techniques, most commonly in patients with focal cortical dysplasia (FCD) (19,20).

FCD are intrinsically epileptogenic lesions frequently causing refractory seizure both in children and adults patients (21). FCD is histologically well defined by the presence of dysmorphic neurons in FCD IIa and additional balloon cells in FCD IIb (22,23). On MRI, FCDII are often characterized by a combination of increased cortical thickness, increased Flair signal within the dysplastic cortex and blurring of the gray and white matter junction. Detection of these lesions, especially during pre-surgical evaluation, is crucial as it significantly improves the chance of becoming seizure-free postoperatively. However, challenge is that FCD might be overlooked by conventional visual inspection because the changes on MRI are so subtle and the lesions may be only a few millimeters in size (18,20). Post-processing methods of quantitative structural MRI analysis including voxel-based morphometry (VBM), cortical thickness mapping, and structural covariance analysis have the potential to identify subtle lesions undetected in previously MRI-negative patients (9,24). Morphometric MRI analysis is a voxel-based method based on algorithms of the statistical parametric mapping (SPM) software (http://www.fil.ion.ucl.ac.uk/spm). The distribution of gray and white matter is analyzed on a voxel-wise basis and compared with a normal database of healthy subjects. VBM highlights brain regions with blurring of the grey—white matter junction and abnormal extension of grey matter into white matter (i.e., abnormal deep sulci) that are the typical MRI features of FCD (25). It has been shown that VBM method allows a more sensitive localization of subtle epileptic lesion when compared with conventional analysis (26).

On the other hand, metabolic image is able to provide different information of brain activities. Functional neuroimaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), have proved their usefulness in defining the EZ. Multiple studies have demonstrated metabolic changes mostly in areas tightly coupled with the region generating seizure which are concordant with intracranial EEG findings (27). Areas of functional deficit related to EZ on inter-ictal ^{18}F-fluorodeoxyglucose (FDG)-PET are characterized by reduced inter-ictal metabolism. FDG-PET can reveal abnormalities that can prove otherwise difficulty to be detected by structural image, and lead to successful surgical intervention. Nevertheless, considering that PET is an imaging technique of comparatively low spatial resolution, the application of FDG-PET/MRI co-registration can enhance the detection, improving the spatial resolution (28,29). The combination of structural and functional brain imaging has yielded complementary information for guiding clinical decision (30) (*Figure 1*).

SPECT offer the unique information about cerebral blood flow using tracers (e.g., ^{99m}Tc-labeled compounds) that freely cross the blood brain barrier. In the settings of pre-surgical evaluation, ictal SPECT that reflects the specific focal increase of perfusion at the moment of the seizure onset has been established to be superior to inter-ictal SPECT. Furthermore, to improve the sensitivity to the localization of EZ, post-processing of imaging paradigm using computer-aided subtraction of ictal SPECT co-registered to MRI (SISCOM) has been developed by comparing patient ictal scan with inter-ictal to produce subtraction image that is later co-registered to and visualized on patient's MRI (31,32). Patients with a SISCOM region of blood flow increasing concordant with the EZ are most likely to experience a significant reeducation in seizure if the focal cortical resection includes the region of blood-flow change (33). Thus, SISCOM demonstrated the robust usefulness for highlighting the EZ and better understanding the hemodynamic correlates involved in the generation and the propagation of the seizures (*Figure 2*).

Broadband EEG has proved the critical usefulness in defining the EZ

EEG has long been the key tool for the diagnosis of epilepsy and remains at the heart of the pre-surgical evaluation. Conventionally, neurophysiologists largely focused on brain activities in the Berger frequency bands (0.5–30 Hz). Epileptic cortex is characterized by inter-ictal epileptiform discharges (IEDs) that manifest as transient spike, spike and wave or sharp wave typically in this frequency bands. IEDs are thought as the hallmark of epilepsy, and play a pivotal role in the clinical diagnosis and treatment (34). However, IEDs reflecting the irritative zone do not reliably localize the extent of EZ (35,36). Over the past decades, there is significant development on EEG technique with analog

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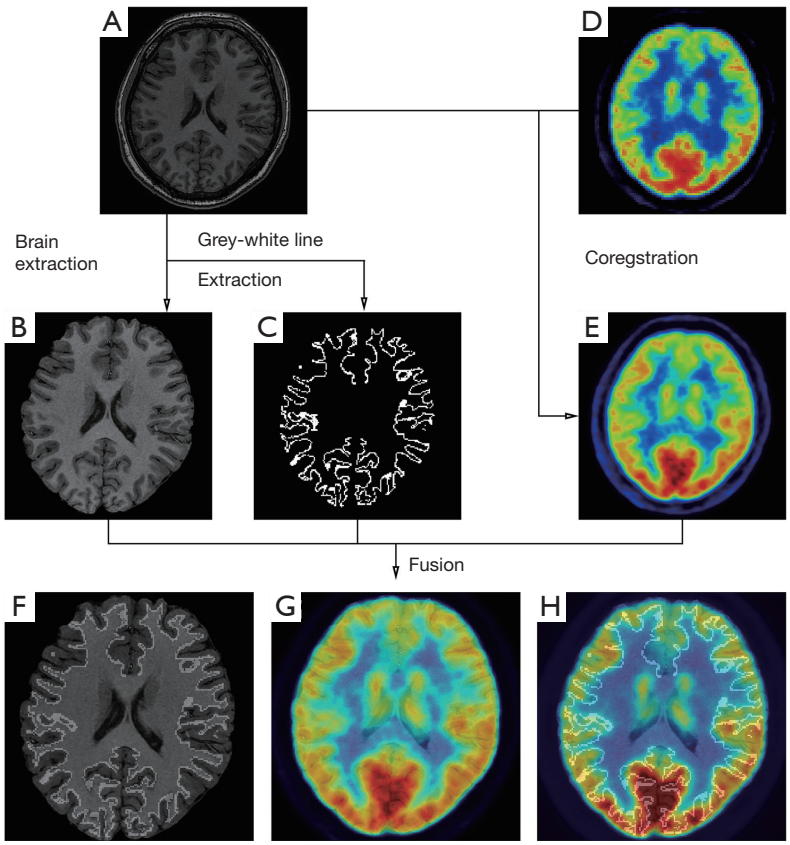

Figure 1 A 23-year-old female presented with frequency nocturnal hypermotor seizure since she was 2 years old, which was refractory to medical therapy. MRI and FDG-PET image were unremarkable. To detect possible epileptic lesion, MRI-PET coregistration was performed. Based on raw 3D T1 MRI (A), brain (B) was extracted. The junction line of gray and white matter line (C) was also extracted. Meanwhile, raw FDG-PET (E) was coregistered on raw 3DT1 MRI (D). 3D T1 MRI was overlaid with junction line of gray and white matter line (F). On the fused image with MRI and PET (G), slight hypo-metabolism was observed on right anterior cingulate cortex (arrow), but it was likely to be overlooked. However, it revealed mismatch on the same area by overlaid with additional junction line of gray and white matter line, which highlighted the abnormality on the individual gyrus. (Freesurfer and FSL software were used in data processing). Post-operation histological examination showed focal cortical dysplasia IIa. (Unpublished data).

recording methods replaced by digital EEG. To date, EEG recorded from the human brain span a wide range of spatiotemporal scales that extend well beyond traditional clinical EEG, ranging from ultra-slow to HFOs. Broadband EEG holds the promise to deep understanding of the pathophysiology of epilepsy and to develop new clinical diagnostic methods (37,38).

If EEG is recorded with an infinite time constant, slow potentials could be recorded as the direct current (DC) shifts or infraslow activities (IFA). Ictal DC shifts have been observed in the animal epilepsy experiments previously. Recent development of epilepsy surgery and progress in recording techniques facilitate to investigate DC shifts in human brain directly. It has showed that ictal DC shifts most likely occur at the beginning of seizures together with maximal intensity and rapid ictal activities by terms of intracranial recording, reflecting both epileptic neuronal discharges and passively depolarized glial activity as the result of massive depolarization of the neurons with accumulated extracellular potassium (1,39). Compared to a careful interpretation of the conventional ictal EEG recording, ictal DC shifts could provide very important information about core epileptogenicity in patients with refractory focal seizure (40).

On the other hand, wider bandwidth and higher sampling rates are now available on many clinical EEG recording

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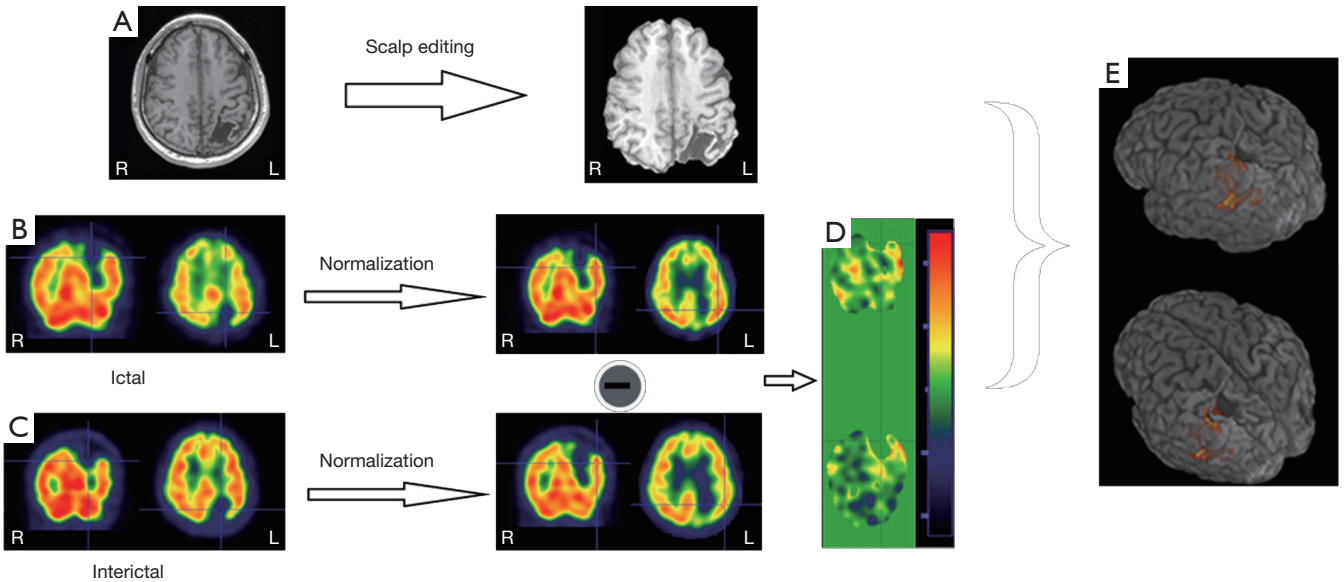

Figure 2 An 18-year-old male was evaluated epilepsy surgery for refractory seizure that began soon after brain injury at 6 years old. MRI showed large encephalomalacia mainly on left parietal lobe. To delineate the epileptogenic zone, inter-ictal, ictal SPECT and then SISCOM were conducted. Firstly, Raw 3D T1 MRI was processed with skull removal (A). Ictal and inter-ictal ^{99m}Tc-SPECT image (B,C) was normalized on normal template followed by the subtracted. Finally, the different image (D) was display on 3D MRI, showing significant hyperfusion on lateral of lesion (3 standard deviations) (E). (SPM software). (Unpublished data).

systems, facilitating the studies of HFOs. HFOs are characterized by transient, rhythmic events with evolving of amplitude and frequency ranging from 80 to 600 Hz. They are further classified in ripples (80–250 Hz) and fast ripples (FRs) (250–600 Hz). Ripples and FRs seem to have different pathophysiological mechanisms. HFOs in the 80–200 Hz (ripple) range may reflect inhibitory field potentials, which synchronize neuronal activity, thus facilitating information transfer over long distances. HFOs of 250–600 Hz, referred to as FRs, may reflect abnormal synchronous burst firing of principal neurons in areas of seizure onset. HFOs were studied more thoroughly after they were recorded with microelectrodes in epileptic rats and in patients, and this expanded when they were found with macro-electrodes with clinical significance (41-43). Initially HFOs were described mainly in TLE associated with hippocampal sclerosis in human. However, HFOs are also present in extra-temporal epilepsies associated with different types of lesions, such as tumors, FCD, and nodular heterotopias in epilepsy without an obvious lesion. It has been showed inter-ictal HFOs are increased in the EZ and that resection of HFO-generating tissue is associated with seizure-free outcomes (44). In particular, as above mentioned, non-lesional epilepsies represent a challenge for improvement of epilepsy surgery and HFOs could help map EZ in this type of epilepsy (45). Hence, inter-ictal HFOs could be reliable biomarkers of the seizure onset zone based on evidence from mounting studies, independently of the location and type of lesion (46) (*Figure 3*). Notably, studies from rodent epilepsy models find that HFOs are a potential biomarker of epileptogenesis for tracking the development of epilepsy.

There is ongoing discussion on the differentiation between physiological and epileptic HFOs since normal neuronal circuits can generate physiological HFOs (47). For example, HFOs in the ripple band recorded on medial temporal structure are observed to be involved in memory formation and reactivation of previous experiences (48). It is assumed that combined analysis of IEDs and HFOs might provide new insights into the argument (49). Wang *et al*. classified neocortical HFOs into type I when superimposed on paroxysmal fast, spike, or sharp wave, and type II when independent of epileptiform discharges (50). It demonstrated that neocortical FRs and type I ripples are specific markers of the SOZ, whereas type II ripples are not. Recently, We studied a distinct electrophysiological pattern of gamma frequency oscillations preceded IEDs (gamma-IEDs) recorded with intracranial EEG brain areas in patients with TLE (51). It revealed that gamma-IEDs were

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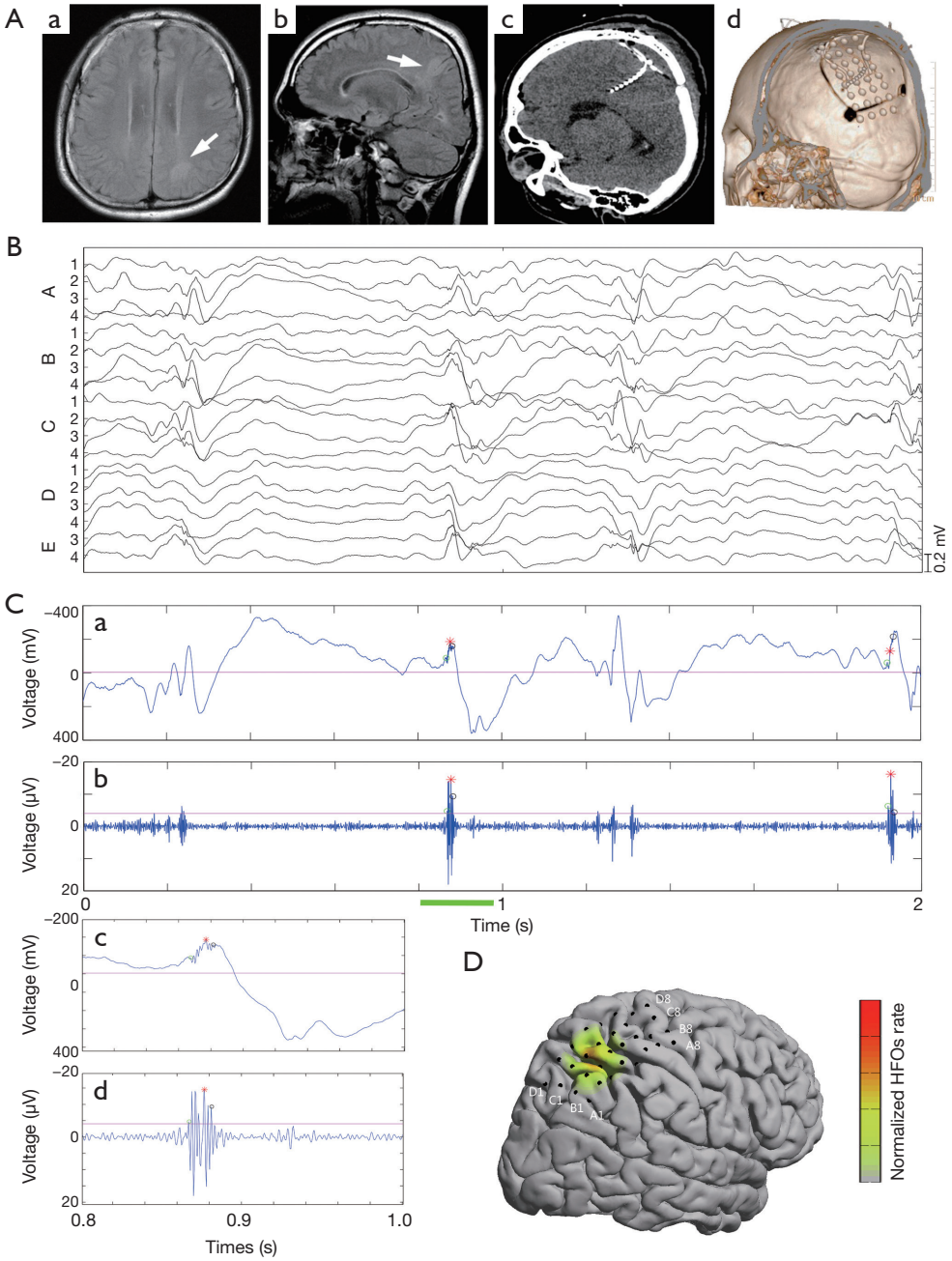

Figure 3 Weekly focal seizures of a 22-year-old male were refractory to rational medical therapy. MRI scans showed subtle increased signal on left parietal lobe (FLAIR) ($A_{a,b}$). The 4*8 subdural electrodes as well as one depth electrode ($A_{c,d}$) aiming to probe the activities in the structural lesion were implanted to localize epileptogenic zone precisely. The 2 s intracranial EEG epoch (B) was displayed with selected channels (sampling frequency 2,000 Hz). Automatic detection of high frequency oscillations (HFOs) was conducted with at higher than three standard deviations of background (pink line indicated the threshold) and at least 4 continued peaks (C, one represented channel from electrode C2). C_a indicated the raw EEG signal with detected results, and C_b showed the detected results on signal of frequency band filtered ranging from 200 to 600 Hz. Notably, two HFOs were detected (green circle indicate the first peak, red star indicated highest peak, and black circle represent the last peak). The first HFOs were zoomed in (C_c and C_d). Based on the automatic detection, HFOs rate (times per minute) was calculated and normalized (from 0 to 1). The HFOs spatial distribution was mapped on brain surface (D). Patient has been seizure freedom for 4 years after tailed cortical resection surgery according to HFOs map. Post-operation histological examination revealed focal cortical dysplasia IIa. (Unpublished data).

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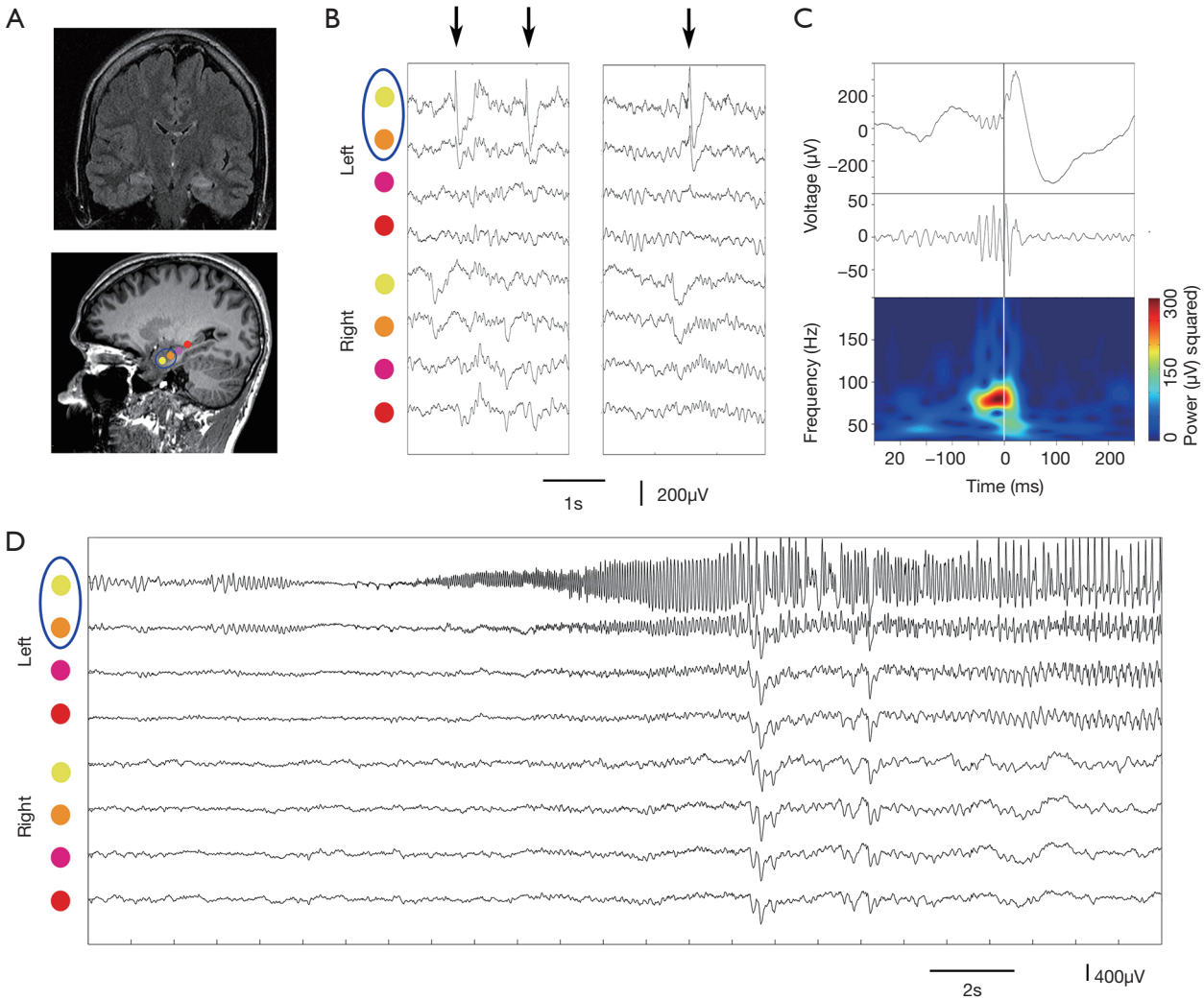

Figure 4 (A) MRI scans showed location of 3 macroelectrode contacts implanted in the hippocampus of a patient with hippocampal sclerosis and drug-resistant temporal lobe epilepsy (arrow points to electrode trajectory artifacts and a blue circle marks the seizure onset zone). (B) Raw intracranial EEG traces were centered around 3 inter-ictal epileptiform discharge (IED) detections (arrows) recorded on 8 color-coded electrodes as in A (seizure onset zone marked in the circle). (C) Upper panel is an amplified view of the third IED from the uppermost channel in B aligned with its gamma-filtered (30–120 Hz) signal and its power spectrogram below (central lines indicate the common IED onset at time 0). The spectral power changes are plotted across 30- to 200-Hz frequency range in the time course of the IED recording above to highlight increased gamma power preceding the IED waveform. (D) Recordings show the onset of ictal discharge (red line), on the 2 uppermost electrodes (circled), which was the location of gamma-IEDs. [From reference (51)].

strongly associated with electrodes in the seizure onset zone (SOZ) compared with the surrounding brain regions. The potential clinical application of gamma-IEDs for mapping pathologic brain regions is intriguing (*Figure 4*). Thus, we term the combination of HFO with IEDs as 'HFO plus', which seems to be more reliable and specific to describe the EZ than HFO or IED separately.

Intracranial EEG deepen our understanding of the spatiotemporal dynamics of seizure

There is no doubt that accurate localization of the EZ is a key to the success of resection surgery for intractable epilepsy. In the pre-surgical evaluation work-up, non-invasive investigations are sufficient for delineating the EZ in the majority of patients suffering from drug-resistant

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focal seizures, whereas intracranial implantation is needed when the results from non-invasive investigations are obviously discordant or mapping of cortical function is needed because of EZ adjacent or overlapping with eloquent cortex. In essential, it was clear that the placement of intracranial electrodes would be inadequate and surgical results would be probably poor if the localization hypotheses were wrong when considering the intracranial EEG (iEEG) method. Clinical iEEG including subdural grids, strips, depth, and stereoelectroencephalography (SEEG) have been in use for more than 50 years, yet also continues to hold an important role in the precise definition of EZ, offering the unique opportunity to record neural signal direct from brain issues compared with other investigations (52).

Among iEEG, SEEG was firstly developed by Talairach and Bancaud at Hospital Sainte Anne, Paris, and French. The clinical and scientific interest has grown throughout the years due to the advent of high-resolution imaging and robotic stereotactic systems, which contributed to the technical evolution of SEEG (53-55). As a rule, SEEG methodology firstly requires a comprehensive scrutiny of all available information obtained by the non-invasive investigation to formulate a coherent localization hypothesis (56). Different from depth electrodes, commonly used for lateralizing seizure onset, SEEG is aiming to define the EZ using a larger number of stereotaxic trajectories arranged according to the specific anatomo-electro-clinical requirements of each patient (57). Briefly, SEEG is targeted to the more likely structure(s) of ictal onset, the anatomic lesion (if present), and the possible propagation pathway to evaluate the spread of the discharge adequately (*Figure 5*). Despite the number of electrodes, SEEG is obtained with a very low complication rate (58).

There has been a slight shift in the understanding of EZ in recent years. A substantial body of epilepsy research has shown that EZ influence brain areas crossing ensembles of functionally and anatomically connected brain areas (40). Classical concept of a highly localized structure that forms EZ has recently given way to the notion of a distributed network of modules with intrinsic properties that integrate in the presence of seizure. Since SEEG emphasizes the importance to study the spatiotemporal dynamics of seizure discharges, accounting for the dynamic, multidirectional spatiotemporal organization of the ictal discharges, it has greatly deepen our understanding of ictal clinical semiology of focal seizure by terms of offering stereotactic 3D view of the ictal discharges.

SEEG also offer the chance to perform the minimal invasive neurosurgical techniques in epilepsy surgery (59). There is a long history for the exploration of minimal invasive alternatives in classical open epilepsy surgery. In recent years, the advent of modern imaging techniques and increasing accuracy of stereotactic targeting has paved the way for this treatment modality. Recent promising results from retrospective and small case series have been reported (60,61). In detail, the procedure is based on findings provided by SEEG recording, and stereotactic radiofrequency thermocoagulation (RF-THC) that caused a permanent lesion by heating brain tissue was accomplished efficiently using the same electrodes employed for recording. There are mounting evidences that patients with hypothalamic hamartomas, grey-matter nodular heterotopy and hippocampal sclerosis might be good candidates for minimal invasive treatment with RF-THC (62). It also showed that RF-THC does not implicate additional risks beyond those of a standard SEEG implantation. Hence, SEEG is not only a powerful diagnostic tool for the definition of the EZ but a potential therapeutic technique in carefully selected cases.

Summary

Over past decade, advanced techniques have made a colossal impact on the diagnosis and management of epilepsies. Refinement of advances and future developments of modality would improve our understanding of the dynamics of brain with high spatial and temporal resolutions dramatically. Precision medicine in epilepsy surgery requires integrated broad range of techniques and approaches to ensure the success of subsequent surgery. We are on the way to pursue the best surgical treatment of medical refractory epilepsy individually.

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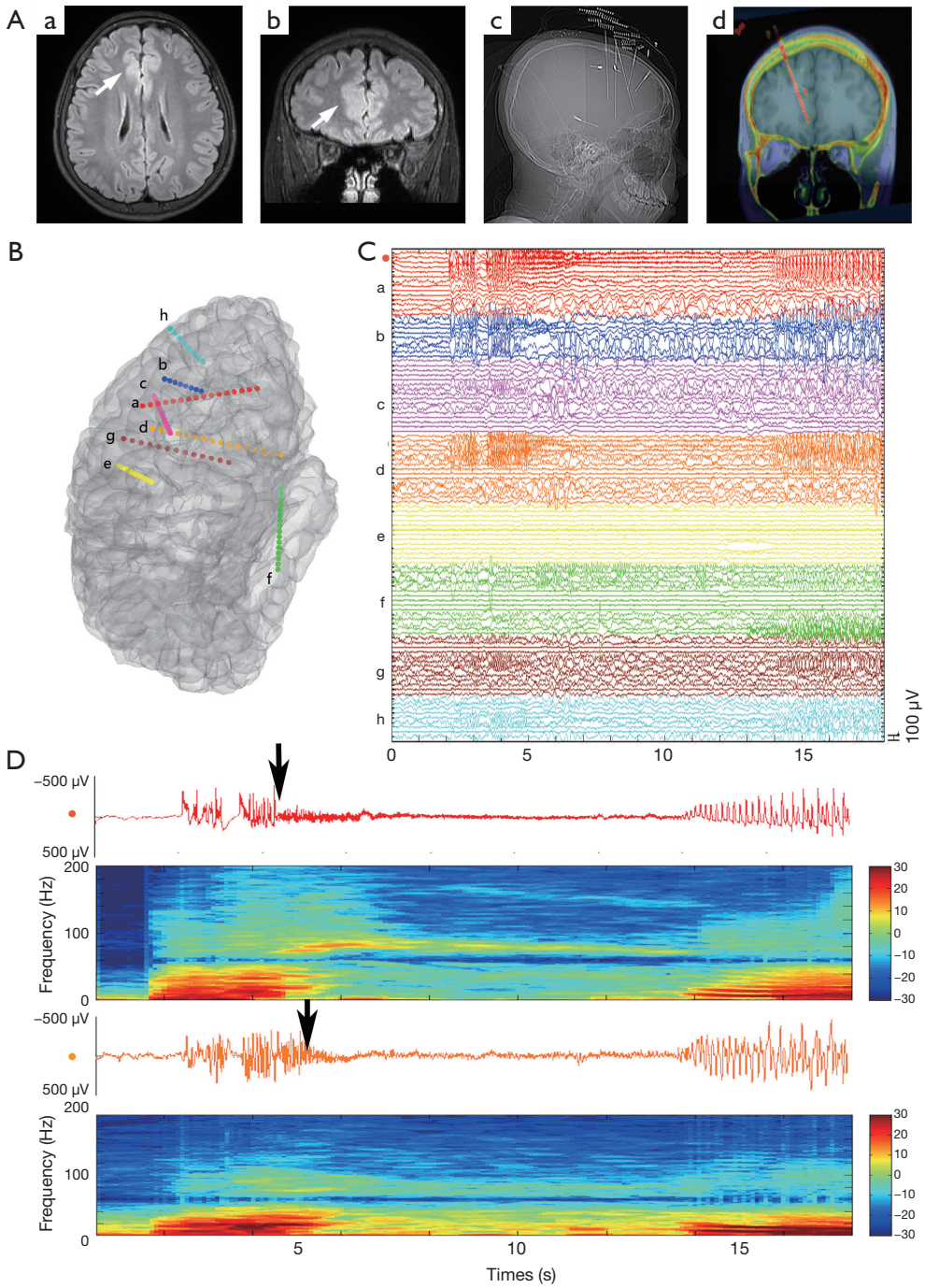

Figure 5 A 17-year-old male presented with refractory focal seizure since he is 4 years old. Habitual seizure manifested with aura with fear, followed by integrated gestural motor behavior lasting from 10 to 30 s. MRI scan showed subtle signal alteration on right anterior cingulate gyrus ($A_{a,b}$). SEEG was implanted based on the assumed seizure onset zone (anterior cingulate gyrus) and possible seizure network involved (A_c). Post-operation CT was coregistered on pre-operation 3D MRI (A_d) to get the spatial location of each electrode precisely. Ictal SEEG epoch and the reconstruction of electrodes and brain were displayed (B). It showed seizure onset from the inner contacts (small numbers) of electrode A rather than outer contacts (large numbers). To highlight the seizure propagation, brain activities on electrode A2 (anterior cingulate cortex, red) and on electrode D2 (obito-frontal lobe, orange) were further demonstrated together with time-frequency analysis. It showed typical seizure onset with fast activity (about 80–100 Hz) on electrode A2 is about 1 s earlier than D2 (arrows). Post-operation histological examination showed focal cortical dysplasia IIa. (Unpublished data).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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