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Seminars in PEDIATRIC NEUROLOGY

Localizing the Epileptogenic Zone with Novel Biomarkers

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Several noninvasive methods, such as high-density EEG or magnetoencephalography, are currently used to delineate the epileptogenic zone (EZ) during the presurgical evaluation of patients with drug resistant epilepsy (DRE). Yet, none of these methods can reliably identify the EZ by their own. In most cases a multimodal approach is needed. Challenging cases often require the implantation of intracranial electrodes, either through stereo-taxic EEG or electro-corticography. Recently, a growing body of literature introduces novel biomarkers of epilepsy that can be used for analyzing both invasive as well as noninvasive electrophysiological data. Some of these biomarkers are able to delineate the EZ with high precision, augment the presurgical evaluation, and predict the surgical outcome of patients with DRE undergoing surgery. However, the use of these epilepsy biomarkers in clinical practice is limited. Here, we summarize and discuss the latest technological advances in the presurgical neurophysiological evaluation of children with DRE with emphasis on electric and magnetic source imaging, high frequency oscillations, and functional connectivity.

Introduction

Up to 30% of children with epilepsy are unable to control their seizures with antiseizure medications (ASM) and suffer from drug resistant epilepsy (DRE).[1] Children with DRE are at increased risk for poor long-term intellectual and psychosocial outcomes, along with a poor health-related life quality.[2] For these children, epilepsy surgery is the best available treatment since it offers higher rate of seizure freedom and better outcome with respect to behavior and quality of life compared to drug therapy alone.[3] To be successful, epilepsy surgery requires the complete resection of the epileptogenic zone (EZ), the brain area that is indispensable for the generation of seizures.[4] Precise localization of the EZ is necessary to guide resection or focal ablation.[5] Eloquent brain areas for essential tasks, such as language and movements, should also be identified and preserved. Current practice uses the seizure onset zone (SOZ), the brain area where seizures initiate, as the most approximate estimator of the EZ. However, the identification of this zone is challenging since it requires the recording of several spontaneous stereotyped seizures at the expense of human and financial resources. Moreover, these methods may not represent the full extent of the EZ. The noninvasive delineation of the EZ is currently performed through mapping several overlapping cortical zones using a variety of noninvasive diagnostic tests. The most common cortical zones to be considered are the irritative zone, the SOZ, the functional deficit zone, and the eloquent areas (Fig. 1).

In approximately 20% of patients with DRE, the findings of noninvasive tests are either inconclusive or non-concordant. Thus, a clear hypothesis about the location of the EZ cannot be formulated and patients require intracranial EEG (iEEG), which is performed either through stereo-electroencephalography (sEEG) with depth electrodes or electro-corticography (ECoG) with grids and strips. These invasive procedures, particularly

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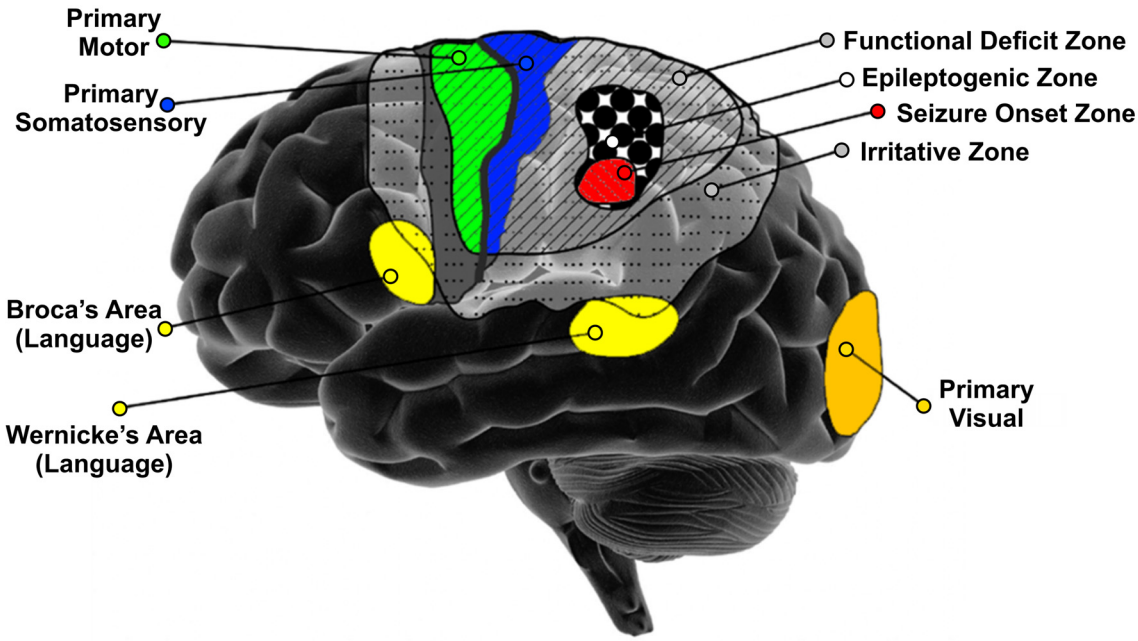

Figure 1 Overlapping cortical zones for the delineation of the EZ. Eloquent areas mainly consist of the primary motor (green), primary somatosensory (blue), primary visual (orange), and language areas (Broca's and Wernicke's areas; yellow); eloquent areas are responsible for basic physiological brain functions. Irritative Zone (dotted grey area): cortical area that generates interictal spikes in the EEG. Functional deficit zone (diagonal lined grey area): cortical area that is functionally abnormal during the interictal period as it can be identified by neurological examination or neuropsychological testing. Seizure Onset Zone (red area): the brain area where seizures initiate. (Color version of figure is available online.)

the sEEG, are generally well-tolerated and can correctly identify the EZ in ~60% of patients.[6] Yet, iEEG recordings have several limitations due to their invasiveness,[7,8] and offer limited spatial sampling since iEEG electrodes record activity only in their direct vicinity and are blind to other areas. This makes it difficult to judge whether the activity at the seizure onset truly represents the seizure generator or is the result of propagation from other regions. Thus, the actual focus and extent of the SOZ may be missed, leading to surgical failure. Furthermore, the interpretation of invasive ictal studies requires the recording of several stereotyped clinical seizures to allow for a secure identification of the SOZ. Thus, in some patients, iEEG recordings from several days to weeks are necessary to acquire enough ictal information. As a result, there is an urgent need for better presurgical tools that can localize the EZ with high precision. This focused review aims to highlight the latest technological and neurophysiological advances in presurgical evaluation with specific emphasis on electric and magnetic source imaging (ESI and MSI), high frequency oscillations (HFOs), and functional connectivity (FC).

Electric and Magnetic Source Imaging

ESI and MSI are currently used for the noninvasive localization of the irritative zone during the surgical work-up of patients with DRE. Several studies investigated the contribution of ESI/MSI in the presurgical evaluation process by assessing their localization accuracy and clinical utility. ESI and MSI can localize the irritative zone with an accuracy that ranges from ~7 to ~30 mm using a variety of source localization methods.[9-11] MSI seems to be more accurate than ESI though the difference in localization accuracy between the two modalities is on the order of mm.[11] Yet, this assessment is based on data of MEG and high-density EEG (HD-EEG) having unequal number of sensors (ie, 306 sensors distributed in 102 locations for MEG vs 72 channels for HD-EEG). Further comparison studies are necessary that consider the same number of sensors for the two modalities. ESI and MSI have high sensitivity (up to 90%) and diagnostic odds ratio (up to 7.9) but low specificity (up to 54%).[12] MSI has shown to change the surgical management plan in 21% to 33% of patients and was associated with long-term seizure control.[13,14] Proximity of ESI/MSI solutions to resection has also be linked to outcome.[11,15,16] Thus, ESI/MSI solutions can be interpreted as presurgical indicators of the EZ location. This contribution is not limited to the use of highly sophisticated techniques, such as HD-EEG or MEG, but also when the ESI is performed on conventional low-density EEG (ie, 19 channels) interictal[11] or ictal recordings[17] (Fig. 2). The role of ESI/MSI is even more critical in patients with normal MRI or MRI with subtle or non-focal findings. Both ESI and MSI solutions can facilitate the surgical planning for these patients and limit the reliance on invasive monitoring, since they can estimate the SOZ and irritative zone with high precision when appropriate methods are used.[18,19]

Despite numerous studies showing that ESI and MSI provide reliable findings and yield clinical utility in the

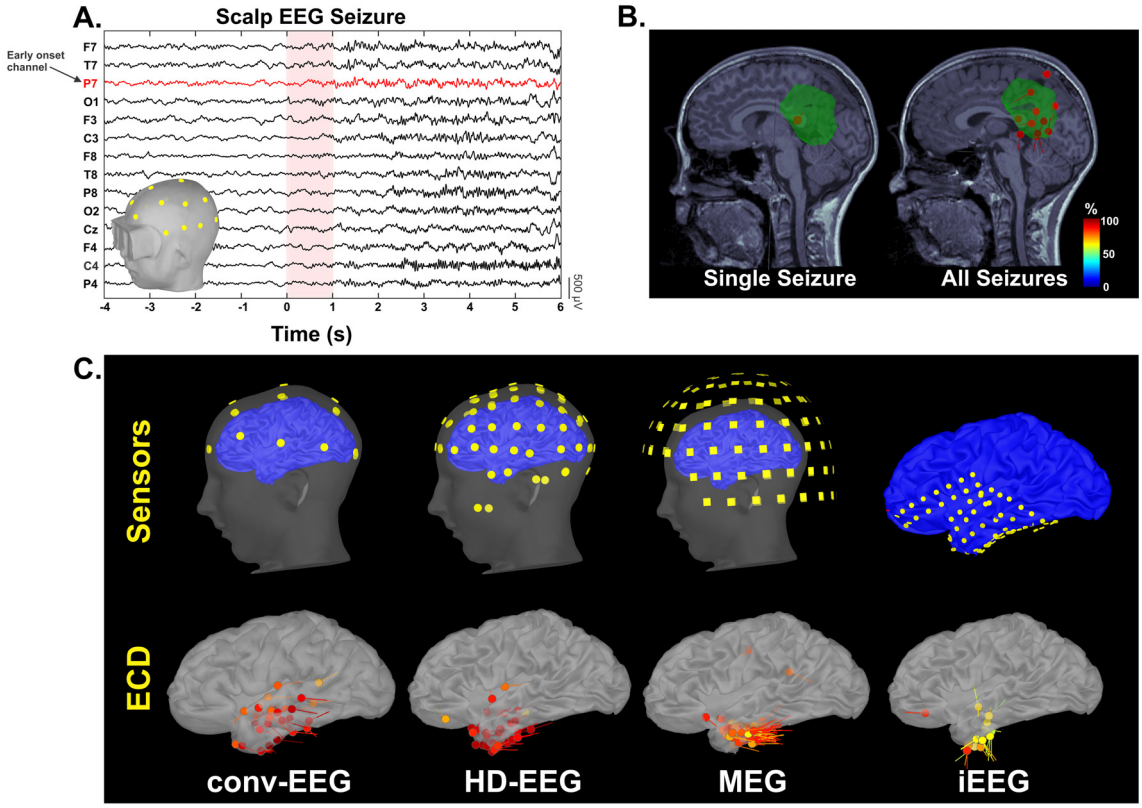

Figure 2 ESI and MSI solutions on ictal and interictal data. (A) Seizure onset (vertical red highlight area) on low-density conventional scalp EEG (selection of a -4 to 6 s time window) from a 9-year-old boy with DRE. (B) Source localization of the SOZ with Equivalent Current Dipole (ECD) of a single seizure and all seizures color-coded based on their goodness of fit (GOF) overlaid on resection (green area). (C) Sensor locations and source localization of interictal spikes with ECD in a 13-year-old girl with DRE for conventional low-density (19 channels) scalp EEG, HD-EEG (72 channels), MEG (306 sensors), and iEEG (72 subdural electrodes).[11] (Color version of figure is available online.)

presurgical evaluation of patients with DRE, few epilepsy centers integrate these modalities in their standard clinical practice. A recent survey from a large consortium in Europe, comprising 25 epilepsy centers, showed that less than half of the centers used these methods for presurgical evaluation.[20] In most centers, the irritative zone and SOZ are approximated noninvasively through visual inspection of the EEG signal; the scalp region where the peak negativity of the discharges (phase reversal) is identified and regarded as the area of interest. Yet, this approach can lead to misleading findings since peak negativity can be recorded over a different lobe and even different side than the actual source due to volume conduction. Moreover, MSI/ESI solutions, if and/or when used, are rarely combined despite the complementary information they contain. A recent prospective study,[21] showed that although the localization accuracy of the combined MSI/ESI was not significantly different from conventional neuroimaging, these two modalities complemented each other since their combined solution was able to localize the source in cases in which the conventional methods did not.

ESI can prove beneficial even when applied to iEEG data. Due to its limited spatial sampling, iEEG can result in misleading localization since the location of the recording contacts may differ from the actual source of the recorded activity.[22,23] In a recent iEEG study, Alhilani *et al.*,[24] determined the surgical utility of ESI on ictal and interictal iEEG data recorded from children with DRE. In a cohort of patients with focal cortical dysplasia, they showed that intracranial ESI of ictal and interictal activity can delineate the irritative zone and SOZ with a higher prognostic value for surgical outcome compared to the conventional approach for iEEG interpretation (Fig. 3).

High Frequency Oscillations (HFOs)

For the past two decades, HFOs have attracted the attention of the research community developing electrophysiological epilepsy biomarkers. Interictal HFOs are defined as brief spontaneous low-amplitude oscillations between 80 and 500 Hz standing out of the background iEEG signal. HFOs are strongly bound to the SOZ and their resection correlates with surgical outcome[25-27]; they seem to be more specific biomarkers of the EZ than spikes though recent findings challenged this notion.[28] HFOs are classified into ripples (80-250 Hz) and fast ripples (250-500 Hz).[29] Very-HFOs

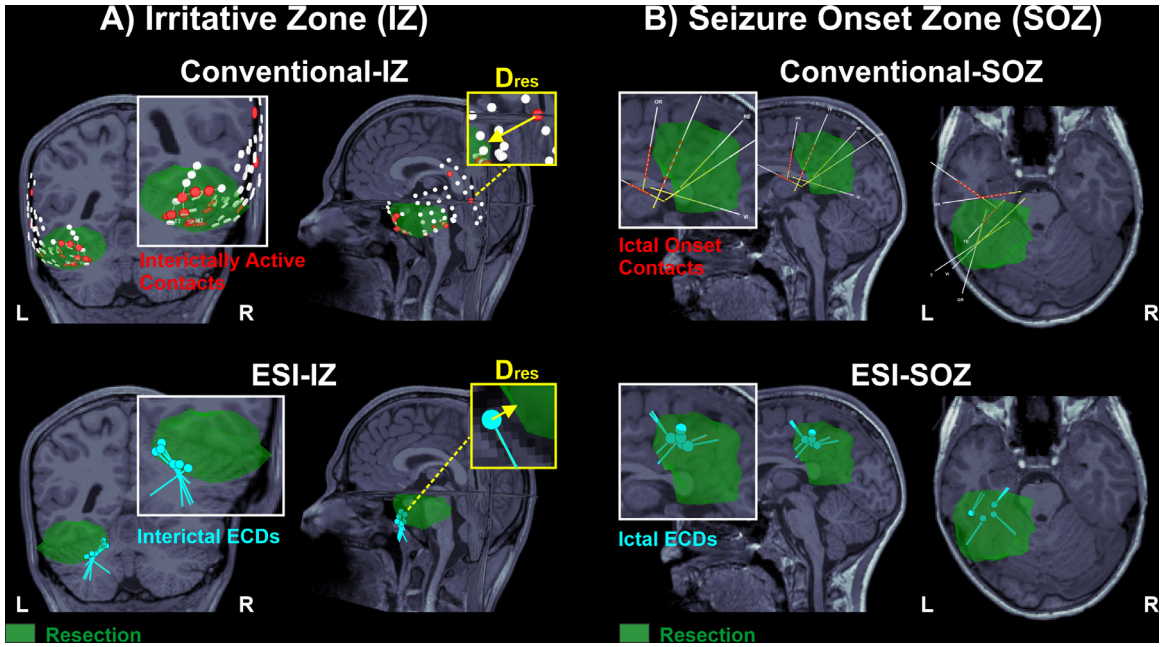

Figure 3 Delineation of the irritative zone (IZ) and SOZ using ESI on iEEG data. (A) Delineation of the IZ for a 18-year old boy underwent surgery (good outcome). Top panels show the irritative zone defined with the conventional approach by using the coordinates of most interictally active contacts (red) overlaid on patients pre-operative MRI overlaid on resection (green). Bottom panels show the irritative zone defined by ESI (cyan dipoles). (B) Delineation of the SOZ for the same patient. The figure has been obtained from[24] after permission. (Color version of figure is available online.)

(>1,000 Hz) have been also seen in patients with epilepsy[30] but their clinical utility is unclear. Ripples are observed in most patients but have low specificity since they can also occur in non-epileptogenic regions (physiological ripples). Fast ripples are more specific biomarkers than ripples[31,32] since they are more focal but may not be recorded with conventional macroelectrodes.[33]

The superiority of HFOs compared to other biomarkers was challenged by two recent iEEG studies. A multicenter study in 53 patients showed that HFOs, on a patient level, were useful for the identification of the EZ in only 67% of patients.[34] Another study showed the absence of statistical evidence to support that HFOs or its variants (combinations of HFOs overlapping with spikes) are globally better biomarkers than spikes.[28] The absence of statistical evidence was attributed to the observation that HFOs were better biomarkers than spikes in some patients but spikes were better in the others. This variable performance of HFOs and spikes can most likely be explained by the presence of physiological ripples and the large distribution of spikes. In an attempt to differentiate pathological from physiological ripples, two independent research groups recently showed that ripples propagate across iEEG electrodes and that surgical resection of the onset of this propagation (ripples onset) is more predictive of the surgical outcome compared to areas of spread.[35,36] In a cohort of pediatric patients with DRE undergoing surgery, Tamilia *et al.*,[35] identified propagation sequences of ripples across multiple iEEG contacts which were different from the propagation of spikes. This previously undescribed phenomenon may reflect a hierarchical epileptogenic brain organization: onset-ripples are more epileptogenic than spread-ripples or isolated ripples which occur sporadically (Fig. 4). Similar findings were seen in a cohort of seizure-free adults with focal epilepsy after neurosurgery;[36] ripples and fast-ripples did not occur as isolated events, but rather as a pathophysiological activity that was organized in networks. In line with Tamilia *et al.*,[35] onset areas of the ripple and fast ripple network were frequently seen in resected tissue. However, contrarily to Tamilia *et al.*,[35] surgical resection of these areas was not superior compared to iEEG channels with the highest rates of HFOs. Such contradictory findings may be explained by the fact that the two studies examined different population cohorts (ie, adults vs children). While in adults the onset of HFOs may also correspond to the highest rate contacts, in children other areas (eg, non-epileptogenic and non-onset) may also present high rates of HFOs (thus physiological HFOs). Considering the limitations of ripples, research groups recently examined the role of fast ripples as accurate biomarkers of the EZ. Nevalainen *et al.*,[37] analyzed overnight stereo-EEG recordings from adult patients with DRE and hypothesized that different measures of fast ripples (ie, resection ratio, maximal rate, and distribution) can predict outcome. Fast ripples were accurate in predicting outcome at the individual level, while absence of channels with high rates of fast ripples or absence of one dominant fast ripples area was a poor prognostic factor. In line with these findings, van't Klooster[38] examined whether HFOs and spikes in combined pre− and post-resection ECoG can predict outcome in different tailoring approaches. They found that (for different tailoring

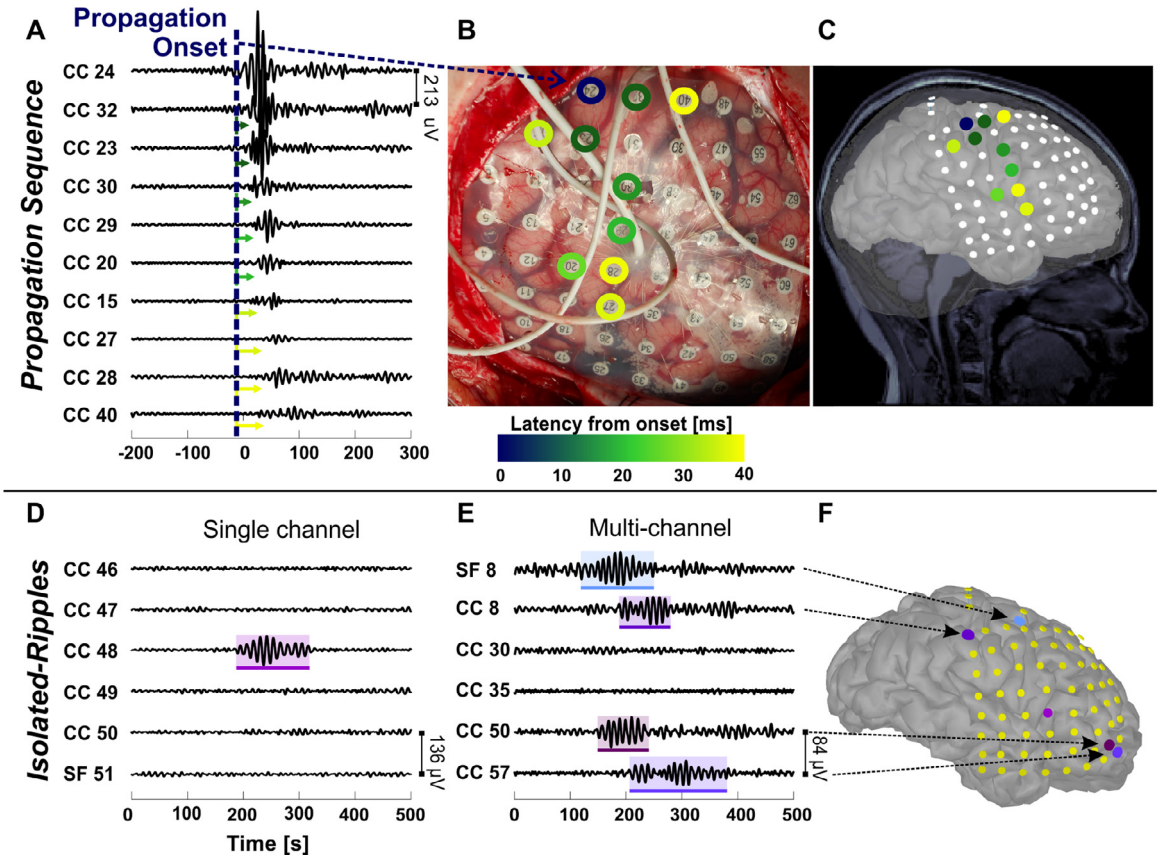

Figure 4 Spatiotemporal propagation of HFOs (ripples). (A) Propagating ripples on filtered iEEG data (80-250 Hz) from a 10-year-old-boy with DRE. (B) Spatiotemporal propagation of ripples displayed on intraoperative photo of implanted grid of patient's cortex and on the 3D cortical reconstruction of patient's preoperative MRI (C) [color-coded for latency from onset (ms)]. (D) Isolated ripples (occurred either in a single channel or multi-channel) not participating on propagations.[35] (Color version of figure is available online.)

approaches) fast ripples that persist before and after resection predict poor outcome.

So far, HFOs have been mostly investigated using iEEG due to their low amplitude. But iEEG is not always performed prior to surgery. An emerging body of literature has provided strong evidence that HFOs can be recorded noninvasively from ictal and non-ictal recordings with high-density EEG or MEG (for a review see[39]). HFOs were first reported ictally on scalp EEG at the onset of epileptic spasms in children with epilepsy[40,41] and tonic seizures in patients suffering from Lennox-Gastaut syndrome.[42] Interictally, HFOs were first reported on EEG in children with sleep-induced electrical status epilepticus[43] and patients with focal epilepsy.[44] Since these early studies, several groups have shown that HFOs can be detected non-invasively with either EEG,[45-52] MEG,[53-59] or simultaneous recordings.[52,60,61] Despite these findings the clinical utility of noninvasively recorded HFOs is limited in clinical practice. This may be attributed to the lack of studies that: (1) elucidate the spatial relationship between the gold standard (typically defined by the iEEG HFOs) and the generators of scalp recorded HFOs; and (2) differentiate scalp recorded pathological from physiological HFOs. To this aim, Tamilia *et al.*,[52] recently showed that noninvasive source imaging (via HD-EEG or MEG) localizes ripples with high precision to the intracranial gold standard in children with DRE. Scalp-recorded ripples that co-occur with spikes were prognostic biomarkers of epileptogenicity contrarily to scalp ripples-alone, which more likely reflect physiological events. In another recent study from the same group, Tamilia *et al.*,[61] showed the noninvasive mapping of interictal ripple propagation in a cohort of children with DRE using ESI and MSI with HD-EEG and MEG, respectively. In line with previous iEEG studies,[10,36] this study showed that ripple propagations, captured by non-invasively estimated virtual sensors, reflect a hierarchical epileptogenic organization where the ripple onset generator estimates the EZ better than mapping the area of spread as well as all ripple generators independently from propagation (Fig. 5). Although these findings indicate that scalp recorded ripples (and particularly the onset of ripple propagations) may be a presurgical asset with significant clinical utility, their low detectability represents the prime challenge, which demands further research with longer recordings, optimized protocols, and the development of instrumentation for high-frequency recordings.

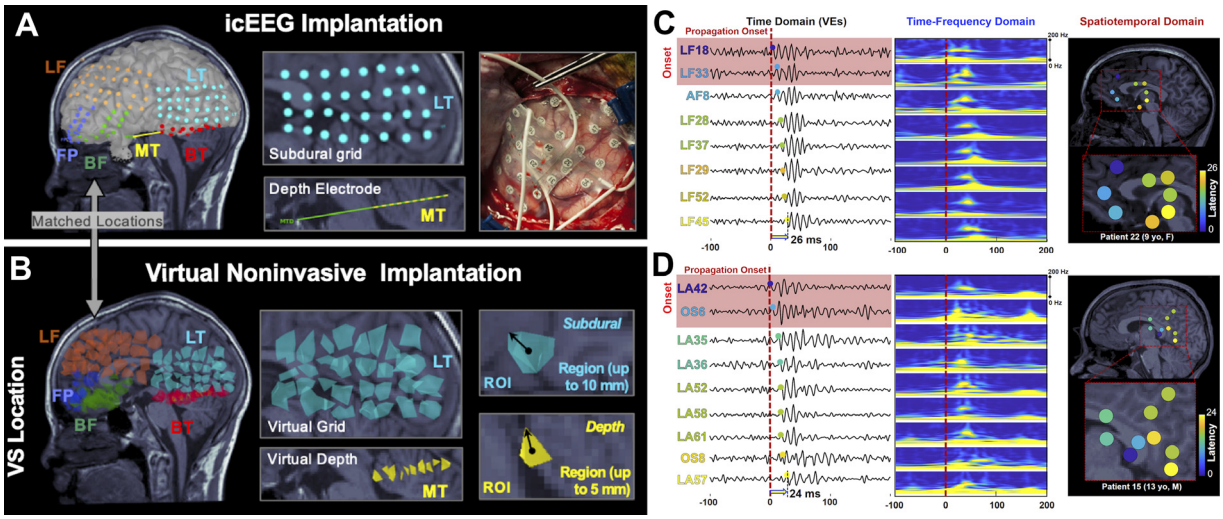

Figure 5 Virtual sensor implantation with MEG and HD-EEG for mapping noninvasively propagation of HFOs across large brain areas. (A) Example of iEEG implantation with both subdural and depth electrodes on the left temporal and medial temporal lobe of a 12-year-old boy with DRE. (B) Virtual channel placement based on the coordinates of iEEG electrodes (matched locations). Ripple propagation on MEG (C) and HD-EEG (D) virtual sensors across time.[61] (Color version of figure is available online.)

Functional Connectivity

Over the last decade, there is an increasing interest in embedding connectivity analysis into the preoperative evaluation of patients with DRE. This trend has led to a transition from the concept of epilepsy as a "focal" to a "network" brain disorder.[62] Several studies have reported altered networks reflecting neuropathology in patients with focal epilepsy[63-65] as well as generalized epilepsy.[66-69] A meta-analysis that examined the most commonly used metrics in whole-brain networks showed increased average path length and mean average clustering coefficient for patients with epilepsy compared to healthy controls.[65] These findings indicate that -at a group level- focal epilepsy shows widespread detrimental effects, that is, reduced integration and increased segregation, on whole brain interictal network. Such connectivity changes may relate to the co-morbid cognitive and behavioral impairments often reported in patients with focal epilepsy. Several recent iEEG studies have also showed that FC is a potentially useful marker for the localization of the EZ.[70,71] FC is a statistical concept, which is defined as the temporal dependency of neuronal activation patterns from anatomically segregated brain regions (Fig. 6). Therefore, the extent to which different brain areas are functionally connected depends on the level of synchronous temporal activity.[62] Most studies report increased FC in the EZ compared to the rest areas of the brain,[72-74] though few others report the opposite effect.[75-77] In a recent study, Shah *et al.*,[78] showed higher connectivity for iEEG electrodes localized within the resection area for good outcome patients compared to patients with poorer postoperative seizure control (Fig. 7). Importantly, these measures are derived from interictal data; thus, they offer the opportunity to delineate the EZ without

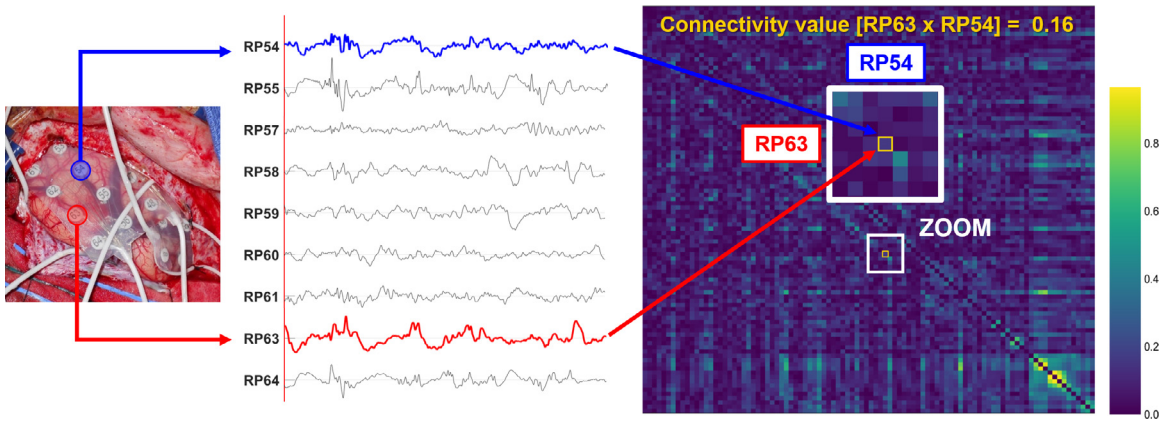

Figure 6 FC estimates from iEEG. Pairwise FC matrices (right) are estimated from iEEG. The connectivity matrix for a brain network comprising N channels is a N × N matrix: diagonal elements of the matrix represent the connectivity of each node with itself (therefore we will assume that they contain only zero values); off-diagonal elements of the connectivity matrix represent the connectivity between pairs of distinct channels. (Color version of figure is available online.)

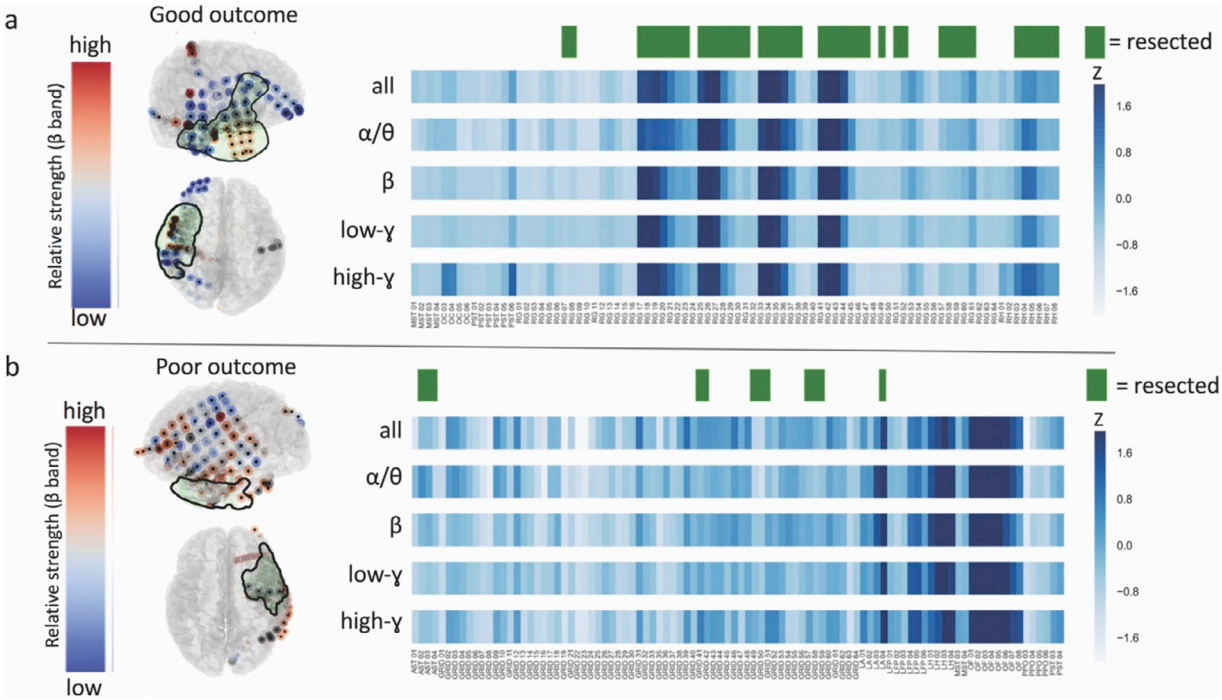

Figure 7 Patient-level strength selectivity analysis based on iEEG data. Spatial maps of FC (nodal strength in beta band) (left) along with corresponding 2D heat maps of nodal strength in all frequency maps (right) for a patient with good (A) and poor (B) surgical outcome. Resection zones are highlighted in green. The figure has been obtained from[71] after permission. (Color version of figure is available online.)

having to provoke a seizure (eg, by medication withdraw and sleep deprivation) or wait for a seizure to occur.

Yet, all these studies were performed on iEEG which has limited field of view and may thus miss the EZ. Measures of FC using noninvasive techniques (ie, MEG or HD-EEG) have been recently proposed by several groups using virtual sensors that allow an extensive coverage of the entire brain (for a review see[79]). Nissen *et al.*,[80] showed that pathological hubs, localized using an atlas-based beamforming on MEG data, had a 100% specificity and 73% accuracy to delineate the EZ. A similar MEG study from the same group reinforced these findings by showing that FC measures estimated noninvasively with virtual sensors correlate with the ones estimated invasively through iEEG.[81] These recent findings open up the possibility of using noninvasive methods, such as MEG, to "predict" later iEEG findings at various cerebrocortical locations, and to use this information for optimal placement of iEEG electrodes in order to sufficiently cover the EZ.

Discussion

The main challenge in the presurgical evaluation of patients with DRE is the successful localization of the EZ while preserving eloquent areas. Such a task requires the precise mapping of different cortical areas, such as the irritative zone and SOZ, ideally by using noninvasive techniques that can delineate these areas with high precision. Emerging technological developments in neuroimaging currently allows the simultaneous recording of MEG and HD-EEG from > 550 sensors (when combined together) covering the entire head (Fig. 8), which offer complementary information about the underlying EZ.[82] These developments, particularly when accompanied by advanced source localization methods, can offer critical information about the precise localization of these epileptogenic areas. Yet, the use of these methods is limited in clinical practice, mostly due to: (1) their complexity; (2) lack of experts knowledgeable about these technologies and practices; (3) lack of multicenter large prospective studies examining their effectiveness in improving presurgical evaluation and predicting surgical outcome for patients with DRE; (4) skepticism of epileptologists to rely on their findings; and (5) "disconnection" of software and hardware developers from clinical practice that will allow the simplified use of these methods in a timely manner. Recent developments give hope that novel and more effective biomarkers of epilepsy, such as interictal pathological HFOs, can be localized noninvasively using these tools. These biomarkers would allow augmenting the presurgical evaluation by applying it to an earlier stage in the workup, guiding the implantation of iEEG electrodes, and facilitating patients' surgical prognosis. Recent FC studies also give hope that these measures can map network hubs in the EZ vicinity having a pathological role in the propagation of epileptic activity to the rest of the brain. Removal of these pathological hubs (instead of the entire EZ), or their disconnection from the EZ, might lead to good surgical outcome. This would be particularly beneficial in patients who were previously not eligible for surgery due to overlap of the EZ with the eloquent cortex.

Figure 8 Novel technological improvements in mapping the EZ. Pediatric HD-EEG recordings (A) that can be performed simultaneously with MEG (B) at Cook Children's Medical Center (Fort Worth, TX, USA). Permission has been obtained from the parents of the child to use his image for the purposes and dissemination of knowledge. (Color version of figure is available online.)

Conclusions

Emerging technological developments are on the horizon for precise delineation of the EZ. Such developments may result in more efficient, less invasive, and less time-demanding presurgical evaluation. Yet, more work is needed to translate these developments into effective clinical tools used in a regular basis in clinical practice.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Ryvlin P, Cross JH, Rheims S: Epilepsy surgery in children and adults. Lancet Neurol 13:1114-1126, 2014
2. Baca CB, Vickrey BG, Caplan R, et al: Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. Pediatrics 128:e1532-e1543, 2011
3. Dwivedi R, Ramanujam B, Chandra PS, et al: Surgery for Drug-Resistant Epilepsy in Children. N Engl J Med 377:1639-1647, 2017
4. Rosenow F, Lüders H: Presurgical evaluation of epilepsy. Brain 124(Pt 9):1683-1700, 2001
5. Willie JT, Laxpati NG, Drane DL, et al: Real-time magnetic resonance-guided stereotactic laser amygdalohippocampotomy for mesial temporal lobe epilepsy. Neurosurgery 74:569-584, 2014
6. Cardinale F, Rizzi M, Vignati E, et al: Stereoelectroencephalography: Retrospective analysis of 742 procedures in a single centrer. Brain 142:2688-2704, 2019
7. Önal C, Otsubo H, Araki T, et al: Complications of invasive subdural grid monitoring in children with epilepsy. J Neurosurg 98:1017-1026, 2003
8. Hader WJ, Tellez Zenteno J, Metcalfe A, et al: Complications of epilepsy surgery: A systematic review of focal surgical resections and invasive EEG monitoring. Epilepsia 54:840-847, 2013
9. Murakami H, Wang ZI, Marashly A, et al: Alexopoulos AV. Correlating magnetoencephalography to stereo-electroencephalography in patients undergoing epilepsy surgery. Brain 139:2935-2947, 2016
10. Sohrabpour A, Cai Z, Ye S, et al: He B. Noninvasive electromagnetic source imaging of spatiotemporally distributed epileptogenic brain sources. Nat Commun 11:1946, 2020
11. Tamilia E, AlHilani M, Tanaka N, et al: Assessing the localization accuracy and clinical utility of electric and magnetic source imaging in children with epilepsy. Clin Neurophysiol 130:491-504, 2019
12. Sharma P, Seeck M, Beniczky S: Accuracy of interictal and ictal electric and magnetic source imaging: A systematic review and meta-analysis. Front. Neurol. 10:1250, 2019
13. Knowlton RC, Razdan SN, Limdi N, et al: Effect of epilepsy magnetic source imaging on intracranial electrode placement. Ann Neurol 65:716-723, 2009
14. De Tiège X, Carrette E, Legros B, et al: Clinical added value of magnetic source imaging in the presurgical evaluation of refractory focal epilepsy. J Neurol Neurosurg Psychiatry 83:417-423, 2012
15. Rampp S, Stefan H, Wu X, et al: Magnetoencephalography for epileptic focus localization in a series of 1000 cases. Brain 142:3059-3071, 2019
16. Plummer C, Vogrin SJ, Woods WP: Interictal and ictal source localization for epilepsy surgery using high-density EEG with MEG: a prospective long-term study. Brain 142:932-951, 2019
17. Ricci L, Tamilia E, Alhilani M, et al: Source imaging of seizure onset predicts surgical outcome in pediatric epilepsy. Clin Neurophysiol 132:1622-1635, 2021
18. Mohamed IS, Toffa DH, Robert M, et al: Utility of magnetic source imaging in nonlesional focal epilepsy: A prospective study. Neurosurg Focus 48:E16, 2020
19. Ntolkeras G, Tamilia E, AlHilani M, et al: Presurgical accuracy of dipole clustering in MRI-negative pediatric patients with epilepsy: Validation against intracranial EEG and resection. Clin Neurophysiol S1388-2457:00480-00486, 2021
20. Mouthaan BE, Rados M, Barsi P, et al: Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across. Europe. Epilepsia. 57:770-776, 2016

21. Duez L, Tankisi H, Hansen PO, et al: Fuglsang-Frederiksen A, Beniczky S. Electromagnetic source imaging in presurgical workup of patients with epilepsy: A prospective study. Neurology 92:e576-e586, 2019
22. Ramantani G, Kadish NE, Strobl K, et al: Seizure and cognitive outcomes of epilepsy surgery in infancy and early childhood. Eur J Paediatr Neurol 17:498-506, 2013
23. Tao J, Ebersole JS: Subdural electrode corticography. In: Ebersole JS (ed): Current Practice of Clinical Electroencephalography, Philadelphia, PA: Wolters Kluwer Health, 2014
24. Alhilani M, Tamilia E, Ricci L, et al: Ictal and interictal source imaging on intracranial EEG predicts epilepsy surgery outcome in children with focal cortical dysplasia. Clin Neurophysiol 131:734-743, 2020
25. Akiyama T, McCoy B, Go CY, et al: Focal resection of fast ripples on extraoperative intracranial EEG improves seizure outcome in pediatric epilepsy. Epilepsia 52:1802-1811, 2011
26. Cho JR, Joo EY, Koo DL, et al: Clinical utility of interictal high-frequency oscillations recorded with subdural macroelectrodes in partial epilepsy. J Clin Neurol 8:22-34, 2012
27. Kerber K, Dümpelmann M, Schelter B, et al: Differentiation of specific ripple patterns helps to identify epileptogenic areas for surgical procedures. Clin Neurophysiol 125:1339-1345, 2014
28. Roehri N, Pizzo F, Lagarde S, et al: High-frequency oscillations are not better biomarkers of epileptogenic tissues than spikes. Ann Neurol 83:84-97, 2018
29. Zijlmans M, Jiruska P, Zelmann R, et al: High-frequency oscillations as a new biomarker in epilepsy. Ann Neurol 71:169-178, 2012
30. Usui N, Terada K, Baba K, et al: Clinical significance of ictal high frequency oscillations in medial temporal lobe epilepsy. Clin Neurophysiol 122:1693-1700, 2011
31. Urrestarazu E, Chander R, Dubeau F, Gotman J: Interictal high-frequency oscillations (100−500 Hz) in the intracerebral EEG of epileptic patients. Brain 130:2354-2366, 2007
32. Jacobs J, Zijlmans M, Zelmann R, et al: High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol 67:209-220, 2010
33. Schevon CA, Trevelyan AJ, Schroeder CE, et al: Spatial characterization of interictal high frequency oscillations in epileptic neocortex. Brain 132:3047-3059, 2009
34. Jacobs J, Wu JY, Perucca P, et al: Removing high-frequency oscillations: A prospective multicenter study on seizure outcome. Neurology 91: e1040-e1052, 2018
35. Tamilia E, Park EH, Percivati S, et al: Surgical resection of ripple onset predicts outcome in pediatric epilepsy. Ann Neurol 84:331-346, 2018
36. González Otárula KA, von Ellenrieder N, Cuello Oderiz C, et al: High-frequency oscillation networks and surgical outcome in adult focal epilepsy. Ann Neurol 85:485-494, 2019
37. Nevalainen P, von Ellenrieder N, Klimeš P, et al: Association of fast ripples on intracranial EEG and outcomes after epilepsy surgery. Neurology 95:e2235-e2245, 2020
38. van 't Klooster MA, van Klink NEC, van Blooijs D, et al: Evoked versus spontaneous high frequency oscillations in the chronic electrocorticogram in focal epilepsy. Clin Neurophysiol 128:858-866, 2017
39. Tamilia E, Madsen JR, Grant PE, Pearl PL: Papadelis C. current and emerging potential of magnetoencephalography in the detection and localization of high-frequency oscillations in epilepsy. Front Neurol 8:14, 2017
40. Kobayashi K, Oka M, Akiyama T, et al: Very fast rhythmic activity on scalp EEG associated with epileptic spasms. Epilepsia 45:488-496, 2004
41. Inoue T, Kobayashi K, Oka M, et al: Spectral characteristics of EEG gamma rhythms associated with epileptic spasms. Brain Dev 30:321-328, 2008
42. Kobayashi K, Jacobs J, Gotman J: Detection of changes of high-frequency activity by statistical time-frequency analysis in epileptic spikes. Clin Neurophysiol 120:1070-1077, 2009
43. Kobayashi K, Watanabe Y, Inoue T, et al: Scalp-recorded high-frequency oscillations in childhood sleep induced electrical status epilepticus. Epilepsia 51:2190-2194, 2010
44. Andrade Valenca LP, Dubeau F, Mari F, et al: Interictal scalp fast oscillations as a marker of the seizure onset zone. Neurology 77:524-531, 2011
45. Zelmann R, Lina JM, Schulze Bonhage A, et al: Scalp EEG is not a blur: it can see high frequency oscillations although their generators are small. Brain Topogr 27:683-704, 2014
46. Xiang J, Liu Y, Wang Y, et al: Frequency and spatial characteristics of high-frequency neuromagnetic signals in childhood epilepsy. Epileptic Disord 11:113-125, 2009
47. Zweiphenning WJEM, Keijzer HM, van Diessen E, et al: Increased gamma and decreased fast ripple connections of epileptic tissue: A high-frequency directed network approach. Epilepsia 60:1908-1920, 2019
48. van Klink N, Mol A, Ferrier C: Beamforming applied to surface EEG improves ripple visibility. Clin Neurophysiol 129:101-111, 2018
49. Cuello Oderiz C, von Ellenrieder N, Dubeau F, Gotman J: Influence of the location and type of epileptogenic lesion on scalp interictal epileptiform discharges and high-frequency oscillations. Epilepsia 58:2153-2163, 2017
50. Kuhnke N, Klus C, Dümpelmann M, et al: Simultaneously recorded intracranial and scalp high frequency oscillations help identify patients with poor postsurgical seizure outcome. Clin Neurophysiol 130:128-137, 2019
51. Kramer MA, Ostrowski LM, Song DY, et al: Scalp recorded spike ripples predict seizure risk in childhood epilepsy better than spikes. Brain 142:1296-1309, 2019
52. Tamilia E, Dirodi M, Alhilani M, et al: Scalp ripples as prognostic biomarkers of epileptogenicity in pediatric surgery. Ann Clin Transl Neurol 7:329-342, 2020
53. Dirodi M, Tamilia E, Grant PE, et al: Noninvasive Localization of High-Frequency Oscillations in Children with Epilepsy: Validation against Intracranial Gold-Standard. Annu Int Conf IEEE Eng Med Biol Soc: 1555-1558, 2019
54. van Klink N, Hillebrand A, Zijlmans M: Identification of epileptic high frequency oscillations in the time domain by using MEG beamformer-based virtual sensors. Clin Neurophysiol 127:197-208, 2016
55. van Klink N, van Rosmalen F, Nenonen J, et al: Automatic detection and visualisation of MEG ripple oscillations in epilepsy. Neuroimage Clin 15:689-701, 2017
56. van Klink N, Mooij A, Huiskamp G, et al: Simultaneous MEG and EEG to detect ripples in people with focal epilepsy. Clin Neurophysiol 130:1175-1183, 2019
57. von Ellenrieder N, Dubeau F, Gotman J, Frauscher B: Physiological and pathological high-frequency oscillations have distinct sleep-homeostatic properties. Neuroimage Clin 14:566-573, 2017
58. Velmurugan J, Nagarajan SS, Mariyappa N, et al: Magnetoencephalography imaging of high frequency oscillations strengthens presurgical localization and outcome prediction. Brain 142:3514-3529, 2019
59. Yin C, Zhang X, Xiang J, et al: Altered effective connectivity network in patients with insular epilepsy: A high-frequency oscillations magnetoencephalography study. Clin Neurophysiol 131:377-384, 2020
60. Papadelis C, Tamilia E, Stufflebeam S, et al: Interictal high frequency oscillations detected with simultaneous magnetoencephalography and electroencephalography as biomarker of pediatric epilepsy. J Vis Exp: 54883, 2016
61. Tamilia E, Matarrese MAG, Ntolkeras G, et al: Noninvasive mapping of ripple onset predicts outcome in epilepsy surgery. Ann Neurol 89:911-925, 2021
62. van Diessen E, Hanemaaijer JI, Otte WM, et al: Are high frequency oscillations associated with altered network topology in partial epilepsy? Neuroimage 82:564-573, 2013
63. Coito A, Genetti M, Pittau F, et al: Altered directed functional connectivity in temporal lobe epilepsy in the absence of interictal spikes: A high density EEG study. Epilepsia 57:402-411, 2016
64. Englot DJ, Konrad PE, Morgan VL: Regional and global connectivity disturbances in focal epilepsy, related neurocognitive sequelae, and potential mechanistic underpinnings. Epilepsia 57:1546-1557, 2016
65. van Diessen E, Zweiphenning WJ, Jansen FE, et al: Brain network organization in focal epilepsy: A systematic review and meta-analysis. PLoS One 9:e114606, 2014
66. Chavez M, Valencia M, Navarro V, et al: Functional modularity of background activities in normal and epileptic brain networks. Phys Rev Lett 104:118701, 2010

67. Elshahabi A, Klamer S, Sahib AK, et al: Magnetoencephalography reveals a widespread increase in network connectivity in idiopathic/genetic generalized epilepsy. PLoS One 10:e0138119, 2015
68. Niso G, Bruña R, Pereda E, et al: HERMES: towards an integrated toolbox to characterize functional and effective brain connectivity. Neuroinformatics 11:405-434, 2013
69. Zhang Z, Liao W, Chen H, et al: Altered functional-structural coupling of large-scale brain networks in idiopathic generalized epilepsy. Brain 134(Pt 10):2912-2928, 2011
70. Nissen IA, Stam CJ, Reijneveld JC, et al: Identifying the epileptogenic zone in interictal resting-state MEG source-space networks. Epilepsia 58:137-148, 2017
71. Shah P, Bernabei JM, Kini LG, et al: High interictal connectivity within the resection zone is associated with favorable post-surgical outcomes in focal epilepsy patients. Neuroimage Clin 23:101908, 2019
72. Wilke C, Worrell G, He B: Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 52:84-93, 2011
73. Varotto G, Tassi L, Franceschetti S, Spreafico R, Panzica F: Epileptogenic networks of type II focal cortical dysplasia: a stereo-EEG study. Neuroimage 61:591-598, 2012
74. Centeno M, Vollmar C, Stretton J, et al: Structural changes in the temporal lobe and piriform cortex in frontal lobe epilepsy. Epilepsy Res 108:978-981, 2014
75. Ortega GJ, Peco IH, Sola RG, Pastor J: Impaired mesial synchronization in temporal lobe epilepsy. Clin Neurophysiol 122:1106-1116, 2011
76. Pittau F, Grova C, Moeller F, et al: Patterns of altered functional connectivity in mesial temporal lobe epilepsy. Epilepsia 53:1013-1023, 2012
77. van Diessen E, Zweiphenning WJ, Jansen FE, et al: Brain network organization in focal epilepsy: A systematic review and meta-analysis. PLoS One 9:e114606, 2014
78. Shah P, Bernabei JM, Kini LG, et al: High interictal connectivity within the resection zone is associated with favorable post-surgical outcomes in focal epilepsy patients. Neuroimage Clin 23:101908, 2019
79. van Mierlo P, Höller Y, Focke NK, Vulliemoz S: Network Perspectives on Epilepsy Using EEG/MEG Source Connectivity. Front Neurol. 10:721, 2019
80. Nissen IA, van Klink NE, Zijlmans M, et al: Brain areas with epileptic high frequency oscillations are functionally isolated in MEG virtual electrode networks. Clin Neurophysiol 127:2581-2591, 2016
81. Juárez Martinez EL, Nissen IA, Idema S, et al: Virtual localization of the seizure onset zone: Using non-invasive MEG virtual electrodes at stereo-EEG electrode locations in refractory epilepsy patients. Neuroimage Clin 19:758-766, 2018
82. Papadelis C, Chen YH: Pediatric Magnetoencephalography in Clinical Practice and Research. Neuroimaging Clin N Am 30:239-248, 2020