Title

Magnetoencephalography imaging of high frequency oscillations strengthens presurgical localization and outcome prediction

Journal

Brain, 142(11)

ISSN

0006-8950

Authors

Velmurugan, Jayabal
Nagarajan, Srikantan S
Mariyappa, Narayanan
et al.

Publication Date

2019-11-01

DOI

10.1093/brain/awz284

Peer reviewed

doi:10.1093/brain/awz284 BRAIN 2019: 142; 3514–3529 | 3514

BRAIN
A JOURNAL OF NEUROLOGY

Magnetoencephalography imaging of high frequency oscillations strengthens presurgical localization and outcome prediction

Jayabal Velmurugan,[1,2,3,4] Srikantan S. Nagarajan,[4] Narayanan Mariyappa,[2] Ravindranadh C. Mundlamuri,[3] Kenchaiah Raghavendra,[3] Rose Dawn Bharath,[5] Jitender Saini,[5] Arimappamagan Arivazhagan,[6] Jamuna Rajeswaran,[7] Anita Mahadevan,[8] Bhaskara Rao Malla,[6] Parthasarathy Satishchandra[2,3] and Sanjib Sinha[2,3]

See van Klink and Zijlmans (doi:10.1093/brain/awz321) for a scientific commentary on this article.

In patients with medically refractory epilepsy, resective surgery is the mainstay of therapy to achieve seizure freedom. However, ~20–50% of cases have intractable seizures post-surgery due to the imprecise determination of epileptogenic zone. Recent intracranial studies suggest that high frequency oscillations between 80 and 200 Hz could serve as one of the consistent epileptogenicity biomarkers for localization of the epileptogenic zone. However, these high frequency oscillations are not adopted in the clinical setting because of difficult non-invasive detection. Here, we investigated non-invasive detection and localization of high frequency oscillations and its clinical utility in accurate pre-surgical assessment and post-surgical outcome prediction. We prospectively recruited 52 patients with medically refractory epilepsy who underwent standard pre-surgical workup including magnetoencephalography (MEG) followed by resective surgery after determination of the epileptogenic zone. The post-surgical outcome was assessed after 22.14 ± 10.05 months. Interictal epileptic spikes were expertly identified, and interictal epileptic oscillations across the neural activity frequency spectrum from 8 to 200 Hz were localized using adaptive spatial filtering methods. Localization results were compared with epileptogenic zone and resected cortex for congruence assessment and validated against the clinical outcome. The concordance rate of high frequency oscillations sources (80–200 Hz) with the presumed epileptogenic zone and the resected cortex were 75.0% and 78.8%, respectively, which is superior to that of other frequency bands and standard dipole fitting methods. High frequency oscillation sources corresponding with the resected cortex, had the best sensitivity of 78.0%, positive predictive value of 100% and an accuracy of 78.84% to predict the patient's surgical outcome, among all other frequency bands. If high frequency oscillation sources were spatially congruent with resected cortex, patients had an odds ratio of 5.67 and 82.4% probability of achieving a favourable surgical outcome. If high frequency oscillations sources were discordant with the epileptogenic zone or resection area, patient has an odds ratio of 0.18 and only 14.3% probability of achieving good outcome, and mostly tended to have an unfavourable outcome (χ^2 = 5.22; P = 0.02; = −0.317). In receiver operating characteristic curve analyses, only sources of high-frequency oscillations demonstrated the best sensitivity and specificity profile in determining the patient's surgical outcome with area under the curve of 0.76, whereas other frequency bands indicate a poor predictive performance. Our study is the first non-invasive study to detect high frequency oscillations, address the efficacy of high frequency oscillations over the different neural oscillatory frequencies, localize them and clinically validate them with the post-surgical outcome in patients with medically refractory epilepsy. The evidence presented in the current study supports the fact that HFOs might significantly improve the presurgical assessment, and post-surgical outcome prediction, where it could widely be used in a clinical setting as a non-invasive biomarker.

Received December 9, 2018. Revised June 12, 2019. Accepted July 11, 2019. Advance Access publication September 23, 2019

1 Department of Clinical Neurosciences, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
2 MEG Research Center, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
3 Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
4 Department of Radiology and Biomedical Imaging, University of California San Francisco (UCSF), San Francisco, USA
5 Department of NIIR, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
6 Department of Neurosurgery, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
7 Department of Neuropsychology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India
8 Department of Pathology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India

Correspondence to: Prof. Srikantan Nagarajan
Director, Biomagnetic Imaging Laboratory
Department of Radiology and Biomedical Imaging
University of California, San Francisco
513 Parnassus Avenue, S362
San Francisco, CA 94143, USA
E-mail: sri@ucsf.edu

Correspondence may also be addressed to: Prof. Sanjib Sinha
Department of Neurology
First floor, Neuroscience Faculty block
National Institute of Mental Health and Neurosciences (NIMHANS)
Bangalore, India 560 029
E-mail: sanjib_sinha2004@yahoo.co.in

Keywords: magnetoencephalography; high frequency oscillation; ripple; biomarker; surgical outcome

Abbreviations: ECD = equivalent current dipole; FNE = focal neocortical epilepsy; HFO = high frequency oscillation; IED = interictal epileptiform discharge; iEEG = intracranial EEG; MEG = magnetoencephalography; MTLE = mesial temporal lobe epilepsy

Introduction

In about one-third of patients with epilepsy, seizures are refractory to medical treatment producing significant morbidity (Choi *et al.*, 2008). In patients with such medically refractory epilepsy, resective surgery of the epileptogenic zone is the mainstay of therapy. The epileptogenic zone is the hypothetical minimal volume of cortex that should be surgically resected out to achieve seizure freedom (Lüders *et al.*, 2006), ultimately resulting in a better quality of life (Elliott *et al.*, 2012). However, ~20–40% of cases with mesial temporal lobe epilepsy (MTLE) and ~50% of cases with focal neocortical epilepsy (FNE) have intractable seizures after surgery (Englot *et al.*, 2013) primarily due to inaccurate identification and incomplete resection (Salanova *et al.*, 2004).

Therefore, there is a considerable need for reliable biomarkers to determine the epileptogenic zone and assist further in the surgical resection, to contribute a better clinical outcome. High frequency oscillations (HFOs) co-occurring with spikes have been explored and are proposed to be one of the consistent epileptogenicity biomarkers for localization of the epileptogenic zone (Zijlmans *et al.*, 2009) in presurgical evaluation (Cho *et al.*, 2012; Kerber *et al.*, 2014) and predicting the surgical outcome (Jacobs *et al.*, 2010). These HFOs in focal epilepsy have been mainly investigated in intracranial EEG (iEEG) studies with microelectrodes (Worrell *et al.*, 2008; Schevon *et al.*, 2009), depth and subdural electrodes (Jacobs *et al.*, 2008; Haegelen *et al.*, 2013). Studies have reported better post-surgical seizure outcome if brain regions generating HFOs had been resected out (Haegelen *et al.*, 2013; Wang *et al.*, 2017) compared to the spikes or HFOs in the non-seizure onset zone electrodes (Zijlmans *et al.*, 2011). Recently, a prospective study revealed that HFOs did reliably predict the post-surgical outcome at the group level, but only in two-thirds of the patients at the individual level (Jacobs *et al.*, 2018). The results of the invasive recordings are quite promising and are implemented in clinics (Frauscher *et al.*, 2017). However, HFOs are yet to be adopted widely in the clinical setting, because of the difficulty in detecting and localizing the HFOs non-invasively (Engel and da Silva, 2012; Jacobs *et al.*, 2012).

Magnetoencephalography (MEG) non-invasively measures direct neuronal activity with a better spatial resolution than EEG (Baumgartner, 2004). As a result, HFO detection in MEG would provide us a better spatial extent of the epileptogenic zone, compared to EEG. Reliability of HFOs as a marker of the epileptogenic zone depends remarkably on the iEEG electrode coverage. However, to minimize the morbidity, iEEG electrodes are placed over the predefined/presumed epileptogenic regions, with limited spatial sampling. Compared to iEEG, MEG non-invasively records whole-brain activity and are readily available for many patients in the initial stages of evaluation for diagnosis. Therefore, MEG would be convenient and favourable to investigate this non-invasive biomarker. Although, there is recent evidence that epileptic gamma or ripples (HFOs) can be non-invasively detected and/or source localized with scalp EEG (Kobayashi *et al.*, 2010; Andrade-Valenca *et al.*,

2011; Melani *et al.*, 2013; Zelmann *et al.*, 2014; Pizzo *et al.*, 2016), MEG (van Klink *et al.*, 2016, 2017; von Ellenrieder *et al.*, 2016; Nissen *et al.*, 2016) or simultaneously with both MEG and EEG (Papadelis *et al.*, 2016) at a smaller scale. However, to the best of our knowledge, none of the non-invasive electrophysiological studies have addressed the clinical utility and efficacy of HFOs in localizing the epileptogenic tissue for surgery and further establish its association with clinical outcome (gold standard).

The primary goal of the present work is to investigate whether HFOs can be used clinically for accurate presurgical assessment and post-surgical outcome prediction, with the following objectives: (i) detect the short lasting HFOs on the cortical source time series; (ii) source localize the HFO (80–200 Hz) for delineating the presurgical epileptogenic zone; (iii) source localize the oscillatory activities across frequency spectrum [alpha (8–14 Hz), beta (14–30 Hz), low-gamma (30–54 Hz), high-gamma (54–80 Hz); to address the HFO efficacy; (iv) establish the relationship of detected and source localized oscillatory activities with the surgical resection; and (v) to validate the observations clinically with the post-surgical outcome.

Material and methods

Patient selection

Study epileptologists (V.J., S.S., and P.S.C.) evaluated the patients to obtain clinical information including seizure semiology, disease duration, and frequency. Patients were then prospectively recruited for MEG to delineate the epileptogenic area. Criteria for including the patients in this study were as follows: (i) patients with medically refractory epilepsy, i.e. who had at least one to two seizures/month in the past 2 years despite the use of two or more anti-epileptic drugs (AEDs); (ii) patients who underwent presurgical investigations including EEG, video-EEG, MRI and neuropsychological assessment; and (iii) only patients with frequent interictal epileptiform discharges (IEDs) at the rate of at least one per minute in scalp EEG or MEG and a focal lesion on MRI. Recruited patients eventually had resective surgery and were longitudinally followed-up to assess the clinical outcome, at least after 1 year. The current cohort of 52 patients included 25 patients with MTLE and 27 patients with FNE. Clinical data including patient age, gender, seizure semiology, frequency, duration, AEDs, the results of EEG, MEG and neuroimaging studies, the region of surgery and histopathological reports were recorded. The demographic details of the patients were: male 71.2%, right-handed 98.1%, and mean age at evaluation 22.94 ± 8.95 years (range: 10–43 years) (Table 1). The Institutional Review Board had approved the study. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Table 1 Clinical features of the cohort

Characteristic	Value
Age, years	22.94 ± 8.95
Gender proportion, *n* (%)	
Male	37 (71.2)
Female	15 (28.8)
History of febrile convulsions, *n* (%)	10 (19.2)
Family history of seizures, *n* (%)	4 (7.7)
History of secondary GTCS, *n* (%)	36 (69.2)
Handedness of the patient, *n* (%)	
Left	1 (1.9)
Right	51 (98.1)
Total duration of epilepsy, years	11.4 ± 7.73
Total frequency of seizures (per week)	8.87 ± 12
Consciousness sparing (per week)	0.74 ± 2.8
Consciousness impairing (per week)	7.94 ± 11.7
Secondary GTCS (per week)	0.196 ± 0.25
Number of anti-epileptic agents (current)	2.8 ± 0.81 (3)
Side of resection	
Left-sided surgery, *n* (%)	35 (67.3)
Right-sided surgery, *n* (%)	17 (32.7)
Ictal EEG findings, *n* (%)	
Well localized	34 (65.4)
Lateralized but:	
Not localized	13 (25)
Poorly lateralized	5 (9.6)
MRI focal and lesional, *n* (%)	52 (100)
PET, *n* (%)	
Yes	15 (28.8) all are abnormal
No	37 (71.2)
Post-surgical follow-up assessment, months (range) [median]	22.14 ±10 (12.17–45.7) [21.7]

Values are presented as percentage values or mean ± standard deviation. GTCS = generalized tonic-clonic seizure.

MRI and MEG data acquisition

Pre- and postoperative T_1-weighted structural MRI and epilepsy protocol MRI, were acquired using an 8-channel head coil in a 3 T MRI system (Siemens), with a vitamin E marker placed over the fiducials. MEG was recorded using a 306-channel MEG system (Elekta Neuromag® TRIUX) while lying in a comfortable supine position and with eyes closed. A day before MEG, patients were instructed to deprive themselves of sleep to augment the odds of IED detection. Fiducials and other anatomical boundaries were marked with 3D-Polhemus FASTRAK® digitizer, which supported the co-registration of structural and functional data. Patient's data were acquired at a sampling rate of 2000 Hz for 120-min duration, in a passband of DC-660 Hz. During MEG data acquisition, five head position indicator coils were placed on the scalp, which perpetually ascertained the relative head movements. Patients were briefed to keep their heads still and avoid

any movements including swallowing or chewing. MEG data segments with head movements more than 5 mm were rejected.

Identification and source reconstruction of interictal epileptic spikes

Raw MEG data were band-pass filtered in 1–70 Hz using a finite impulse response filter (FIR). After the rejection of segments with artefacts and drifts, non-propagated primary IEDs were marked. Each IED was marked at its peak (regarded as time point '0') (Fig. 1). It was ensured that no other events (spikes or artefacts) occurred during the period of ±1000 ms from the marked spike peak and this interval was defined as the IED epoch. For standard clinical interpretation, the spatial topography of each IED was examined at every time point from the early rising phase of the spike peak until peak (peri-spike period), to detect the stable and strong dipolar source without any rotation. Further source localization was carried out using an equivalent current dipole (ECD) model (Elekta source modelling software). For each patient, dipole sources only with goodness of fit >80% were considered for the final interpretation. Spike localization and MEG clinical reporting were carried out in accordance with standard ACMEGS guidelines (Bagić *et al.*, 2011).

Detection and imaging of the interictal epileptic oscillations in virtual sensors across the frequency spectrum

IED epochs of each patient were concatenated. Beamformer weights were calculated on the whole-data covariance. Such normalized beamformer weights were applied to reconstruct the source time series for all the locations in the cortex, regarded as virtual sensors (Hillebrand *et al.*, 2005). For each patient, 1459 virtual sensors were generated in the grey matter, excluding the cerebellum. Virtual sensor locations were then interpolated and parcellated using the Automated Anatomical Labeling atlas (AAL), for the purpose of labelling. Extracted source time series was filtered further in each frequency band. An HFO event was marked, if at least four oscillations were seen distinct from the background activity, lasting unto 100 ms, with at least 10 ms inter-event interval, in the frequency range of 80–200 Hz (Velmurugan *et al.*, 2018). HFO events (Bénar *et al.*, 2010) with an isolated spectral peak (island) in the time-frequency map (Burnos *et al.*, 2014) were selected, to circumvent filtering effects.

The raw MRI image was reoriented and translated, to fix the anterior commissure (AC) as the origin and aligned in the AC-PC plane using the SPM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) in MATLAB. Coarse and fine affine transformation followed by normalization was carried out by warping the patient-specific anatomy to MNI template anatomy. The forward model was constructed using a semi-realistic head model, where the whole brain is discretized into a regular 3D grid voxel of 10-mm resolution. Oscillatory activities co-occurring with IEDs for each patient were source localized at each frequency band using minimum variance adaptive beamformer (MVAB) (Sekihara *et al.*, 2001). This adaptive spatial filter is based on attenuating the source power at a specified location, subject to unit-gain constraint. Lead field matrix was then determined at each grid position. Subsequently, the cross-spectral density (CSD) matrix on a Fourier transformed data were calculated at five distinct frequency bands: (i) alpha band (α) 8–14 Hz; (ii) beta band (β) 14–30 Hz; (iii) low-gamma band (γ-L) 30–54 Hz; (iv) high-gamma band (γ-H) 55–80 Hz; and (v) ripple band or HFO band 80–200 Hz (with isolated spectral blob). On these, the spatial filter estimated the source generators of the oscillatory activities. Within a single patient, robust and reliable epileptic source activations were obtained at each cortical location with nonparametric t-statistics. Further, cluster-based randomization test using the Monte Carlo method was used for controlling multiple-comparisons (Oostenveld *et al.*, 2011).

Determining the epileptogenic zone for surgical intervention

From the patient's clinical information, a consensus was acheived during the presurgical meeting to define the presumed epileptogenic zone, by a team consisting of an epileptologist, a neuroradiologist, and a neurosurgeon. The clinical data comprised findings from clinical history, ictal and interictal EEG, MRI, PET-CT, and neuropsychological assessment. The presumed epileptogenic zone was unilateral in 49 patients, while bilateral in three patients, i.e. Patients S18 and S27 had bilateral hippocampal sclerosis (right > left side), and Patient S51 had bilateral occipital gliosis (left > right side). Eventually, all 52 patients were subjected to resective surgery, taking into account the information from presumed the epileptogenic zone. The epileptogenic zone determined the limit of resection so that the resected volume included it. For MTLE patients, anterior temporal lobectomy with resection of anterior mesial structures (amygdala and hippocampus) was performed. FNE patients had a focal resection of a discrete lesion involving peri-lesional parenchymal cortices. Intraoperative electrocorticography was carried out in most patients with FNE, to guide the extent of resection. Neuropathological observations of the surgical specimens were recorded. The post-surgical clinical outcome was evaluated periodically using the Engel classification system (Engel *et al.*, 1993). The Engel class I outcome (IA-ID) was regarded as a favourable or good surgical outcome whereas patients with Engel class II-IV were considered to have an unfavourable or poor surgical outcome.

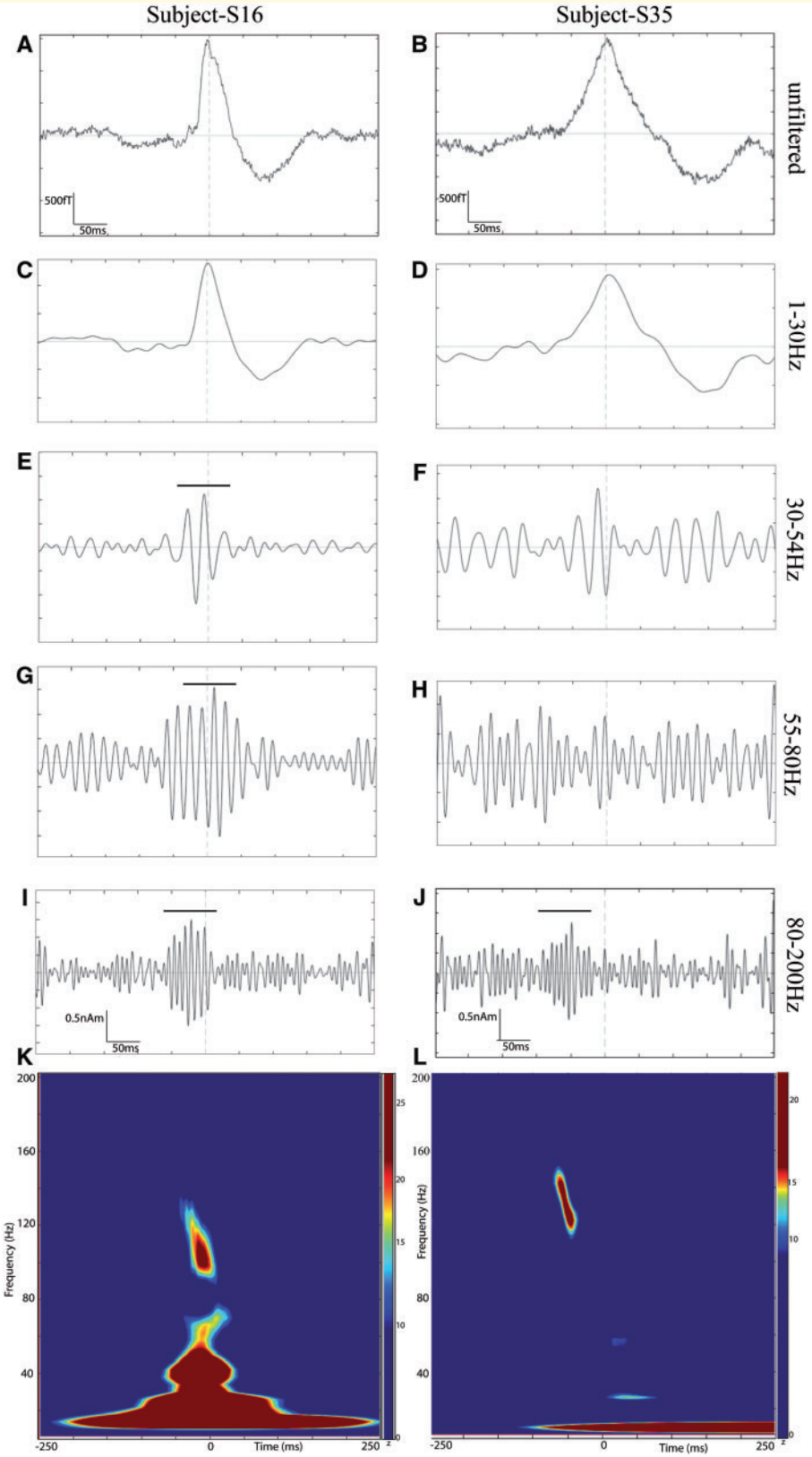

Figure 1 Detection of HFOs and other oscillatory activities in source time series. Epileptic spikes and co-occurring oscillatory activities (marked with a black overlay line) is demonstrated in Patient S16 with left temporal lobe focal cortical dysplasia (FCD) (**A**, **C**, **E**, **G**, **I** and **K**) and in Patient S35 with right frontal FCD (**B**, **D**, **F**, **H**, **J** and **L**). Beamformer weights were used to reconstruct the source time series throughout the cortex. A visual review of the virtual sensors in the left inferior temporal gyrus shows short lasting low-gamma, high-gamma and ripple oscillations (**E**, **G** and **I**). In Patient S35, only short lasting HFOs were observed in the right superior frontal gyrus virtual sensor (**J**). Detected HFOs have a corresponding isolated blob of spectral density in an 80–200 Hz frequency range on time-frequency map (**K** and **L**).

Congruence assessment and validation against clinical outcome

We assessed whether the localized areas of HFO or other frequency-specific oscillatory activities co-localized with the epileptogenic zone and, after surgically resection, if the patient achieved seizure freedom. Each frequency band's efficacy in pre-surgical localization and surgical resection was investigated by localizing frequency-specific oscillatory activities in the subject-specific pre- and post-operative MRIs. Postoperative MRIs aided us to locate the resected anatomical boundary. Concordance rates were determined by comparing the locations of each generated source results with the epileptogenic zone and resected cortex (Velmurugan *et al.*, 2018). This was established primarily at two levels as follows: (i) concordant category: when the sources were co-localizing with epileptogenic zone (or resected cortex) (Supplementary Fig. 1A) or together with an additional non-specific source (Supplementary Fig. 1B); and (ii) non-concordant category: when the sources were lateralizing to the pathologic hemisphere but different site than epileptogenic zone (or resected cortex) (Supplementary Fig. 1C) or contralateral to the epileptogenic zone (or resected cortex) hemisphere (Supplementary Fig. 1D). Congruency of the source localization outputs across the oscillatory spectrum was determined with reference modalities including ECD modelling, presumed epileptogenic zone, and the resected cortex. Further, the relationship between the patient's clinical outcome with the occurrence of HFOs (in virtual sensors) and the frequency-specific source localization outputs were evaluated. In addition, to understand the differences, we separately examined source localization of spikes in HFO bands that did not have a specific island of HFO activity in the 80–200 Hz range and calculated their concordance with the epileptogenic zone and relation to the surgical outcome.

Statistical analysis

Non-parametric methods of analysis, namely the Wilcoxon signed-rank test for paired comparisons, Mann-Whitney U-test for unpaired comparisons, and Kruskal-Wallis for multiple group comparisons were used. Logistic regression analysis was carried out with the clinical parameters and multi-frequency source reconstruction results, to investigate the predictors of surgical outcome. The strength of agreement between source localization outputs with each reference modality was quantified by kappa statistic. Sensitivity, positive predictive values (PPV) and accuracy (degree of proximity to the resection area) were calculated to assess the efficacy of each frequency-specific source generators in determining the outcome. Receiver operating characteristic (ROC) curves were calculated for each frequency-specific source reconstruction outputs to assess the post-surgical clinical outcome (ground truth or gold standard). Data were represented as mean ± standard deviation. The statistical level of significance was estimated at $P < 0.05$.

Data availability

If required, the clinical data used in the current paper can be made available upon reasonable request. However, because of the sensitive nature of patients' clinical information, the ethics protocol does not permit open data sharing.

Results

Cohort clinical characteristics

The clinical and demographic parameters are summarized in Tables 1 and 2. The current cohort included MTLE (n = 25) and FNE (n = 27) patients who had resective surgeries. Patients had the following pathologies: mesial temporal sclerosis in 22 (42.31%), tumour in 13 (25%), focal cortical dysplasia in nine (17.31%), gliotic changes in six (11.54%), and other pathologies in two (3.85%). Patients with FNE had a higher probability of presenting with early onset of the disease (U = 141; $P < 0.001$), developmental lesion (e.g. focal cortical dysplasia) (χ^2 = 17.74; $P < 0.001$), a higher frequency of focal impaired awareness seizures (U = 200; P = 0.01) and a higher frequency of secondary generalized tonic-clonic seizures (U = 177; $P < 0.001$) as compared to the patients with MTLE. The number of AEDs prescribed (U = 258.5; P = 0.12), epilepsy duration (U = 265; P = 0.18), family history of epilepsy (χ^2 = 2; P = 0.15), past febrile convulsions (χ^2 = 1.78; P = 0.18), did not correlate well with either type of epilepsy (MTLE or FNE). In our study, 1534 spikes with an average of 30.6 ± 14.9 (range = 6–67/patient) were reconstructed in source space, of which 598 spikes (39%) with an average of 11.5 ± 7.41 (range = 1–34/patient) were marked as having HFOs with an isolated spectral blob at 80–200 Hz (in source space). Postoperatively, the patient's outcome was assessed after a mean follow-up of 22.14 ± 10.05 months (range = 12.17–45.7 months), which were comparable across the outcome groups (U = 142; P = 0.56). Patients who were left-handed (χ^2 = 5.6; P = 0.01) or with a positive familial history (χ^2 = 25.8; $P < 0.001$) or higher frequency of focal impaired awareness seizures (U = 99.5; $P < 0.05$) tended to have poor surgical outcome. Although 22.2% of FNE and 8% of MTLE patients had poor surgical outcome, there were no statistical differences (χ^2 = 2; P = 0.15). The probability of achieving seizure freedom did not correlate with the frequency of focal aware seizures (U = 134.5; P = 0.32), or secondarily generalized seizures (U = 166; P = 0.865), the number of AEDs (U = 133; P = 0.32), epilepsy duration (U = 141.5; P = 0.79), the hemisphere of surgery (χ^2 = 0.09; P = 0.75) or length of the postoperative follow-up (U = 142; P = 0.51). However, the seizure freedom was negatively correlated with the focal impaired awareness seizures (β = −0.75; z = 4.9; P = 0.03; logistic regression).

Table 2 Clinical characteristics of the patients across surgical outcome

Clinical parameters	Good outcome (n = 44) Engel I (n = 43) Engel IB-ID (n = 1)	Poor outcome (n = 8) Engel II (n = 2) Engel III (n = 5) Engel IV (n = 1)	Test statistic
Age	23.53 ± 1.4	19.68 ± 1.9	P = 0.1
Gender			χ^2 = 1.23; P = 0.26
Female	14 (31.8)	1 (12.5)	
Male	30 (68.2)	7 (87.5)	
Handedness			χ^2 = 5.6; P = 0.01*
Right	44 (100)	7 (87.5)	
Left	-	1 (12.5)	
Febrile convulsion h/o			χ^2 = 2.25; P = 0.13
Yes	10 (22.7)	-	
No	34 (77.3)	8 (100)	
Family h/o seizures			χ^2 = 25.8; P < 0.001*
Yes	2 (4.5)	6 (75)	
No	42 (95.5)	2 (25)	
Secondary GTCS h/o			χ^2 = 1.48; P = 0.22
Yes	29 (65.9)	7 (87.5)	
No	15 (34.1)	1 (12.5)	
Frequency of SPS (per week)	0.81 ± 0.46	0.31 ± 0.19	P = 0.32
Frequency of CPS (per week)	6.5 ± 1.6	15.5 ± 4.8	P = 0.05*
Frequency of 2^0 GTCS (per week)	0.19 ± 0.03	0.2 ± 0.05	P = 0.86
Total frequency of seizure (per week)	7.6 ± 1.7	16 ± 4.9	P = 0.14
Seizure burden	77.5 ± 19.4	153.58 ± 62.7	P = 0.28
Number of AEDs	2.75 ± 0.11	3.1 ± 0.35	P = 0.33
Duration of epilepsy	11.5 ± 7.3	10.62 ± 1.16	P = 0.79
Side of surgery			χ^2 = 0.09; P = 0.75
Left	30 (68.2)	5 (62.5)	
Right	14 (31.8)	3 (37.5)	
Epilepsy group			χ^2 = 2; P = 0.15
MTLE	23 (52.3)	2 (25)	
FNE	21 (47.7)	6 (75)	
Histopathological findings			
Developmental	9 (20.5)	5 (62.5)	χ^2 = 6; P = 0.01*
Acquired	35 (79.5)	3 (37.5)	
Early	19 (43.5)	6 (75)	χ^2 = 2.745; P = 0.09
Late	25 (56.8)	2 (25)	
Post-surgical follow-up, months	22.53 ± 1.5 (12.7–45.7)	20.1 ± 3.4 (12.1–35.3)	P = 0.51

CPS = complex partial seizures; GTCS = generalized tonic-clonic seizures; h/o = history of; 2° = secondary; SPS = simple partial seizures.
Categorical and continuous variables are tested with χ^2 and t-test (or Mann-Whitney U-test), respectively.
*Statistically significant observations (P < 0.05) in the test statistic.

Source localization of the oscillatory activities

Co-occurrence of frequency-specific oscillations (including ripples) with epileptic spikes in the virtual sensors are illustrated in MTLE (Patient S16) and FNE (Patient S35) patients (Fig. 1). Beamformer generated virtual sensors and the source time series, to detect the 1–30 Hz, low-gamma, high-gamma and short lasting HFOs on the filtered data, with corresponding spectral changes (Fig. 1). Typical examples of source localization in MTLE and FNE patient are illustrated in Figs 2 and 3. Patients diagnosed with right hippocampal sclerosis (Patient S28) (Fig. 2A) and low-grade left frontal tumour (Patient S32) (Fig. 3A), underwent presurgical assessment, during which interictal spikes were source localized (Figs 2B and 3B). Spike-associated oscillatory activities across the spectrum were source localized to identify the abnormal epileptogenic tissue. Source localization of low-gamma, high-gamma, and HFO oscillatory activities appear to be spatially congruent with the resected cortex (Figs 2D–H and 3D–H). Subsequent to the epileptogenic zone resection (Figs 2C and 3C), patient's post-surgical outcome was assessed and found to be Engel class I.

These source generators were compared with the presumed epileptogenic zone and the resected cortex to

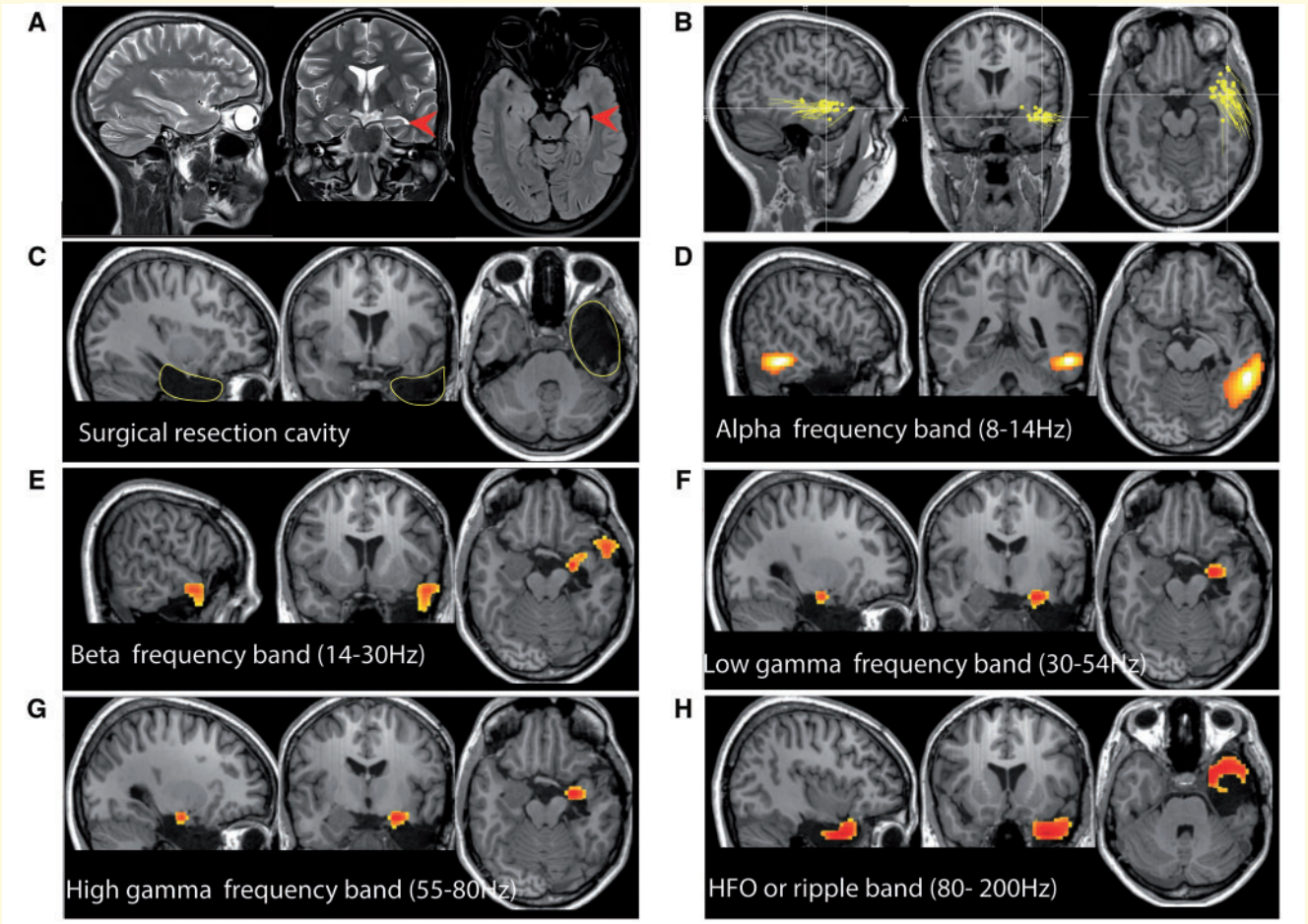

Figure 2 Source localization of oscillatory activities in a patient with mesial temporal lobe epilepsy. Data from a 19-year-old female patient (Patient S28) diagnosed with right hippocampal sclerosis, with epilepsy duration of 8 years is shown. (**A**) T_2-FLAIR MRI showing right hippocampal sclerosis (red arrow). (**B**) Right temporal clusters of dipoles obtained from the localization of a single time point in interictal spikes, (**C**) surgically resected area of the presumed epileptogenic zone (area within the yellow border), and (**D**–**H**) illustrates MEG source reporting on subject-specific normalized MRI images, at the following frequency bands as (**D**) alpha band (8–14 Hz), (**E**) beta band (14–30 Hz), (**F**) low-gamma band (30–54 Hz), (**G**) high-gamma band (54–80 Hz) and (**H**) HFO or ripple band (80–200 Hz). Statistical source localization map on the subject-specific MRI is thresholded to the maximum t-clusters for each frequency band.

determine the concordance rates and strength of agreement. Source localization of HFOs (with an isolated spectral blob) appears to have demonstrated a stronger concordance rate and agreement of 75.0% (k = 0.54 ± 0.12) with the presumed epileptogenic zone and 78.8% (k = 0.56 ± 0.1) with the resected cortex (Fig. 4). The concordance and agreement of source localized oscillatory activities with presumed epileptogenic zone were in the decreasing order as follows: HFO (75%), followed by low-gamma (65.6%), high-gamma (63.9%), alpha (63.9%) and beta (62.3%) frequency bands. Likewise, the decreasing order of concordance and agreement with resected cortex were for HFO band (78.8%) followed by alpha (61.5%), low-gamma (61.5%), high-gamma (59.6%) and beta (57.7%) frequency bands. In addition, the source localization of spikes without an isolated spectral blob (HFO) in the 80–200 Hz frequency band was performed. The concordance and agreement with presumed epileptogenic zone for spikes without HFOs (absence of island of HFO activity) was 58.82% (k = 0.28 ± 0.08), which is comparatively lower than the concordance rate of spikes with HFOs (presence of island of HFO activity) i.e. 75% (k = 0.54 ± 0.12).

Moreover, source localization results were compared with the current clinical standard, ECD model of interictal spikes. ECD concordance rate and agreement with the epileptogenic zone and the resected cortex seems to be lower than the HFO source localization (57.7% versus 75.0% and 59.0% versus 78.8%; $P < 0.001$). Yet, the rates are comparable and equivalent to the other frequency source localization ($P > 0.05$). The concordance rates were also examined in patients in the MTLE and FNE groups. In patients with MTLE, source localization of HFOs alone had higher odds of epileptogenic source identification that are concordant with the resected cortex (χ^2 = 4.84; P = 0.03) (Supplementary Fig. 2). However, in patients with FNE, source localization at any of the five frequency

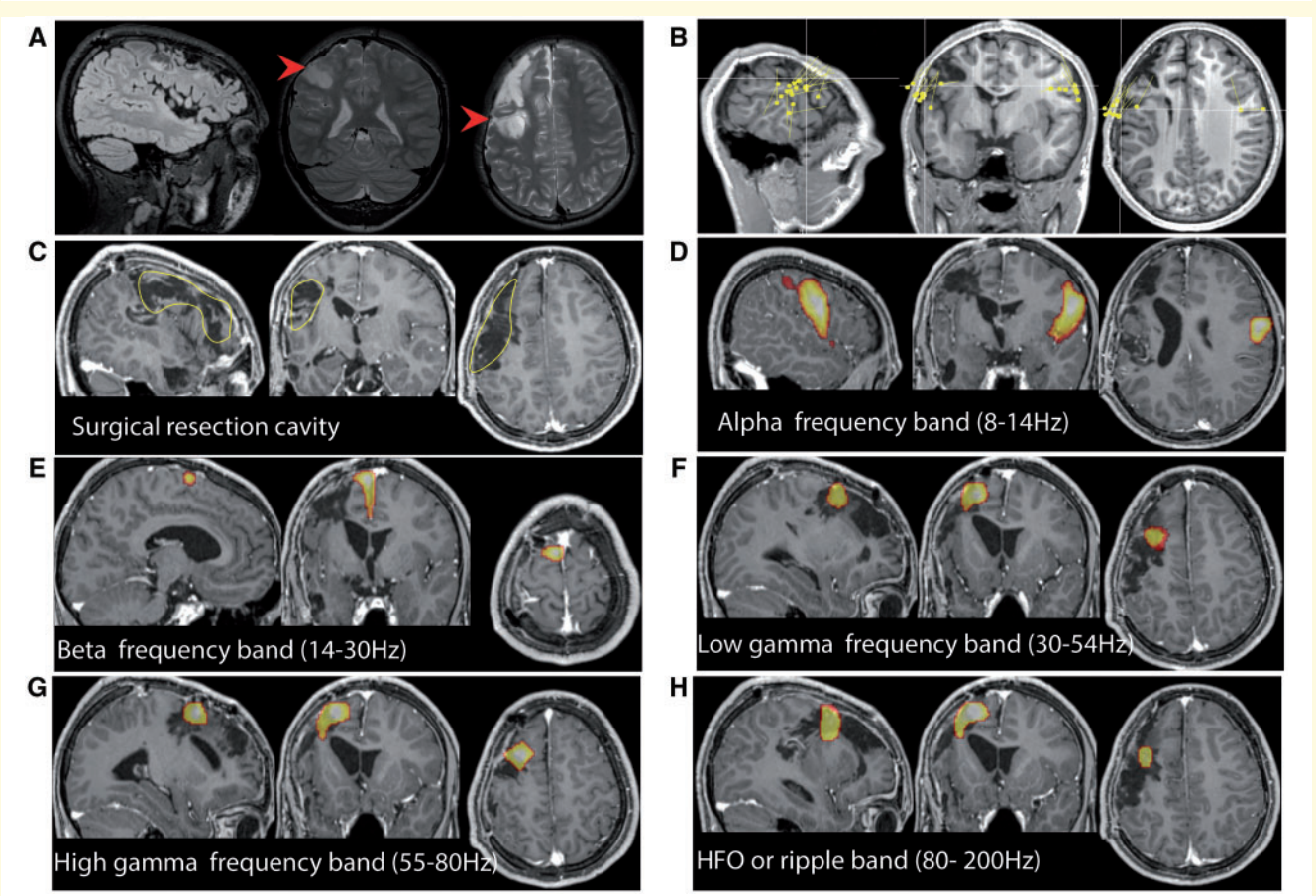

Figure 3 Source localization of oscillatory activities in a patient with focal neocortical epilepsy. Data from a male patient (Patient S32) aged 14 years with epilepsy duration of 7 years, diagnosed with left frontal lobe low-grade tumour shown on (**A**) T_2-FLAIR MRI (red arrow); (**B**) showing left frontal and temporal MEG dipoles obtained from single time point interictal spikes; (**C**) surgically resected area of the presumed epileptogenic zone (area within yellow border). Subsections (**D**–**H**) illustrate MEG source reporting on subject-specific normalized MRI images, at the following frequency bands as (**D**) alpha band (8–14 Hz), (**E**) beta band (14–30 Hz), (**F**) low-gamma band (30–54 Hz), (**G**) high-gamma band (54–80 Hz) and (**H**) HFO or ripple band (80–200 Hz).

bands had a chance of detecting the concordant epileptogenic sources, compared to the discordant sources ($P < 0.05$).

Relationship between sources of oscillatory activities and surgical outcome

The relationship of spatial congruency with the patient's surgical outcome was assessed (Figs 4 and 5). Patients attained favourable surgical outcome (Engel class IA-D) if HFO sources were spatially congruent with epileptogenic zone and then resected out. On the other hand, if HFO sources were discordant with the epileptogenic zone or resection area, patients tended to have an unfavourable post-surgical outcome ($\chi^2 = 5.22$; $P = 0.02$; $\phi = -0.317$). Moreover, spatial congruency at other frequency bands including spikes without an island of HFO activity in 80–200 Hz and interictal spike localization with standard ECD modelling did not correlate with surgical outcome ($P > 0.05$). Patient's surgical outcome was predicted from clinical parameters and frequency-specific concordance rates using logistic regression analysis. Patients had an odds ratio (OR) of 5.67 [95% confidence interval (CI) = 1.2–27.9; $P < 0.05$] and 82.4% probability of achieving a favourable surgical outcome, if HFO sources were spatially congruent with resected cortex when compared to the patients with HFO discordance. If HFO sources were discordant with the epileptogenic zone or resection area, the patient had an OR of 0.18 (95% CI = 0.036–0.87) and only 14.3% probability of achieving favourable surgical outcome. Patients with the highest frequency of focal impaired awareness seizures had the lowest likelihood of achieving the favourable surgical outcome (OR = 0.92; 95% CI = 0.87–0.99; $P < 0.05$).

Furthermore, to determine the clinical outcome, sensitivity, PPV, and accuracy for each frequency-specific source were computed. Subsequently, a ROC analysis was conducted (Fig. 5). HFO sources congruent with the resected

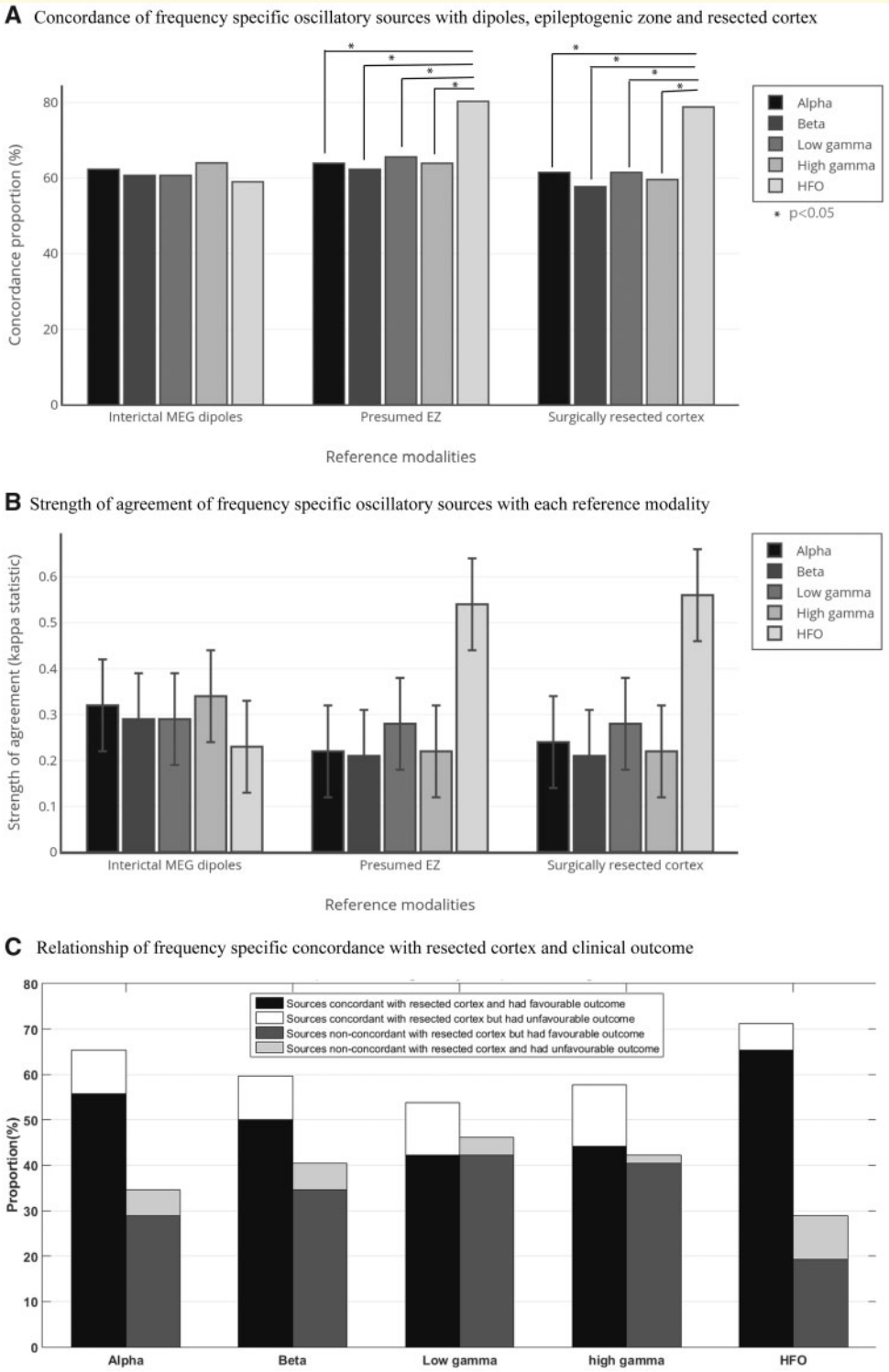

Figure 4 Congruency, the strength of agreement and association between frequency specific MEG sources with reference modalities and clinical outcome. (**A**) The concordance and (**B**) the strength of agreement (quantified by kappa statistic) of each frequency specific sources with the interictal MEG dipoles, presumed epileptogenic zone, and surgically resected cortex is illustrated with bar graph and standard error of the mean. The maximal concordance and strength of agreement were for HFO. (**C**) The association between concordance of each frequency specific sources and surgical outcome is demonstrated. The chances of achieving the favourable outcome (Engel class IA-D) with surgery was highest if the HFO sources were concordant with the surgically resected cortex.

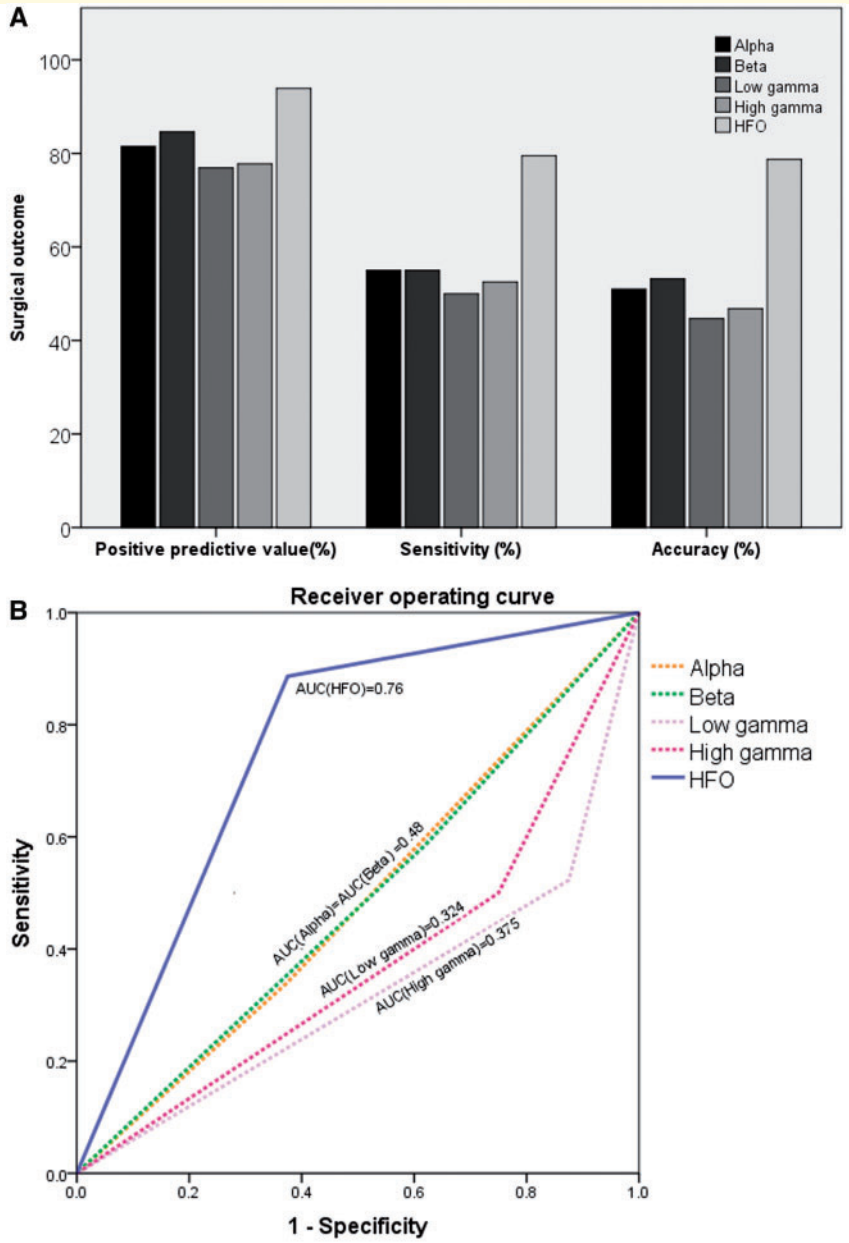

Figure 5 Assessment of each frequency specific sources in determining epileptogenic zone and post-surgical outcome. (**A**) Sensitivity, PPV, accuracy for each frequency band. (**B**) ROC analysis to determine the outcome. HFO source imaging has the best sensitivity (78%), PPV (100%) and accuracy (78.84%) in predicting the patients with favourable surgical outcome, compared to other frequency bands; ROC (receiver operating curve) analysis, shows that only HFO source concordance has the best sensitivity and specificity profile in determining the patient's surgical outcome with an area under the curve (AUC) = 0.76 (95% CI = 0.6–0.966; P = 0.02).

cortex, had the best sensitivity of 78%, PPV of 100% and an accuracy of 78.84% to predict the patient's surgical outcome, among all other frequency bands. In ROC analysis, sources of HFOs demonstrated the best sensitivity and specificity profile in determining the patient's surgical outcome with the AUC = 0.76 (95% CI = 0.6–0.966; P = 0.02), whereas other frequency bands indicates a poor predictive performance with poor sensitivity of below 55% and AUC was below 0.5 ($P > 0.05$).

Discussion

To the best of our knowledge, the present study is the first largest (n = 52) longitudinal study to comprehensively investigate the efficacy and clinical utility of HFOs for presurgical localization of the epileptogenic zone and prediction of surgical outcome. The current study showed the possibility of identification, source localization and clinical role of non-invasive HFOs in patients with medically

refractory epilepsy. Subsequently, the efficacy of HFO source imaging over other frequency band and their ability to predict surgical outcome was demonstrated. The principal findings in our study were as follows: (i) source generators of the oscillatory activities for each frequency band (alpha to HFO) were successfully identified in all patients (n = 52/52); (ii) HFO source localization outperformed over other frequency bands in the presurgical diagnosis of the epileptogenic zone and in delineating the cortex for resection, with a concordance rate of 75% and 78.8%, respectively; (iii) patients had 82.4% probability and OR 5.67 of favouring seizure freedom when they had a resection of spatially congruent HFO sources with the epileptogenic zone; and (iv) HFO source localization had the best sensitivity (78%) and specificity (100%) profile in predicting the surgical outcome in the present study.

Sources of HFO role in pre-surgical diagnosis and surgical resection

Previous EEG and MEG studies mostly detected HFOs in the time domain; however, the sources that generate these HFOs were not known. Systematic investigations are necessary to localize these HFOs in the brain using source localization techniques because scalp recorded HFOs represent the summation of spatially distinct and conglomerate focal sources (Zelmann *et al.*, 2014). There are a couple of MEG studies that source localized HFOs using wavelet-based inverse approach (Xiang *et al.*, 2010; Papadelis *et al.*, 2016; von Ellenrieder *et al.*, 2016). However, their observations are limited to the smaller cohort (two to eight patients with medically refractory epilepsy). The current study performed source localization of fast oscillations using beamformer, in a larger group of 52 patients with medically refractory epilepsy.

One of the most compelling findings is that the HFO source localization had the highest concordance and agreement rate of 75% (k = 0.54 ± 0.12) with the epileptogenic zone compared to source localization of oscillatory activities at other frequency bands. This concordance rates match with an earlier iEEG study (Andrade-Valença *et al.*, 2012), but higher than recently reported MEG concordance of 50% (n = 4/8) (von Ellenrieder *et al.*, 2016). These lower rates could be attributed to a smaller sample and type of epilepsies. HFO sources in our study had the highest accuracy of 78.84% (versus 59% for spikes) in delineating the epileptogenic cortex, which agreed with the surgical resection area. Our findings accord with the precision of previous iEEG study (76% versus 44% for spikes) (Andrade-Valença *et al.*, 2012), and scalp EEG studies (81% versus 43% for spikes) (Andrade-Valenca *et al.*, 2011; Melani *et al.*, 2013) for correspondence of ripples with the surgically resected region. Observations from our study suggest that HFOs can be source localized and might be used for presurgical assessment of the epileptogenic zone and in delineating the cortex for surgical resection.

Role of HFOs in predicting surgical outcome

Our patients achieved a favourable outcome when the resected cortex had a higher degree of ripples, compared to the non-resected cortex. This observation concurs with iEEG studies where ripple analysis was correlated with surgical outcome (Fujiwara *et al.*, 2012; van Klink *et al.*, 2014; van't Klooster *et al.*, 2015). Studies also show patients had an unfavourable outcome when all the HFO areas were not removed (Fedele *et al.*, 2017). Moderate concordance has been found with the location of MEG ripples in patients who have a better outcome (n = 4/5) and poor outcome (n = 2/3) (van Klink *et al.*, 2017). It is imperative to validate source localization results of the oscillatory activities. Although two MEG studies compared the HFO source localization, with the epileptogenic zone (n = 11) (von Ellenrieder *et al.*, 2016) and with iEEG (n = 1) (Papadelis *et al.*, 2016), they were unable to perform further validations. Furthermore, the robust approach of validation would be comparing HFO source localization with the post-surgical outcome. In our study, HFO source generators were validated with the patient's post-surgical outcome.

One of the significant observations in the current study was that patients demonstrating congruent HFO sources always tended to have a favourable surgical outcome with the probability of 82.4% (OR = 5.67). In conjunction, HFO source localization was able to predict the patient's post-surgical outcome, with 78% sensitivity and 79% accuracy (AUC = 0.76). It is also exciting to note that the patients with additional HFO sources that were not surgically resected, eventually had higher odds of seizure recurrence, i.e. unfavourable outcome. Hence, it might be speculated that patients with residual non-resected and non-concordant HFO sources, will probably attain a poor surgical outcome. This observation concurs with the findings from the intracranial EEG study wherein patients with residual fast ripples on electrocorticography after resection achieved unfavourable seizure outcome (van't Klooster *et al.*, 2015). Ultimately, these patients warrant subsequent repeat and careful presurgical evaluations. The HFO source generators appear to predict our patient's post-surgical outcome precisely.

Efficacy of HFO source localization in comparison to other oscillatory activity source generators

It is evident from the existing literature and the current study that fast oscillations localize the epileptogenic zone and predict the surgical outcome with high accuracy. Yet,

the performance of other frequency bands in epileptogenic zone localization and outcome prediction, and the efficacy of HFOs among other oscillatory sources are unknown.

Different frequencies specify different spatiotemporal scales of information for brain integration, and the number of oscillations determines how quickly the information can be propagated (Lopes da Silva *et al.*, 2003). Brain distinctly tries to maintain the equilibrium of dynamics, for instance, fast oscillations generated by fewer inhibitory interneurons, interact over a short latency, are appropriate for local integrations (Buzsáki and Draguhn, 2004). However, very slow oscillations encompass a multitude of neurons synchronizing over a vast spatial domain are necessary for distant integrations (Buzsáki and Draguhn, 2004). Studies usually examine oscillatory neuronal activities within a single frequency band. On the contrary, it might be complementary and can provide a better perspective if oscillations are studied in conjunction with more than one frequency band.

In our study, source localization of spikes co-occurring with alpha, beta, low-gamma, high-gamma, and HFOs was performed. Except for the HFO band, the concordance rate for other frequency bands was ~60% with the epileptogenic zone and resected cortex (Fig. 4). These rates agree approximately with the following published works: gamma source localizations are concordant with the epileptogenic zone (n = 5) (Rampp *et al.*, 2010) and also enabled to define the surgical locations (n = 5) (Lu *et al.*, 2014). Spike locked beta and gamma sources reported localizing the epileptogenic zone and resected cortex with 85% accuracy (Guggisberg *et al.*, 2008), whereas a concordance rate of 40% is observed in some studies (Jeong *et al.*, 2013; von Ellenrieder *et al.*, 2016). In another study, activities up to 910 Hz were reported to correlate with the epileptogenic zone (Xiang *et al.*, 2009). Although our results support and extend these findings, variable concordance rates with the epileptogenic zone are reported in these studies (ranging from 40% to 85%). This might be because the source reconstruction was performed over different sample size (range 3–30), age group, type of epilepsies and with different source reconstruction algorithms (maximum entropy of mean, synthetic aperture magnetometry, beamformer, and ECD). Therefore, the results indicate that there was a preponderance for an explicit frequency band dependence and specificity for sources of the oscillatory activities.

HFO source localization compared to the conventional equivalent current dipole model

In clinical analysis, ECD remains the most widely used method for analysis of interictal spikes on a single time point during the early phase of the spike peak (Knowlton *et al.*, 1997, 2006). The resultant dipoles were interpreted for concordance assessment with the epileptogenic zone and resected cortex. However, compared to the ECD model, source localization of HFO oscillatory activities with beamformer had the highest spatial congruence in this study (78.8% versus 59% concordance). This finding is consistent with recent MEG study source localizing 1–70 Hz activities (83% versus 70% concordance) (Pellegrino *et al.*, 2018) and with the observations from iEEG studies demonstrating the sensitivity for seizure onset zone identification (52% versus 33%) (Jacobs *et al.*, 2008). ECD modelling showed poor spatial congruence with epileptogenic zone and resected cortex and could not predict the surgical outcome. Together, the findings indicate that HFOs are more specific for epileptogenic zone and the resected cortex, compared to spikes, which is consistent with EEG and iEEG studies (Jacobs *et al.*, 2009). HFOs are described to be more specific for the seizure onset zone than spikes (Jiruska *et al.*, 2017), despite HFO co-occurrence with spikes for at least 80% of the time (Urrestarazu *et al.*, 2007). MTLE patients are weak candidates for ECD localization (Pataraia *et al.*, 2005). However, beamformer can model such distributed and deep generators (Sekihara *et al.*, 2001). For detecting the epileptogenic zone in the current cohort, HFO source localization with beamformer outperformed the ECD model and other frequency source imaging. This result is in line with the previous study, where wavelet based maximum entropy on the mean (wMEM) performed better than ECD in MTLE patients (Pellegrino *et al.*, 2018).

The significance of the current approach against conventional approach in detection and imaging of HFOs

Earlier, it was proposed that ripples could not be detected in MEG and EEG because of the smaller underlying generators (von Ellenrieder *et al.*, 2014). Though recent EEG studies are detecting the ripples at the channel level (von Ellenrieder *et al.*, 2012), MEG is still best suited to extend and complement the study of these ripples because of its high-density coverage and simple forward model computation. Source–space analysis would be more appropriate, predominantly when detecting transient subtle changes in alpha to high-frequency activities. Besides, such analysis permits us to directly compare the fast oscillations with the epileptic focus and surgical resection area. Usually, the monomorphic spikes with similar scalp topography are averaged to increase the signal-to-noise ratio in clinical analysis. Nevertheless, given the transient behaviour, low signal-to-noise ratio, low amplitude and non-phase locking nature of the fast oscillations, it is inappropriate to average them, plus weak localization accuracy has been reported with ECD models (Fujiwara *et al.*, 2012). Further, the ECD model may yield a misleading result if the epileptic spike has an extended source. This is because of the assumption that observed MEG field distribution is produced by a few point sources (Kobayashi *et al.*, 2005). Hence, to

localize this low amplitude activity with low signal-to-noise ratio such as gamma oscillations and HFOs, the ECD model may not be suitable (Sakuma *et al.*, 1999). Moreover, HFOs in the time domain is rarely investigated in MEG studies because of the background noise of the MEG signals, which attenuate fast oscillations (Vrba, 2002). Indeed, HFOs may be identified, by increasing the signal-to-noise ratio of the raw MEG signals. Furthermore, HFOs can be source localized on adopting an optimal source reconstruction algorithm.

The analysis in our study was broadly carried out in two stages. During the first stage, the MEG signal's signal-to-noise ratio was increased with beamformer to detect HFOs. Beamformer weights were computed on the data recorded from all MEG physical sensors. Beamformer acts as a spatial filter where their weights are used to reconstruct the neuronal activity at a particular source location by attenuating noise from other sources (Sekihara *et al.*, 2001) and each source position is considered as a virtual sensor (Hillebrand and Barnes, 2005). These virtual sensors are created either in the limited predefined regions (van Klink *et al.*, 2016) or throughout the whole brain (Migliorelli *et al.*, 2017; van Klink *et al.*, 2017). HFOs are detected in these virtual sensors mainly in the epileptogenic region or the irritative zone. However, in these studies, recognized ripple events are neither source localized nor validated with clinical outcome. In the current study, virtual sensors were generated throughout the cortex, for reconstructing whole-brain source time series and detecting HFOs and other oscillations.

In the second stage, beamformer algorithm source localized the oscillatory activities in five frequency bands, i.e. alpha, beta, low-gamma, high-gamma, and HFO. Recently, signal-to-noise ratio has been augmented in the spatial domain using advanced source reconstruction algorithms including beamformer (Sekihara *et al.*, 2001) and wMEM (von Ellenrieder *et al.*, 2016). HFOs source localization has been attempted previously using wMEM (Papadelis *et al.*, 2016; von Ellenrieder *et al.*, 2016). However, the current study preferred beamformer (MVAB) (Sekihara *et al.*, 2001) with a single optimal current orientation at a voxel because it enabled us to reconstruct whole-brain source time series as well as source localization. Further, these advanced methods allow statistical thresholding at a single subject level, as performed in the present study. For source reconstruction of non-phase locked or non-time locked oscillatory events, the beamformer algorithm would be better because of analysis on a wider time window (to include the complete event), compared to analysis over a single time point as in ECD (Vrba and Robinson, 2001). Besides beamformer analyses requires source stability over the time window of analyses. However, during ECD analysis the choice of narrower time windows allows for the earliest source prior to propagation but with reduced signal-to-noise ratio and sensitivity due to the fewer time samples used for reconstructions. Indeed, while source localization algorithms used in the study made use of spatiotemporal activity, traditional dipole fit methods usually focus either on single time points or a few time samples around the upward slope of the peak of an interictal spike. While this choice of time window for dipole fits allows for examination of the earliest source without potential contamination of propagation, it is highly sensitive to noise and overfitting for more complex source configurations. In our recent study, the current approach has been effectively used to localize the HFOs during seizure activity (Velmurugan *et al.*, 2018).

Overall, the following steps were used in this study to increase the signal-to-noise ratio in the temporo-spatial domain and enhance the likelihood of ripple detection and source localization: (i) to prevent the ringing effect, an FIR filter was used to band-pass filter the data; (ii) source time series were reconstructed from virtual sensors, which were placed throughout the cortex in contrary to few predetermined locations in previous work (van Klink *et al.*, 2016); (iii) to circumvent spurious HFO detection, HFO events were marked using visual review. Subsequently, HFOs were selected if they had an isolated spectral peak (Bénar *et al.*, 2010) (Velmurugan *et al.*, 2018); and (iv) These HFOs were source localized using beamformer with a regularization parameter of 15% for improvising the spatial accuracy (Robinson and Vrba, 1999).

Evidence for clinical utility of HFOs

Clinical utility of HFOs in pre-surgical assessment and surgical planning in patients with epilepsy is at a primitive stage of development because of potential challenges. One such challenge is the ability to non-invasively record and localize the HFOs; non-invasive localization of HFOs with MEG would potentially broaden the clinical utility of these biomarkers (Engel and da Silva, 2012). This is the first non-invasive study to detect the HFOs, localize them and clinically validate with the post-surgical outcome. The evidence presented thus far supports the fact that HFOs could widely be used in a clinical setting. In line with our study, if HFOs are recorded and localized non-invasively with MEG, one can precisely delineate the epileptogenic tissues for surgery and improve post-surgical outcome. The characteristics of HFOs that constitute the degree of epileptogenicity including amplitude, duration, and rates, were not quantified in our study. To understand the underlying mechanism and relationship between non-invasive and invasive HFOs, HFOs should be evaluated in simultaneous MEG-iEEG recordings. Current observations warrant further non-invasive prospective studies in a large cohort to demonstrate that HFOs can delineate the epileptogenic tissue and improve the clinical outcome further. To conclude, non-invasive identification and localization of HFOs with island of spectral blob in the 80–200 Hz band might

significantly improve the pre-surgical assessment, surgical resection and post-surgical outcome in patients with medically refractory epilepsies, thereby supplementing the HFOs role as a non-invasive biomarker for epilepsy. The current approach is feasible in a clinical setting and HFOs seems to have potential implication in the clinical utility.

Acknowledgements

The authors would like to thank Dr Veena and Dr Preetish for the critical review of the manuscript and Mrs Kiran Jyothi and Mr Prasanth for MEG acquisition.

Funding

This study was partially supported from the educational grants from TVS-NIMHANS bursary (TVSB/003/304/2015/00796) Fulbright-Nehru India doctoral research fellowship (2016-2017) (PS00219079), NIH grants (R01EB022717, R01DC013979, R01NS100440, R01AG062196), and University of California (UCOP-MRP-17-454755).

Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

References

Andrade-Valenca LP, Dubeau F, Mari F, Zelmann R, Gotman J. Interictal scalp fast oscillations as a marker of the seizure onset zone. Neurology 2011; 77: 524–31.

Andrade-Valença L, Mari F, Jacobs J, Zijlmans M, Olivier A, Gotman J, et al. Interictal high frequency oscillations (HFOs) in patients with focal epilepsy and normal MRI. Clin Neurophysiol 2012; 123: 100–5.

Bagić AI, Knowlton RC, Rose DF, Ebersole JS. American clinical magnetoencephalography society clinical practice guideline 3: MEG-EEG reporting. J Clin Neurophysiol 2011; 28: 362–3.

Baumgartner C. Controversies in clinical neurophysiology. MEG is superior to EEG in the localization of interictal epileptiform activity: Con. Clin Neurophysiol 2004; 115: 1010–20.

Bénar CG, Chauvière L, Bartolomei F, Wendling F. Pitfalls of high-pass filtering for detecting epileptic oscillations: a technical note on 'false' ripples. Clin Neurophysiol 2010; 121: 301–10.

Burnos S, Hilfiker P, Sürücü O, Scholkmann F, Krayenbühl N, Grunwald T, et al. Human intracranial high frequency oscillations (HFOs) detected by automatic time-frequency analysis. PLoS One 2014; 9: e94381.

Buzsáki G, Draguhn A. Neuronal oscillations in cortical networks. Science (80-) 2004; 304: 1926–9.

Cho JR, Joo EY, Koo DL, Hong SC, Hong SB. Clinical utility of interictal high-frequency oscillations recorded with subdural macroelectrodes in partial epilepsy. J Clin Neurol 2012; 8: 22–34.

Choi H, Sell RL, Lenert L, Muennig P, Goodman RR, Gilliam FG, et al. Epilepsy surgery for pharmacoresistant temporal lobe epilepsy. JAMA 2008; 300: 2497.

Elliott I, Kadis DS, Lach L, Olds J, McCleary L, Whiting S, et al. Quality of life in young adults who underwent resective surgery for epilepsy in childhood. Epilepsia 2012; 53: 1577–86.

Engel J, da Silva FL. High-frequency oscillations-where we are and where we need to go. Prog Neurobiol 2012; 98: 316–8.

Engel J, Van Ness PC, Resmussen TB et al. Outcome with respect to epileptic seizures. In Engel J Jr, editor. Surgical treatment of the epilepsies. New York; 1993. p. 609–21.

Englot DJ, Rolston JD, Wang DD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after temporal lobectomy in pediatric patients. J Neurosurg Pediatr 2013; 12: 134–41.

Fedele T, Burnos S, Boran E, Krayenbühl N, Hilfiker P, Grunwald T, et al. Resection of high frequency oscillations predicts seizure outcome in the individual patient. Sci Rep 2017; 7: 1–10.

Frauscher B, Bartolomei F, Kobayashi K, Cimbalnik J, van 't Klooster MA, Rampp S, et al. High-frequency oscillations: the state of clinical research. Epilepsia 2017; 58: 1316–29.

Fujiwara H, Greiner HM, Lee KH, Holland-Bouley KD, Seo JH, Arthur T, et al. Resection of ictal high-frequency oscillations leads to favorable surgical outcome in pediatric epilepsy. Epilepsia 2012; 53: 1607–17.

Guggisberg AG, Honma SM, Findlay AM, Dalal SS, Kirsch HE, Berger MS, et al. Mapping functional connectivity in patients with brain lesions. Ann Neurol 2008; 63: 193–203.

Haegelen C, Perucca P, Châtillon CE, Andrade-Valença L, Zelmann R, Jacobs J, et al. High-frequency oscillations, extent of surgical resection, and surgical outcome in drug-resistant focal epilepsy. Epilepsia 2013; 54: 848–57.

Hillebrand A, Barnes GR. Beamformer analysis of MEG data. Int Rev Neurobiol 2005; 68: 149–71.

Hillebrand A, Singh KD, Holliday IE, Furlong PL, Barnes GR. A new approach to neuroimaging with magnetoencephalography. Hum Brain Mapp 2005; 25: 199–211.

Jacobs J, LeVan P, Chander R, Hall J, Dubeau F, Gotman J. Interictal high-frequency oscillations (80-500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. Epilepsia 2008; 49: 1893–907.

Jacobs J, Levan P, Chtillon CD, Olivier A, Dubeau F, Gotman J. High frequency oscillations in intracranial EEGs mark epileptogenicity rather than lesion type. Brain 2009; 132: 1022–37.

Jacobs J, Staba R, Asano E, Otsubo H, Wu JY, Zijlmans M, et al. High-frequency oscillations (HFOs) in clinical epilepsy. Prog Neurobiol 2012; 98: 302–15.

Jacobs J, Wu JY, Perucca P, Zelmann R, Mader M, Dubeau F, et al. Removing high-frequency oscillations. Neurology 2018; 91: e1040–52.

Jacobs J, Zijlmans M, Zelmann R, Chatillon CÉ, Hall J, Olivier A, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol 2010; 67: 209–20.

Jeong W, Kim JS, Chung CK. Localization of MEG pathologic gamma oscillations in adult epilepsy patients with focal cortical dysplasia. NeuroImage Clin 2013; 3: 507–14.

Jiruska P, Alvarado-Rojas C, Schevon CA, Staba R, Stacey W, Wendling F, et al. Update on the mechanisms and roles of high-frequency oscillations in seizures and epileptic disorders. Epilepsia 2017; 58: 1330–9.

Kerber K, Dümpelmann M, Schelter B, Le Van P, Korinthenberg R, Schulze-Bonhage A, et al. Differentiation of specific ripple patterns helps to identify epileptogenic areas for surgical procedures. Clin Neurophysiol 2014; 125: 1339–45.

Knowlton RC, Elgavish R, Howell J, Blount J, Burneo JG, Faught E, et al. Magnetic source imaging versus intracranial

electroencephalogram in epilepsy surgery: a prospective study. Ann Neurol 2006; 59: 835–42.
Knowlton RC, Laxer KD, Aminoff MJ, Roberts TPL, Wong STC, Rowley HA. Magnetoencephalography in partial epilepsy: clinical yield and localization accuracy. Ann Neurol 1997; 42: 622–31.
Kobayashi K, Watanabe Y, Inoue T, Oka M, Yoshinaga H, Ohtsuka Y. Scalp-recorded high-frequency oscillations in childhood sleep-induced electrical status epilepticus. Epilepsia 2010; 51: 2190–4.
Kobayashi K, Yoshinaga H, Ohtsuka Y, Gotman J. Dipole modeling of epileptic spikes can be accurate or misleading. Epilepsia 2005; 46: 397–408.
Lopes da Silva F, Blanes W, Kalitzin SN, Parra J, Suffczynski P, Velis DN. Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. Epilepsia 2003; 44 Suppl 1: 72–83.
Lüders HO, Najm I, Nair D, Widdess-Walsh P, Bingman W. The epileptogenic zone: general principles. Epileptic Disord 2006; 8: 1–9.
Lu Y, Worrell GA, Zhang HC, Yang L, Brinkmann B, Nelson C, et al. Noninvasive imaging of the high frequency brain activity in focal epilepsy patients. IEEE Trans Biomed Eng 2014; 61: 1660–7.
Melani F, Zelmann R, Dubeau F, Gotman J. Occurrence of scalp-fast oscillations among patients with different spiking rate and their role as epileptogenicity marker. Epilepsy Res 2013; 106: 345–56.
Migliorelli C, Alonso JF, Romero S, Nowak R, Russi A, Mañanas MA. Automated detection of epileptic ripples in MEG using beamformer-based virtual sensors. J Neural Eng 2017; 14: 046013.
Nissen IA, van Klink NEC, Zijlmans M, Stam CJ, Hillebrand A. Brain areas with epileptic high frequency oscillations are functionally isolated in MEG virtual electrode networks. Clin Neurophysiol 2016; 127: 2581–91.
Oostenveld R, Fries P, Maris E, Schoffelen J-M, Oostenveld R, Fries P, et al. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Comput Intell Neurosci 2011; 2011: e156869.
Papadelis C, Tamilia E, Stufflebeam S, Grant PE, Madsen JR, Pearl PL, et al. Interictal high frequency oscillations detected with simultaneous magnetoencephalography and electroencephalography as biomarker of pediatric epilepsy. J Vis Exp 2016; 118: e54883.
Pataraia E, Lindinger G, Deecke L, Mayer D, Baumgartner C. Combined MEG/EEG analysis of the interictal spike complex in mesial temporal lobe epilepsy. Neuroimage 2005; 24: 607–14.
Pellegrino G, Hedrich T, Chowdhury RA, Hall JA, Dubeau F, Lina JM, et al. Clinical yield of magnetoencephalography distributed source imaging in epilepsy: A comparison with equivalent current dipole method. Hum Brain Mapp 2018; 39: 218–31.
Pizzo F, Frauscher B, Ferrari-Marinho T, Amiri M, Dubeau F, Gotman J. Detectability of Fast Ripples (>250 Hz) on the Scalp EEG: a proof-of-principle study with subdermal electrodes. Brain Topogr 2016; 29: 358–67.
Rampp S, Kaltenhäuser M, Weigel D, Buchfelder M, Blümcke I, Dörfler A, et al. MEG correlates of epileptic high gamma oscillations in invasive EEG. Epilepsia 2010; 51: 1638–42.
Robinson SE, Vrba J. Functional neuroimaging by synthetic aperture magnetometry. Recent Adv Biomagn 1999: 302–5.
Sakuma K, Sekihara K, Hashimoto I. Neural source estimation from a time-frequency component of somatic evoked high-frequency magnetic oscillations to posterior tibial nerve stimulation. Clin Neurophysiol 1999; 110: 1585–8.
Salanova V, Markand O, Worth R. Temporal lobe epilepsy: analysis of patients with dual pathology. Acta Neurol Scand 2004; 109: 126–31.
Schevon CA, Trevelyan AJ, Schroeder CE, Goodman RR, McKhann G, Emerson RG. Spatial characterization of interictal high frequency oscillations in epileptic neocortex. Brain 2009; 132: 3047–59.
Sekihara K, Nagarajan S, Poeppel D, Miyashita Y. Reconstructing spatio-temporal activities of neural sources from magnetoencephalographic data using a vector beamformer. 2001 IEEE International Conference on Acoustic, Speech, Signal Processing Proceedings (Cat. No.01CH37221) 2001; 3: 2021–4.
Urrestarazu E, Chander R, Dubeau F, Gotman J. Interictal high-frequency oscillations (10-500 Hz) in the intracerebral EEG of epileptic patients. Brain 2007; 130: 2354–66.
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 2016; 127: 197–208.
van Klink N, van Rosmalen F, Nenonen J, Burnos S, Helle L, Taulu S, et al. Automatic detection and visualisation of MEG ripple oscillations in epilepsy. NeuroImage Clin 2017; 15: 689–701.
van Klink NEC, Van't Klooster MA, Zelmann R, Leijten FSS, Ferrier CH, Braun KPJ, et al. High frequency oscillations in intra-operative electrocorticography before and after epilepsy surgery. Clin Neurophysiol 2014; 125: 2212–9.
van't Klooster MA, Van Klink NEC, Leijten FSS, Zelmann R, Gebbink TA, Gosselaar PH, et al. Residual fast ripples in the intraoperative corticogram predict epilepsy surgery outcome. Neurology 2015; 85: 120–8.
Velmurugan J, Nagarajan SS, Mariyappa N, Ravi SG, Thennarasu K, Mundlamuri RC, et al. Magnetoencephalographic imaging of ictal high-frequency oscillations (80-200 Hz) in pharmacologically resistant focal epilepsy. Epilepsia 2018; 59: 190–202.
von Ellenrieder N, Andrade-Valença LP, Dubeau F, Gotman J. Automatic detection of fast oscillations (40-200Hz) in scalp EEG recordings. Clin Neurophysiol 2012; 123: 670–80.
von Ellenrieder N, Beltrachini L, Perucca P, Gotman J. Size of cortical generators of epileptic interictal events and visibility on scalp EEG. Neuroimage 2014; 94: 47–54.
von Ellenrieder N, Pellegrino G, Hedrich T, Gotman J, Lina JM, Grova C, et al. Detection and magnetic source imaging of fast oscillations (40–160 Hz) recorded with magnetoencephalography in focal epilepsy patients. Brain Topogr 2016; 29: 218–31.
Vrba J. Magnetoencephalography: the art of finding a needle in a haystack. Physica C 2002; 368: 1–9.
Vrba J, Robinson SE. Signal processing in magnetoencephalography. Methods 2001; 25: 249–71.
Wang S, So NK, Jin B, Wang IZ, Bulacio JC, Enatsu R, et al. Interictal ripples nested in epileptiform discharge help to identify the epileptogenic zone in neocortical epilepsy. Clin Neurophysiol 2017; 128: 945–51.
Worrell GA, Gardner AB, Stead SM, Hu S, Goerss S, Cascino GJ, et al. High-frequency oscillations in human temporal lobe: Simultaneous microwire and clinical macroelectrode recordings. Brain 2008; 131: 928–37.
Xiang J, Liu Y, Wang Y, Kotecha R, Kirtman EG, Chen Y, et al. Neuromagnetic correlates of developmental changes in endogenous high-frequency brain oscillations in children: a wavelet-based beamformer study. Brain Res 2009; 1274: 28–39.
Xiang J, Wang Y, Chen Y, Liu Y, Kotecha R, Huo X, et al. Noninvasive localization of epileptogenic zones with ictal high-frequency neuromagnetic signals. J Neurosurg Pediatr 2010; 5: 113–22.
Zelmann R, Lina JM, Schulze-Bonhage A, Gotman J, Jacobs J. Scalp EEG is not a blur: it can see high frequency oscillations although their generators are small. Brain Topogr 2014; 27: 683–704.
Zijlmans M, Jacobs J, Kahn YU, Zelmann R, Dubeau F, Gotman J. Ictal and interictal high frequency oscillations in patients with focal epilepsy. Clin Neurophysiol 2011; 122: 664–71.
Zijlmans M, Jacobs J, Zelmann R, Debeau F, Gotman J. High-frequency oscillations mirror disease activity in patients with epilepsy. Neurology 2009; 72: 979–86.