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Detection of pathological high-frequency oscillations in refractory epilepsy patients undergoing simultaneous stereo-electroencephalography and magnetoencephalography

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ABSTRACT

Background: Stereo-electroencephalography (SEEG) and magnetoencephalography (MEG) have generally been used independently as part of the pre-surgical evaluation of drug-resistant epilepsy (DRE) patients. However, the possibility of simultaneously employing these recording techniques to determine whether MEG has the potential of offering the same information as SEEG less invasively, or whether it could offer a greater spatial indication of the epileptogenic zone (EZ) to aid surgical planning, has not been previously evaluated.
Methods: Data from 24 paediatric and adult DRE patients, undergoing simultaneous SEEG and MEG as part of their pre-surgical evaluation, was analysed employing manual and automated high-frequency oscillations (HFOs) detection, and spectral and source localisation analyses.
Results: Twelve patients (50%) were included in the analysis (4 males; mean age=25.08 years) and showed interictal SEEG and MEG HFOs. HFOs detection was concordant between the two recording modalities, but SEEG displayed higher ability of differentiating between deep and superficial epileptogenic sources. Automated HFO detector in MEG recordings was validated against the manual MEG detection method. Spectral analysis revealed that SEEG and MEG detect distinct epileptic events. The EZ was well correlated with the simultaneously recorded data in 50% patients, while 25% patients displayed poor correlation or discordance.
Conclusion: MEG recordings can detect HFOs, and simultaneous use of SEEG and MEG HFO identification facilitates EZ localisation during the presurgical planning stage for DRE patients. Further studies are necessary to validate these findings and support the translation of automated HFO detectors into routine clinical practice.

1. Introduction

1.1. Introduction to refractory focal epilepsy

Epilepsy affects approximately 0.5–1% of the global population, representing a major cause of comorbidities, stigmatisation, cognitive decline, poor quality of life, and death [1]. Refractory focal epilepsy is a devastating disease, and despite developments in antiepileptic drugs (AEDs) a third of patients continue to develop drug-resistance [2]. One alternative treatment approach for drug-resistant epilepsy (DRE) patients is surgical removal of the epileptogenic zone (EZ), allowing approximately 40% of patients to achieve seizure remission [3,4]. The EZ is defined as the cortical area necessary and sufficient for seizure initiation, whose resection leads to complete elimination of epileptic activity postoperatively [5].

The accurate delineation of the EZ proved technically challenging given the lack of suitable diagnostic methods. As part of presurgical evaluations, aimed at planning the resection while minimising post-operative neurological deficits, data from investigative methods such as electroencephalography (EEG), magnetoencephalography (MEG) and

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magnetic resonance imaging (MRI) are integrated to obtain a potential indication of the EZ. While these techniques are informative, their ability to provide a conclusive biomarker, either structural or functional, for EZ localisation has not been described [6].

1.2. High-Frequency oscillations – characterisation

HFOs are the most common type of high frequency oscillatory activity, having a frequency of over 80 Hz [7]. In the absence of a precise definition, HFOs have been described as spontaneous events comprising of at least four oscillations distinguishable from the background signal (Supplemental material, Figure S1) [8]. Identified both ictally and interictally, they can be subdivided into ripples (80–250 Hz), fast-ripples (250–500 Hz) and very fast ripples (>500 Hz) [9,10].

In healthy individuals, high-frequency oscillations (HFOs) occurring in the mesiotemporal region have been demonstrated to be involved in memory formation and retrieval [11–13]. In epilepsy patients, the presence of HFOs could be correlated with the epileptogenesis-related network reorganisation processes and have been regarded as an epileptogenicity biomarker [14–16].

The pathological nature of HFOs is thought to represent co-firing of abnormally interconnected groups of neurons [17,18]. It has been theorised that these fast ripples are related to of out-of-phase firing of various neuronal populations because of structural, functional, and molecular alterations in neural tissue [19,20].

Multiple overlapping, pathogenic zones have been described in relation to epileptic brains (Supplemental material, Figure S2). Seizure onset zone (SOZ) resection was correlated with postoperative seizure freedom [21–23]. However, despite the SOZ currently representing the gold-standard method for delineating the EZ, unfavourable postoperative outcomes in 40–50% of patients demand for the identification of more informative biomarkers [24,25].

Research on electrophysiological biomarkers resulted in the discovery of HFOs and their spatial association with the SOZ [26]. Multiple lines of evidence demonstrated that HFOs reliably indicate SOZ boundaries with higher specificity compared to interictal EEG spikes [27,28]. This suggests that interictal HFOs reflect the epileptogenic potential of particular groups of neurons [29]. Moreover, surgical resection of regions exhibiting high rates of HFOs resulted in seizure freedom [30,31], while failure to remove these areas was associated with poor postoperative outcomes [32]. Nonetheless, the biomarker potential of HFOs has been refuted by a study employing SEEG in a group of 30 DRE patients, revealing poor correlation between HFOs detection and EZ localisation [33].

1.3. Magnetoencephalography – an introduction

MEG has been increasingly used in the pre-surgical evaluation of DRE patients and recently emerged as a great tool for HFO analysis given its increased spatio-temporal resolution over scalp EEG [34]. The capacity to extracranially detect small cerebral magnetic fields confers MEG millimetric accuracy in localising the source of activity, allowing it to delineate the irritative zone in epilepsy patients (Supplemental material, Figure S2) [35].

Historically, MEG was used to investigate the spectral characteristics of gamma oscillations (50–120 Hz) in epileptic patients [36]. In a study of six patients undergoing preoperative MEG and intracranial EEG (iEEG), the gamma oscillations identified using MEG corresponded to those recorded with iEEG and were strongly associated with the SOZ [37]. More recently, MEG was used to non-invasively detect HFOs in a cohort of 11 patients having undergone iEEG, and the results confirmed concordance between the MEG- and iEEG-identified HFOs in the resected area [34].

Additionally, HFOs detected on ictal MEG data in 67 DRE patients are 95% indicative of the epileptogenic lesion, distinctively overlapping with the presumed EZ identified by alternative techniques [38]. Thus, MEG usage for HFOs localisation early in diagnosis, its availability to a broader patient group, and its relative insensitivity to noise [39] support the clinical utility of HFOs as epilepsy biomarkers [40], identifying surgical candidates earlier and improving postoperative outcomes by accurate EZ delineation.

1.4. Stereotaxic encephalography – an introduction

Stereo-electroencephalography (SEEG) involves stereotactic implantation of intracerebral electrodes, allowing measurements of electrophysiological neuronal activity both cortically and subcortically [41]. SEEG was extensively employed in establishing surgical candidacy and preoperatively defining the EZ in DRE patients, given its high signal-to-noise ratio, increased spatial specificity, and decreased predisposition to artifacts [42]. Invasive placement of multiple electrodes results in accurate detection of electrical activity in adjacent brain areas, but with poor spatial sampling [43]. The identification of the EZ purely by SEEG is, therefore, problematic, given difficulties in ascertaining whether the EZ and the epileptiform activity co-localise or if the EZ lies in the proximity of recorded regions.

The first case of iEEG monitoring for epilepsy surgical treatment was described in 1939 by Penfield at Monreal Neurological Institute in a 32-year-old patient with left temporal lobe meningocerebral scarring [44]. This allowed resection area delineation and speech eloquent cortex preservation, without seizure improvement. Recently, single-centre retrospective study of 46 DRE patients demonstrated 92% accuracy for EZ localisation by SEEG [45]. SEEG has major advantages in comparison with scalp EEG, namely increased temporal resolution, the larger frequency range detected, and the absence of signal attenuation by surrounding non-neural tissue [40,46].

1.5. Relevance of the study

Precise localisation of the EZ in DRE patients is crucial in ensuring safe tissue resection, while avoiding undesired postoperative neurological complications. The efficacy of electrophysiological recording techniques has been previously evaluated to establish their best use in preoperative assessment. Previous comparisons between non-concurrent MEG and SEEG recordings demonstrated that if epileptiform activity identification is concordant, there is a higher likelihood of postoperative seizure freedom [47,48].

A systematic review indicated that evidence supporting the use of HFOs in clinical practice and decision making for epilepsy surgery is limited by the low prevalence of invasive HFO-identification recordings, and by the small number of studies reporting SEEG or MEG use for HFO detection [49]. These are attributable to the highly-restricted patient cohort in which these techniques are justifiable [34], and to the ethical challenges of conducting electrographic monitoring in humans [43].

Building upon previously established work proposing the potential usefulness of HFOs as biomarkers for EZ localisation, this study hypothesized the following:

1. MEG is capable of accurately detecting HFOs.
2. The presence of HFOs accurately indicates the EZ and surgical resection of their source region correlates with postoperative outcomes in DRE patients.

In investigating these hypotheses, this work aimed to:

1. Evaluate the accuracy of MEG HFO detection through comparison of acquired patient data against the current gold standard technique – SEEG.
2. Objectively assess the correlation between HFOs and EZ location and postoperative outcome through spectral analysis involving the comparison of SEEG and MEG HFOs frequencies, and through source analysis integrating SEEG and MEG data to estimate EZ position.

The novelty of this project relates to the simultaneous use of invasive SEEG and non-invasive MEG recordings in a relatively large cohort of patients, to determine the accuracy of SEEG- and MEG-detected HFOs in localising pathological epileptiform activity, which has not been previously addressed in the currently available scientific literature.

2. Methods

2.1. Patient demographics

A single-centre retrospective study of 24 paediatric and adult DRE patients having preoperatively undergone simultaneous interictal SEEG and MEG recordings between January 2017 and December 2019 was conducted. Anonymised SEEG and MEG data and clinical characteristics were obtained from collaborators at Shanghai Jiao Tong University School of Medicine, and retrospectively analysed. The patient clinical characteristics include age at surgery, gender, MRI scan pathology, type of epilepsy surgery, number of implanted SEEG electrodes and associated contacts, duration of SEEG and MEG recordings, and postoperative Engel outcomes.

Included patients were older than 6 years of age, had a confirmed DRE diagnosis and were scheduled to undergo simultaneous SEEG and MEG prior to epilepsy surgery. Patients were excluded if they displayed insufficient or non-significant SEEG or MEG data, or if their SEEG activity was identified as being entirely artefactual upon visual inspection. Additionally, patients with more than 8 implanted electrodes were excluded, considering the spatial constraints imposed by the simultaneous use of the MEG helmet. Postoperative outcome has been recorded at 1 year follow-up. The study obtained ethical approval from Shanghai University Hospital.

2.2. SEEG and MEG manual analysis

2.2.1. SEEG data acquisition and manual processing

SEEG recording data was acquired from all 24 patients. The implantation site and number of required intracranial electrodes (SDE-08: S8, S16, Beijing Sinovation Medical Technology CO., LTD, Beijing, China) were established on an individual case basis according to the position of the presumed epileptogenic focus identified during the preoperative assessment. Electrodes number ranged from 3 to 8 and contacts number ranged from 8 to 16 per individual electrode, with a total maximum of 64 contacts per patient.

SEEG analysis was conducted in Brain Electrical Source Analysis software (BESA GmbH, version 5.2, Germany, https://www.besa.de/, last accessed 20th June 2022) (Figure A3, Appendix). HFOs were bandpass-filtered at a frequency of 80–250 Hz, a gain of 20 μV and 4.0 s. The duration of the simultaneous recordings ranged from 3 to 12 min. Each dataset of intracranial SEEG recordings was visually inspected by two independent observers, and interictal epileptic spikes were manually marked. This remains the accepted gold standard method for HFO identification [50]. The number of HFOs and the electrode contacts of origin for each patient were recorded on Microsoft Excel (Microsoft Excel, 2010) (Table A5, Appendix).

2.2.2. MEG data acquisition and manual processing

MEG recording was performed using a 306-channel, whole-head VectorView MEG system (Elektra Oy, Helsinki, Finland). MEG recording data was analysed in a blinded fashion, without prior knowledge of the corresponding neuroanatomical location of MEG channels and without access to clinical information. The raw MEG data was bandpass-filtered, using BESA, in the ripple-band frequency range of 80–250 Hz, a gain of 150–300 fT and 6.0 s. Data was subsequently systematically screened through all channels around the specific timepoints corresponding to previously identified SEEG HFOs. MEG HFOs have been defined and visually identified as displaying a marked change in amplitude compared to background activity. The number of MEG HFOs and the identity of individual MEG channels associated with the presence of HFOs for each patient were recorded on Microsoft Excel (Microsoft Excel, 2010) (Table A5, Appendix).

2.3. HFOApp automated analysis

2.3.1. HFOApp detector

Considering the low reliability of manual HFO detection [8], coupled with the time-consuming and impractical nature of visually analysing 306 MEG channels for multiple patients, an automated HFO detector was employed. HFOApp is a MATLAB toolbox which allows automated, simultaneous detection and manual validation of SEEG HFOs (Figure A2, Appendix). The toolbox was adapted, by incorporating a 306-channel montage and by changing the filter setting and gain, to permit HFO detection from MEG recordings. The Hilbert Detector was used to allow fully automated detection of ripples, allowing data bandpass-filtering into high-frequency bands (80–250 Hz) characterising HFOs [51]. Automated notch filtering, followed by visual inspection, was employed to eliminate the 50–60 Hz artefactual activity and potential muscle activity signals contaminating the recordings. The automatically-detected HFOs were manually validated by an independent observer, blinded to clinical patient data, and events representing movement artifacts were excluded.

2.3.2. SEEG and MEG montages

The SEEG data was analysed using a bipolar montage which is routinely used in interpreting intracranial EEG recordings, because it provides localised information on the spatial source of electrical fields, minimising unwanted background noise [52]. A monopolar montage, in which electrode signals are determined according to a referential point, was employed in analysing MEG recordings. The number of HFOs and the number of electrodes and channels were determined and recorded for SEEG and MEG data for each patient (Table A4, Appendix).

2.3.3. Validation of MEG automated HFO detector

To determine the sensitivity of MEG to HFO detection, a statistical comparison was performed between the total number of channels displaying HFOs and of significant MEG channels, defined as any MEG channel in which 5 of more events were automatically detected. MEG channels displaying less than 5 events were regarded as non-significant, revealing background noise.

2.4. Data processing

Data processing prior to patient inclusion in statistical analyses was conducted in two phases. Phase I involved manual SEEG and MEG data analysis and phase II involved automated SEEG and MEG data analysis. Patients have been excluded at multiple stages, according to the criteria displayed in Fig. 1.

Qualitative analysis was employed in establishing the concordance between HFOs in the three most active electrodes and channels, and the EZ, defined by clinicians based on information provided by preoperative MRI scans. The EZ was subsequently related to the resection area and to postoperative outcomes, and a similar concordance analysis was conducted. The top 3 SEEG electrodes and the top 3 MEG channels, defined as containing the highest number of HFOs, for individual patients were identified and employed in the analysis to minimise inter-subject variability.

Following automated detection of HFOs in the top 3 SEEG electrodes and MEG channels, the ability of these recording techniques to identify HFOs was assessed through comparison of HFO rates. HFO rate was defined as the percentage value representing the number of HFOs detected in a particular SEEG electrode or MEG channel divided by the total number of detected HFOs.

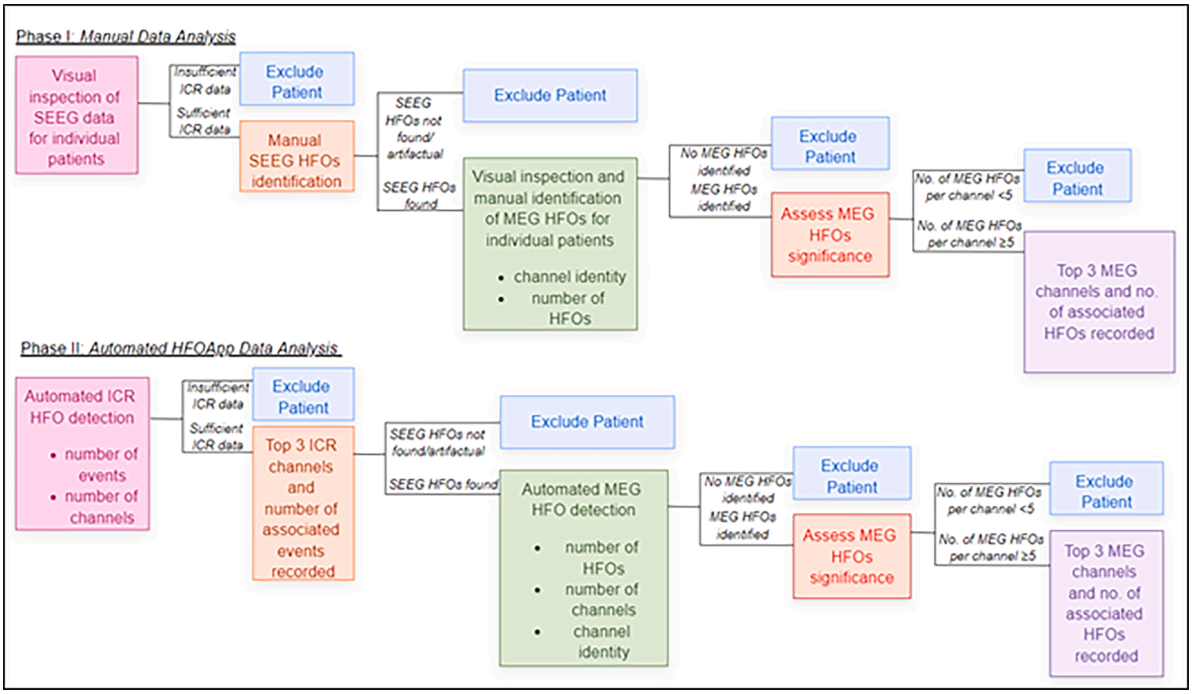

Fig. 1. Criteria for patient inclusion in quantitative, statistical analysis after manual and automated data processing. ICR=intracranial.

2.5. Source localisation

Source localisation has been established on an individual basis by integrating HFO data obtained from the manual SEEG and MEG analysis and from the automated detection of events in the top 3 SEEG electrodes and MEG channels, according to the Elektra Neuromag electrodes scheme [53] (Supplemental material, Figure S3). The epileptogenic foci in individual patients were defined, according to the electrode contacts in which the peak HFO amplitude was recorded, as superficial or deep (Supplemental material, Table S1).

The concordance between manual and automated recording modalities was qualitatively represented through radar plots for individual patients. The locations of the top 3 HFO-containing SEEG electrodes and MEG channels were considered concordant if they were completely overlapping – within the same lobe. Locations were considered partially concordant if they were partially overlapping – only part of them were in the same lobe. If the locations were within distinct lobes, they were regarded as discordant. Each concordance level was assigned a descriptive numerical value: good–1.5; moderate–1.0; poor–0.5. The concordance values were summed for each individual patient and the concordance ratio, defined as the concordance value divided by the maximum possible concordance, was obtained. The overall concordance was considered good if the ratio exceeded 50%.

2.6. Spectral analysis

HFOApp-aided spectral analysis of SEEG and MEG HFOs was performed, with frequency-specific ripples being displayed on the spectrogram synchronised window of the interface, allowing coordinate scrolling through the data and facilitating HFO visualisation.

The HFOApp toolbox ".txt" output file (Figure A1, Appendix) displays the identified HFOs and their characteristics, including frequencies. The frequency of automatically detected SEEG and MEG HFOs identified in the top 3 channels was statistically compared. HFO frequencies from the top 3 channels have been averaged for each patient and presented as mean±standard deviation (SD).

2.7. Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics® for Windows, version 28.0 (IBM Corp., Armonk, NY, USA). Normality of data was assessed using the Shapiro-Wilk test. Nonparametric statistical tests, including the Mann-Whitney U test and Wilcoxon signed-rank test, were employed as appropriate given the small sample size and the non-normal distribution of data. The significance threshold was considered 95% (p-value<0.05).

3. Results

3.1. Patient characteristics

Twenty-four paediatric and adult patients (9 males; mean age=27.76 years) with DRE underwent simultaneous intracranial SEEG and MEG recordings as part of their presurgical evaluation process at Shanghai Jiao Tong University School of Medicine, between 2017 and 2019. The mean recording time was 6.47minutes. The main patient demographic details are summarised in Table 1.

Twelve patients (50%) have been excluded following Phase I ($n = 8$) and Phase II analyses ($n = 4$) (Fig. 1), because of (i) absence of significant MEG channels following automated HFO detection ($n = 8$); (ii)

Table 1
Patient demographics. *B*=bilateral; *F*=female; *L*=left; *M*=male; *R*=right; SD=standard deviation.

Characteristic	All patients	Included patients
Number of patients	$N = 24$	$N = 12$
Sex (M/F)	9 M/16F	4 M/8F
Average Age at Epilepsy Surgery (mean±SD)	27.76 ±11.28	25.08±11.98
Hemisphere of epileptic activity (R/L/B)	4R/6 L/ 14B	0R/4 L/8B
Average duration of SEEG/MEG recording (min) (mean±SD)	6.47±2.69	6.95±3.07
Average number of SEEG electrodes (and electrode contacts) implanted (mean±SD)	4 ± 2 (39 ±15)	5 ± 2 (42 ±14)

absence of significant MEG channels following manual HFO detection ($n = 1$); (iii) absence of SEEG data ($n = 2$); and (iv) absence of HFOs on either SEEG and MEG, due to artefactual background signal ($n = 1$) (Fig. 2; Table A4, Table A5 Appendix).

Twelve patients (50%) were included in the study and further analysis. The age range of included patients was between 9 and 55 years (mean=25.08; SD=11.98), and 4 were male (Supplemental material, Table S1). Six patients displayed MRI-identifiable structural abnormalities, including hippocampal sclerosis ($n = 2$), hippocampal atrophy ($n = 3$), and MRI occipital flair hyperintensity ($n = 1$). In 3 patients, the preoperative MRI scan failed to reveal any structural abnormality. For 3 patients, data regarding the pathology and the resection area was not available.

The most common resection area was the temporal lobe (left $n = 4$; right $n = 1$). Resections of the parietal (left $n = 1$; right $n = 1$), frontal (left $n = 1$) and occipital (left $n = 1$) lobes had also been performed. All patients underwent epilepsy surgery. At 1 year postoperatively, 10 patients achieved seizure freedom (Engel Class I), and 2 exhibited a marked decrease in seizure frequency (Engel Class II).

3.2. SEEG and MEG HFO detection evaluation

SEEG and MEG HFOs have been detected in all included patients. To determine the concordance between the ability of SEEG and MEG to identify HFOs, the number of events was compared between recording modalities, using the manual and the automated data from the top 3 SEEG electrodes and MEG channels (Supplemental material, Figure S4). The number of HFOs was not statistically significantly different between the SEEG and MEG recordings for the manual (Wilcoxon sign rank test, $p = 0.534$, $Z = 40$) and for the automated detection (Wilcoxon sign rank test, $p = 0.239$, $Z = 24$), respectively.

To quantitatively evaluate the automated HFO detectors for SEEG and MEG recordings, a comparison between the HFO rates calculated from the top 3 SEEG electrodes and top 3 MEG channels was conducted (Table A3, Appendix). There was a significant difference between the rate of HFOs detected in SEEG and MEG data (Mann-Whitney U test, $p<0.001$, $Z=-5.287$). SEEG exhibited significantly higher HFO rates (mean HFO rate=16.20%; SD=11.09) compared to MEG recordings (mean HFO rate=6.57%, SD=10.11). Subsequent analysis was performed to determine whether the detection modality impacted the accuracy of HFO identification.

3.3. SEEG HFO detection and epileptic activity source

For SEEG recordings, the number of manually-identified HFOs was significantly lower compared to the number of automatically-detected HFOs (Wilcoxon signed rank test, $p = 0.008$, $Z = 73$), a result which could be attributed to the limitations of visual inspection of recordings.

To further elucidate the origin of this discrepancy, statistical analysis was conducted on subgroups of data corresponding to the differentiation of patients into two groups according to their source of epileptic activity (Supplemental material, Table S1). While for the deep source group, the numbers were similar for the manual and automated detection (Wilcoxon signed rank test, $p = 0.08$, $Z = 14$), for the superficial source group the discrepancy persisted (Wilcoxon signed rank test, $p = 0.043$, $Z = 26$).

3.4. MEG hfo detection

Analysis of MEG HFOs present in the top 3 channels revealed a similar HFO identification ability of manual and automated methods

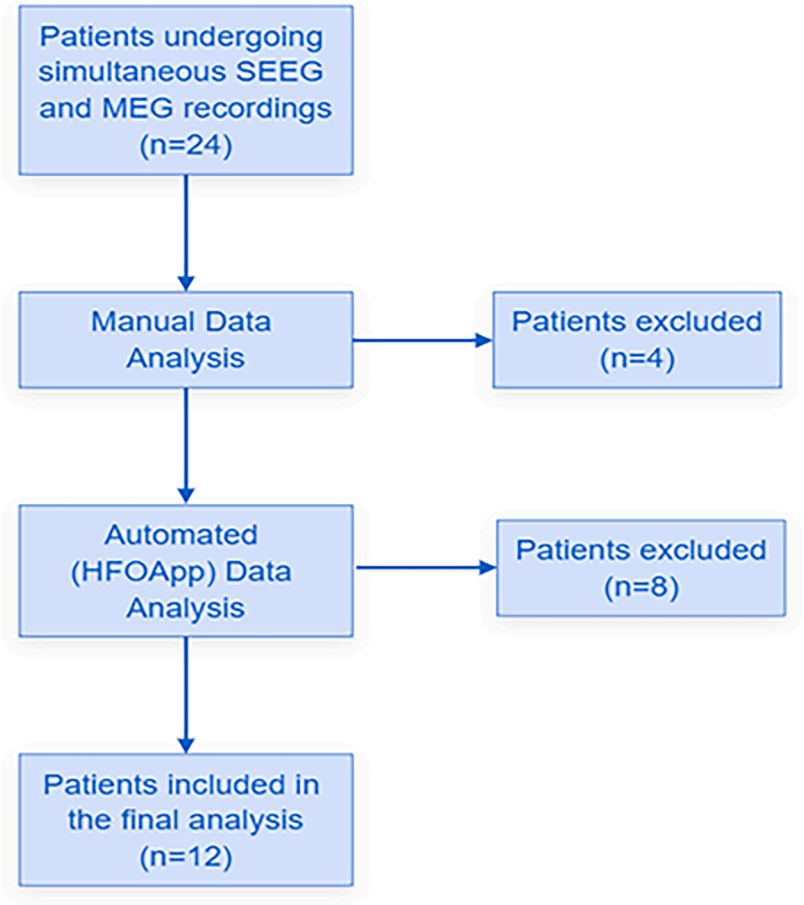

Fig. 2. Flow chart displaying the number of included and excluded patients.

(Wilcoxon signed rank test, $p = 0.195$, $Z = 55.5$) (Supplemental material, Figure S4, Table A3, Appendix), validating the HFOApp detector for MEG automated HFO identification.

To establish the overall level of accuracy of MEG, the number of HFOs detected in significant MEG channels was compared with the total number of MEG-identified HFOs, for manual and automated detection, respectively. The resulting means of the percentage values obtained for each patient (Supplemental material, Table S2) were found to be significantly higher for the automatically detected MEG HFOs (mean=54.08; SD=31.45) compared to the manually identified MEG HFOs (mean=33.52; SD=22.86) (Mann-Whitney U Test, $p = 0.166$, $Z=-1.386$), suggesting that the automated detector has an increased accuracy over manual HFO identification.

3.5. Spectral analysis and the nature of SEEG and MEG HFOs

HFOApp output resulted in individual SEEG and MEG HFO frequencies for every patient (Figure A1, Appendix). Spectrograms were obtained for one HFO from each of the top 3 SEEG electrodes (Supplemental material, Figure S5) and MEG channels (Supplemental material, Figure S6). SEEG HFO spectrograms indicate inter-individual variability in HFO shapes, which are depicted as cone-shaped, high-amplitude bursts, spanning most of the 80–250 Hz range. This characteristic appearance of HFOs is more evident in hippocampal, temporal and insular electrodes. MEG HFO spectrograms revealed HFOs with poorly defined shape, and no correlation pattern emerged between the appearance of HFOs and MEG channel localisation (Table 2).

To evaluate the relationship between SEEG- and MEG-identified HFOs, a statistical comparison of the frequencies of individual SEEG and MEG HFOs per patient was performed (Table A2, Appendix). Four patients had similar HFOs frequencies between the two recording modalities, 3 of whom had a superficial epileptogenic source. In the remaining 8 patients, representing 57% of patients with superficial sources and 50% of patients with deep sources, MEG HFO frequencies were significantly higher compared to SEEG HFO frequencies (Mann-Whitney U Test, $p<0.05$). Overall, MEG HFO frequencies were significantly higher compared to SEEG HFO frequencies (Mann-Whitney U Test, $p<0.001$, $Z=-21.799$) (Fig. 3).

3.6. Source localisation

3.6.1. Concordance ratios and source of epileptogenic activity

Concordance between each 2 of the 4 independent HFO detection methods was qualitatively represented through radar plots for each patient (Fig. 4). Fifty-eight percent of patients displayed good concordance (ratio>50%), while 42% had a poor concordance (ratio<50%). Good concordance was characteristic of 90% of patients with deep epileptogenic sources and in 43% of patients with superficial sources (see Table A1, Appendix).

Examination of the concordance between the HFOs detected on SEEG and MEG manual and automated recordings and the preoperative MRI-based pathology was conducted. In 33% of patients, the resection area coincided with the MRI-identified pathological region, whereas in 17% of patients these areas did not coincide (Supplemental material,

Table 2
Summary of HFO-displaying SEEG electrodes and MEG channels form manual and automated analysis. CING=cingulate; FRONT/front=frontal lobe; HIPP=hippocampus; INS=insula; *L*=left; LH=left hippocampus; N/*A*=not available; No.=number; OCC/occ=occipital lobe; PAR/par=parietal lobe; *R*=right; RF=right frontal; RH=right hippocampus; TEMP/temp=temporal lobe.

Patient No.	Manual Source Localisation			Automated detection Source Localisation			Concordance ratio (%)
	SEEG electrodes	MEG channels	MEG channels localisation	SEEG electrodes [HFO rates %]	MEG channels [HFO rates%]	MEG channels localisation	
1	L_HIPP4–8	M1722, M0432, M0513, M1512	L_occ, L_par, L_front, L_temp	L_HIPP1 [31], L_HIPP2 [35], L_HIPP4 [18]	M1512 [3], M1722 [4], M1732 [3]	L_temp, L_occ	72
2	L_TEMP2,3,5,8	M0113, M0143, M0532, M0612	L_temp, L_front	L_TEMP1 [20], L_TEMP2 [20], L_TEMP7 [20]	M2511 [1], M2122 [1], M2123 [1]	R_occ	56
5	L_HIPP1–8	M1912, M1922, M1732	L_occ	L_HIPP1 [50], L_HIPP2 [27], L_HIPP3 [15]	M1732 [56]	L_occ	56
8	L_TEMP12–16, L_TEMP5–7	M1813, M1333, M2013	L_par, R_temp	L_TEMP4 [14], L_TEMP5 [20], L_TEMP7 [19]	M0821 [12], M0941 [10], M2631 [8]	R_front, L_front, R_temp	50
10	R_FRONT1–4, L_OCC4–8	M1912, M1443, M1333	L_occ, R_temp	R_FRONT7 [13], R_FRONT8 [13], L_OCC7 [11]	M1712 [24], M2533 [19], M1531 [8]	L_occ, R_occ, L_temp	72
12	L_FRONT1–8, L_IN4–6	M1612, M0232, M2113, M2543	L_temp, L_occ, R_occ	L_INS11 [7], L_INS14 [7], L_INS15 [5]	M1423 [4], M1433 [4], M2623 [4]	R_temp	39
13	L_INS15–17, R_TEMP1–4	M2223, M0213, M1013	R_par, L_temp, R_front	L_INS16 [13], R_TEMP1 [19], R_TEMP2 [19]	M1931 [5], M1731 [4], M1941 [3]	L_occ	44
16	L_HIPP1–7, L_FRONT1–4,6–8, R_PAR1–8, E025-E029	M0811, M1411, M1412, M1422, M1541	R_front, L_temp	L_HIPP1 [6], L_FRONT2 [7], R_PAR2 [6], E025 [50], E026 [6]	M0123 [7], M1222 [11], M1413 [9]	R_front, L_front	67
20	L_HIPP8–12, R_HIPP2–3	M0143, M0923, M0111, M0113, M0523	L_temp, R_front, L_front	L_HIPP11 [9], L_HIPP16 [5], R_HIPP13 [5], R_OCC2 [6]	M1413 [4], M1632 [3], M1441 [3]	R_front, L_par, R_temp	67
21	L_HIPP1–3, L_CING9–11	M1433, M2411, M2623	R_temp	L_HIPP1 [30], L_HIPP2 [17], L_HIPP3 [18]	M2612 [1], M1411 [1], M1443 [1]	R_front, R_temp	44
23	L_FRONT2–6, L_HIPP3, L_PAR10–11	M0913, M0923, M1732, M2113	R_front, L_occ	L_FRONT1 [21], L_FRONT2 [12], L_FRONT6 [9]	M1331 [2], M0211 [2], M2421 [2]	R_temp, L_temp	44
24	R_HIPP1–3, R_HIPP8–11, R_INS29–33	M1211, M1311, M1423	R_front, R_temp	R_INS30 [9], R_INS31 [9], R_INS32 [10]	M2113 [1], M2123 [1], M2332 [1]	R_occ, L_occ	44

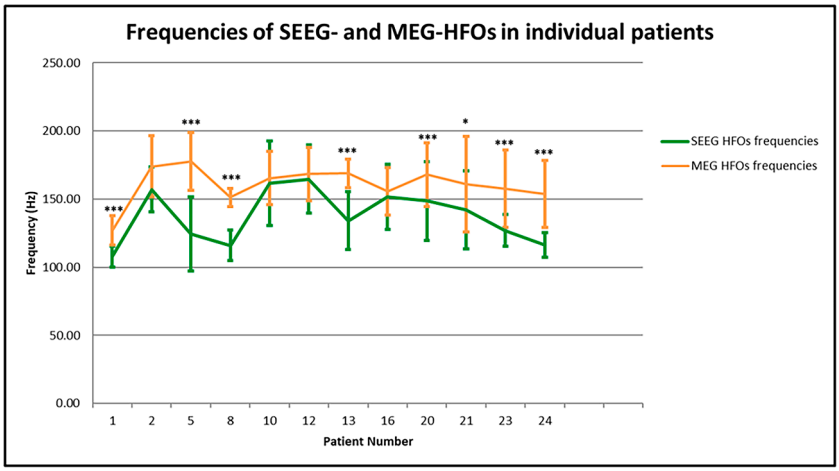

Fig. 3. Graph displaying the mean and SD bars for the frequencies associated with SEEG HFOs and MEG HFOs in individual patients. *$p<0.05$; ***$p \leq 0.001$.

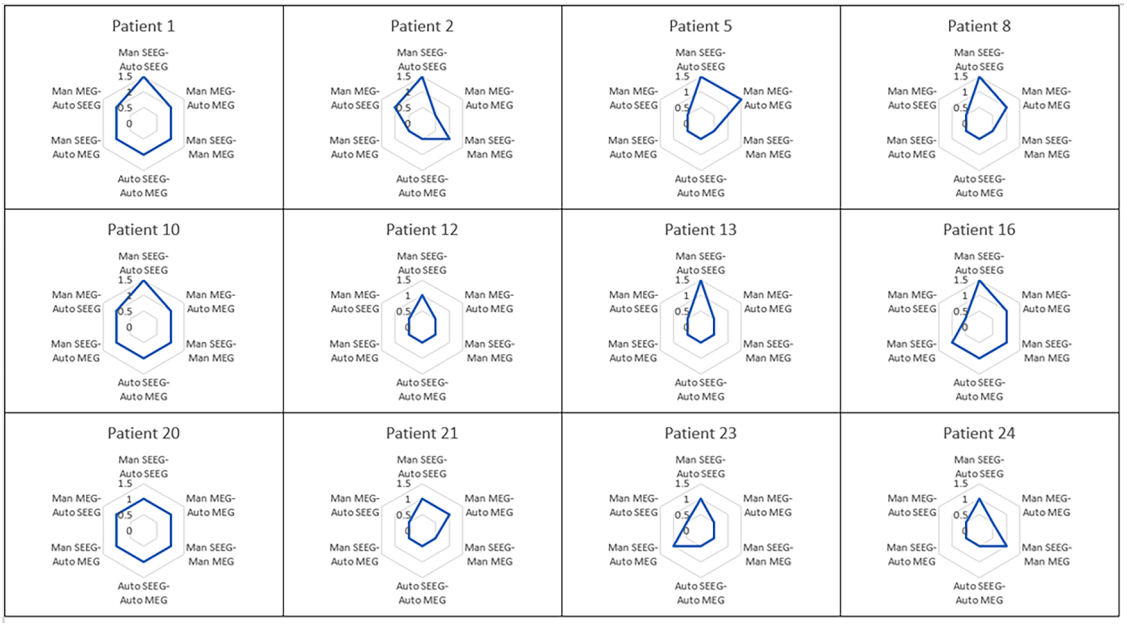

Fig. 4. Radar plots illustrating concordance in HFO-displaying areas of SEEG and MEG.

Table S1, Table 2). Concordance analysis was not performed in 50% of included patients, either because of MRI scan failing to identify any structural abnormality ($n = 3$) or because data regarding pathology area was not available ($n = 3$).

3.6.2. Concordance ratios and resection area

The concordance between MEG and SEEG HFOs and the surgical resection area was determined. Concordance analysis was not performed in 25% of included patients because data regarding resection area was not available ($n = 3$). For 25% of patients, both manual and automated SEEG, but no MEG data, were concordant with the resection area, indicating that SEEG might determine the position of the EZ, while MEG recordings might be more accurate in detecting the propagating epileptic activity, especially as two of these three patients displayed deeply-sourced activity (Supplemental material, Table S1, Table 2). Conversely, in 25% of patients, having superficial epileptogenic sources and poor concordance ratios, MEG HFO localisation was related to the resection area. This supports the hypothesis that MEG can accurately predict the localisation of the EZ in DRE patients.

Discordance between the recording data and resection area was detected in 25% of patients. Nonetheless, for two of these patients having superficial sources, MEG recordings were indicative of the pathological region. This suggests that epileptic activity originating in the EZ has the potential to damage, through propagation, adjacent cortical or subcortical structures subsequently exhibiting altered high-frequency oscillatory activity. One patient failed to display any relationship between the pathology, the resection area and the recording data but managed to achieve seizure freedom.

3.6.3. Concordance ratios and postoperative outcome

Postoperatively, 83% of patients experienced seizure freedom (Engel Class I) (Supplemental material, Table S1). Seizure freedom was achieved in 86% of patients with good concordance between HFO-displaying SEEG and MEG recordings, and in 90% of patients with poor concordance.

Two patients with a good and a poor concordance ratio, respectively, exhibited Engel Class II outcome. For patient 13, this postoperative outcome is potentially attributable to the correlation between the resection area with manually detected SEEG and MEG HFOs, despite the absence of pathology on the preoperative MRI scan. No pathology or

resection area data was available for the second patient (patient 5).

4. Discussion

4.1. Summary of findings

In this study, manual and automated HFO detection was employed in simultaneous SEEG and MEG recordings in a cohort of 12 patients. The analyses demonstrated that SEEG and MEG are similarly accurate in HFO identification, supporting the possibility of employing non-invasive MEG recordings alone in EZ delineation. Quantitative comparison between recording modalities revealed that SEEG exhibited higher HFO rates compared to MEG, suggesting that intracranial recordings can identify deeper neuronal spikes which are not directly available to MEG due to the attenuation of the magnetic signal with the square of distance.

The frequency discrepancy observed following spectral analysis could relate to the fact that SEEG electrical signals are prone to filtering by surrounding tissue, acting as a low pass filter, while MEG signals are relatively insensitive to filtering by skull or brain parenchyma. Alternatively, the nature of observed events might differ, with SEEG potentially detecting HFOs from the EZ and MEG identifying HFOs associated with the propagation of the epileptic activity in adjacent regions, a mechanism possibly underlying seizure generalisation.

Source localisation analysis revealed no clear patterns across the patient sample. This suggests that concordance in simultaneous use of SEEG and MEG is not necessarily required for attainment of seizure freedom, and the results from each recording modality should be contextually interpreted. Moreover, postoperative seizure freedom was achieved in 86% of patients, regardless of concordance ratio, indicating that removal of areas in which HFOs propagate from EZ similarly prevents spreading of epileptogenic activity, seizure initiation and progression.

4.2. Study strengths

This study is one of the first to report the identification of interictal HFOs on simultaneously recorded SEEG and MEG in a relatively large cohort of human DRE patients undergoing epilepsy surgery. The ability to detect interictal HFOs in the absence of seizure activity in patients has multiple advantages, namely: (i) eliminating the requirement to lower AEDs dosage prior to recording, preventing the unpleasantness of seizure re-experiencing; and (ii) contributing to the more effective allocation of healthcare financial resources given the lack of waiting time for seizures to occur for ictal recordings. Currently available literature reporting simultaneously employed SEEG and MEG for presurgical evaluation is limited [37,43,54].

Moreover, this work validated the use of a modified automated MATLAB toolbox in the detection of MEG HFOs, which has potential to increase MEG usage in clinical settings by reducing the extensive time associated with data visualisation and interpretation.

4.3. Study limitations

The limitations of this study are related to the short recording duration and the small cohort size. Nonetheless, these factors could be justified by procedural difficulties, the invasiveness of simultaneously undertaking SEEG and MEG recordings, and the restricted indication of this technique in highly selected patients. Secondly, the surgical implantation of electrodes was not standardised between patients, introducing inter-subject variability related to differently positioned EZ.

Thirdly, the use of the bipolar montage for the SEEG data could have introduced ambiguity and interfered with HFO visibility, considering the poor spatial sampling of intracranial recordings [55,56]. Moreover, the monopolar montage is prone to contamination of the signal with background noise, making results difficult to interpret.

Finally, visual identification and manual marking of HFOs employed in the first part of the analysis could have introduced bias given inter-observer variability, which was resolved by employing two independent observers for manual HFO marking.

4.4. Findings in context and future directions

Previously, the employment of HFOs as clinical biomarkers for EZ identification was hindered by several issues. Firstly, the clinical efficacy of HFOs has been almost exclusively assessed in retrospective studies which pose reliability and reproducibility concerns given the visual analysis of recordings [57,58], so conducting prospective studies using automated detectors would advance translatability of this biomarker.

Secondly, difficulties associated with distinguishing between physiological and pathological HFOs further lowers the specificity and impairs translatability, because of similar morphological features of these events, and because of the varying rates of HFOs across distinct brain regions [59,60]. For instance, the hippocampus and the occipital lobe display permanent physiological high frequency activity [61]. These inter-regional discrepancies need to be accounted for by correcting for topographical localisation of the recording units.

Finally, given that most of the knowledge regarding HFOs originates from invasive intracranial EEG recordings from refractory epilepsy patients [9,26,62], the efficacy and reliability of scalp-detected HFOs was not fully demonstrated, due to artefactual events and low signal-to-noise ratio [63].

Ultimately, this work demonstrates the reliability of combined manual and automated HFO detection and encourages the implementation of a standardised HFO detection protocol in routine clinical practice, to eliminate bias and improve patient care. This study aims to serve as the foundation to future research endeavours focusing on combining various recording techniques to enhance pre-surgical evaluation and surgical planning for patients identified as suitable candidates for surgical treatment.

5. Conclusion

The results of this work provide evidence supporting the ability of MEG to detect HFOs, through comparison with gold-standard SEEG, and demonstrate that simultaneous use of SEEG and MEG for interictal HFO identification facilitates EZ localisation, aiding preoperative evaluation and improving postoperative outcomes in adult and paediatric DRE patients. This approach offers a framework for the integration of local and global information regarding electrical brain activity. Further investigations are required to validate these results in larger patient cohorts and to advocate for the integration of automated SEEG and MEG HFO detectors in clinical environments for presurgical planning.

Declaration of Competing Interest

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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.03.015.

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