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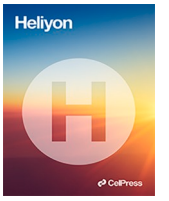

Review article

Application of magnetoencephalography in epilepsy

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ABSTRACT

Magnetoencephalography (MEG) is a non-invasive neuroimaging technique that can detect whole-brain neuroelectromagnetic signals in real-time in a single measurement. Due to excellent temporal and spatial resolution and integration of computed tomography or magnetic resonance imaging data, MEG allows signal source analysis. It can pinpoint epileptic foci as well as functional brain regions, reducing the necessity for invasive electrode implantation.

1. Introduction

Magnetoencephalography (MEG) is a non-invasive neuroimaging technique that detects brain neuroelectromagnetic signals, offering precise temporal and spatial insights into brain electrophysiology [1,2]. MEG measures whole-brain electromagnetic signals in a single measurement, and delivers significant advantages in sensitivity and spatial and temporal resolution by combining various technologies [3–5]. The development of MEG began in the 1960s with a single-channel sensor [6]. By the early 1970s, MEG detection capabilities markedly improved with the introduction of superconducting quantum interference devices (SQUIDs) [7]. Since the 1990s, detection probes have evolved into multi-channel whole-head detectors (up to 306 magnetic channels), rapidly collecting and processing brain neuroelectromagnetic data. Supported by computer image fusion technology and anti-magnetic field interference systems, acquired signals become magnetic field maps and brain magnetic curves. Furthermore, by integrating CT or MRI data, MEG accurately pinpoints brain function locations, reflecting transient functional changes. Nowadays, MEG is extensively applied in advanced brain function research, neurosurgery, pediatric neurological disease diagnosis, epilepsy, and neuroscience [8]. In epilepsy, MEG predominantly records the spike wave during the interictal period of epilepsy. The magnetic source imaging (MSI) reflecting the spike wave primarily pinpoints the epileptogenic zone. However, most epileptic seizures come with noticeable motion artifacts, making it rare for MEG to record discharges during the seizure period, which limits the precise localization of the seizure's onset zone. Additionally, MEG equipment is relatively expensive, and long-term monitoring and recording are not feasible. This review

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summarizes the application of MEG in epilepsy (Fig. 1).

2. Application in the diagnosis of epilepsy

Epilepsy, a common neurological disorder with various etiologies, is characterized by sudden and diverse seizure types that can evoke fear in patients and their families. Epilepsy also presents a high disability and mortality rate, imposing a substantial disease burden. The treatment of intractable epilepsy often necessitates surgical resection of the epileptic focus [9,10]. However, successful resection and favorable surgical outcomes rely on precise preoperative evaluation. MEG offers two primary advantages in preoperative epilepsy assessment, including the localization of the epileptic focus and the localization of brain functional areas [11,12]. Rampp et al. [13] performed a retrospective observational cohort study of 1000 patients with focal epilepsies. Their results showed that MEG provided non-redundant information, which could be applied in selecting epilepsy surgery candidates, added to presurgical localization of epileptic focus, and significantly contributed to long-term seizure freedom after epilepsy surgery. MEG chiefly achieves epileptic focus localization through source analysis, which computes the position, direction and intensity of intracranial signal sources based on detected MEG signals. Commonly used source analysis methods in clinical practice encompass the dipole pattern and synthetic aperture magnetometry (SAM).

2.1. Dipole pattern

Studies have demonstrated that the dipole analysis method of MEG localization exhibits a high degree of consistency with structural imaging and electrocorticography (ECoG), potentially offering insights into the prognosis of epilepsy surgery. Several studies have reported the ability of the dipole method to localize spike and wave complexes during interictal periods [14–17], with localization results aligning well with the epileptic focus area monitored through subsequent intraoperative ECoG or intracranial electrodes [18,19]. Furthermore, for superficial cortical areas, synchronous recordings between MEG and ECoG also demonstrate a high level of agreement [20]. The distribution pattern of dipoles plays a critical role in precise epileptic focus localization. A higher number of spike and wave complexes during interictal periods, coupled with a concentrated dipole distribution, typically signify a correspondence between the dipole distribution area and the seizure onset zone localized by ECoG [14,15]. Conversely, a scattered dipole distribution often suggests an irritability zone that is the cortical region producing spikes during interictal period [14]. In epileptic patients with intracranial structural lesions, sharp wave-related dipoles are predominantly situated in the lesion and its immediate vicinity [16,17,19], displaying a strong correlation with structural lesions. Furthermore, dipole localization assists clinicians in identifying difficult-to-detect or concealed structural lesions [21,22]. Concerning epilepsy surgical prognosis, dipole mode localization of the epileptic focus imparts valuable insights [23], aiding clinicians in predicting surgical outcomes and enhancing patients' quality of life [24]. A concentrated dipole distribution area often signifies favorable postoperative seizure freedom upon complete resection, while incomplete resection typically indicates a less promising prognosis [25–27]. In a recent retrospective clinical study, researchers discovered that a concentrated and directionally stable dipole distribution is indicative of a relatively favorable surgical prognosis, while a dispersed dipole distribution hints at a less favorable outcome [28]. Combining MEG with other preoperative evaluation methods can bolster the predictive power of surgical prognosis. For instance, when MEG results align with stereoelectroencephalography (SEEG), the postoperative seizure-free rate significantly improves. Additionally, combining MEG with EEG for preoperative localization can enhance the effectiveness of gamma knife surgery in treating refractory epilepsy [29]. Yin et al. employed MEG at the source level to detect and pinpoint intracranial high-frequency oscillations (HFOs) in patients with temporal lobe epilepsy, investigating whether HFOs can delineate the epileptogenic zone [30]. Their study utilized new cumulative source imaging (HFOs, wavelets peaking between 80 and 250 Hz) and traditional dipole modeling (peak) methods to analyze MEG data to locate the epileptic focus and evaluate the relationship between focal brain region resection containing interictal HFOs and postoperative seizure outcomes. The results revealed that out of 21 patients clinically diagnosed with temporal lobe epilepsy who underwent surgical treatment, interictal HFOs were localized to the epileptogenic zone in 18 cases. Dipole clusters were observed in the temporal lobe epileptogenic zone of 15 patients. In 14 patients, both HFOs and dipole clusters were located in the insula. The seizure-free rate for the resected brain area generating HFOs was 87 %, compared to 80 % for the resected brain area generating spikes. Patients who underwent complete resection had a significantly higher likelihood of being seizure-free ($P = 0.031$) than those who underwent partial

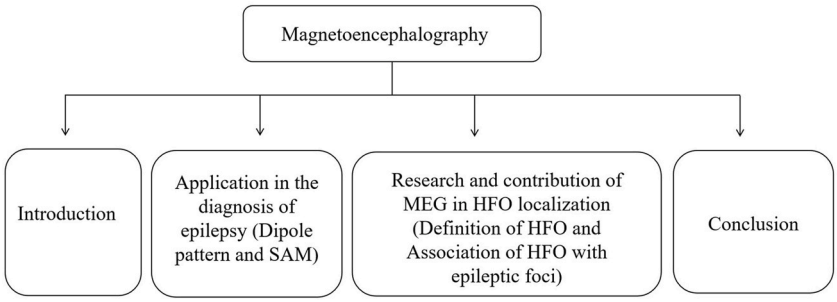

Fig. 1. Graphical illustration summarizing this review.

resection or no resection of the HFO generation area. This difference was not observed in the area generating spikes. The author highlights that HFOs in insular epilepsy can be non-invasively detected and quantitatively evaluated using MEG technology. MEG HFOs (ripples at peak times) may have implications for the localization of the epileptogenic zone in insular epilepsy. Kaur et al. conducted MEG and SPECT examinations on 101 and 57 patients with drug-resistant epilepsy, respectively [31]. The results indicated that the accuracy rates of MEG and SPECT in localizing the epileptic zone were 74.26 % and 78.57 %, respectively. The odds ratios for predicting good surgical outcomes (Engel I) were 2.43 for MEG and 5.0 for SPECT. Although no significant correlation between MEG and good surgical outcomes was observed, patients without SPECT information had a much higher odds ratio for predicting good surgical outcomes at 6.57. Therefore, the authors suggest that while SPECT examination outperforms MEG in predicting good surgical outcomes for drug-resistant epilepsy patients, it may lack information for most patients. Consequently, MEG can serve as a valuable alternative for patients unable to undergo SPECT examination or for whom SPECT localization is unsuccessful. Shawarba et al. conducted a retrospective analysis of 27 patients who underwent reoperation after failed surgery for drug-resistant epilepsy [32]. MEG, neuronavigation, and intraoperative MRI (iopMRI) examinations were performed preoperatively, and seizure outcomes were assessed using the Engel scale. The results indicated that for most drug-resistant epilepsy patients, reoperation following unsuccessful surgery contributes to seizure control. Preoperative MEG supports surgical decision-making, facilitating targeted resection of epileptic tissue through navigation and iopMRI imaging.

2.2. SAM

SAM functions as a signal beamforming method. Its fundamental concept involves partitioning the brain into multiple voxels and employing a signal beamformer to measure signals and obtain a specific function within each voxel. Typically, the maximum value of the probability density distribution of this function signifies the source location [33]. Zhu et al. analyzed brain magnetic map data of a group of patients with left temporal lobe epilepsy using SAM [34]. The results revealed significantly elevated SAM values in the left temporal lobe structure of these patients compared to normal individuals, and this finding exhibited strong alignment with clinical outcomes. Furthermore, Wu et al. analyzed the accuracy of SAM, dipoles, and other methods in localizing patients with drug-resistant epilepsy, utilizing interictal ECoG as the gold standard [35]. The findings indicated that the localization coincidence rates of SAM and dipoles were 68.7 % (11/16) and 62.5 % (10/16), respectively, underscoring SAM's comparable accuracy in localizing drug-resistant epilepsy to the dipole method. Additionally, SAM can also be applied to analyze brain magnetic map data in patients with epilepsy undergoing vagus nerve stimulation therapy [36]. SAM offers the advantage of overcoming artifacts stemming from stimulator interference in raw data, allowing for precise comparison of this type of data. However, SAM may encounter interference from electromyographic artifacts generated by facial muscle contractions during the MEG examination process. Therefore, it is imperative to distinguish these artifacts when interpreting SAM analysis results.

3. Research and contribution of MEG in HFO localization

3.1. Definition of HFO

In the context of rapid advancements in neurophysiology, HFOs have been extensively observed and defined. According to the current unified standard, brain electrical discharge above 80 Hz is classified as HFO, with 100–250 Hz HFO termed "ripple", 200–500 Hz termed "fast ripple", and a third type that is a combination of the two [37]. Researchers assert that the fast ripple of 200–500 Hz pertains to pathological brain electrical oscillations, recordable in the hippocampus and dentate gyrus of patients with mesial temporal lobe epilepsy and even in rodent models, whereas normal ripples remain undetectable in the dentate gyrus. Given that brain electrical activity above 100 Hz is susceptible to interference from the scalp and cranial bone and exhibits a low signal-to-noise ratio, the primary method for recording brain electrical activity remains invasive intracranial electrode implantation. MEG remains unaffected by interference from the scalp, cranial bone, surgical incisions, and other factors. It can accurately, dynamically, and in real-time record abnormal neuronal discharges in patients with mesial temporal lobe epilepsy, including high-frequency discharges above 100 Hz. Studies employing noninvasive recording of HFOs in the clinical setting with MEG have contributed to the understanding and utility of HFOs as a biomarker of epileptogenicity [38,39].

3.2. Association of HFO with epileptic foci

HFOs exhibit a close association with epileptic foci. Various HFO types have been recorded in the hippocampus, olfactory cortex, and patients with temporal lobe epilepsy in rodent models. Consequently, HFOs are increasingly considered a biological marker of epileptic foci [37,40,41]. Concerning interictal HFOs, research has demonstrated that more favorable surgical outcomes can be achieved by resecting the area containing HFOs compared to areas without HFOs, as confirmed through invasive intracranial electrode implantation and intraoperative cortical electrical stimulation [42]. However, some studies have highlighted that even after removing the area producing HFOs, epilepsy may not be effectively controlled [43]. Burnos et al. [44] proposed that HFOs with distinct frequencies and amplitudes exert varying effects on the localization of epileptogenic areas, categorizing HFOs into four types based on morphology: type 1 (regular amplitude and frequency), type 2 (irregular amplitude), type 3 (irregular frequency), and type 4 (irregular amplitude and frequency). All HFO types exhibit higher levels in the epileptogenic zone compared to the surrounding area, particularly types 1 and 2, which display a strong positive correlation with the epileptogenic zone and surgical outcomes. For patients with lateral temporal lobe epilepsy, the removal of the area generating HFOs can lead to successful surgical outcomes. Frauscher et al. [45]

reviewed the evidence of HFOs on the clinical application of epilepsy. They indicated that HFOs were associated with post-surgical seizure outcome, and moreover HFOs were useful to measure disease activity and evaluate treatment response.

In the case of various lesions such as cortical dysplasia, temporal lobe atrophy, and gray matter heterotopia, specific, identifiable HFOs are absent [43]. Collectively, these studies underscore that while HFOs are closely linked to epileptogenic foci and the removal of HFO-containing areas can improve outcomes, not all HFOs can uniformly offer precise epileptic focus localization.

In comparison to interictal HFOs and postictal HFOs, ictal HFOs assume great significance due to their specificity in identifying epileptic foci. In contrast to traditional frequency ictal epileptic waves, ictal HFOs manifest earlier in the seizure onset zone and occupy smaller areas. Resection of the epileptogenic zone with ictal HFOs can yield favorable therapeutic effects [46,47]. Consequently, the precise localization and resection of ictal HFO areas, while preserving normal brain tissue, represents an important research direction. Ictal HFOs play a pivotal role in determining the treatment methods and prognosis of temporal lobe surgery. In patients with medial temporal lobe epilepsy, when spike waves and interictal HFOs point to bilateral temporal lobe epilepsy, ictal HFOs can ascertain the laterality of the epileptic focus and guide the surgical approach [48]. For patients with both medial and lateral temporal lobe epilepsy, ictal HFO analysis can help clarify the sequence of onset and spread of the seizure [49]. These studies collectively emphasize that ictal HFOs markedly aid in determining the side and surgical strategies for epilepsy surgery.

The utilization of interictal HFOs in conjunction with MEG plays a pivotal role in localizing interictal regions. Xiang et al. have observed that the location of high-frequency activity recorded by MEG aligns with the lesions identified by MRI in 70 % of children with focal epilepsy [50]. In patients undergoing epilepsy surgery, MEG, when applied for high-frequency localization, achieves an accuracy rate of 82 % compared to intracranial localization of lesions, which is akin to MEG localization of spike waves. Nonetheless, HFOs, characterized by higher frequencies than spike waves, are more susceptible to noise interference, posing substantial challenges in MEG recordings of HFOs. To address this, Van Klink et al. pioneered the use of a virtual electrode analysis method constructed through beamformer techniques to distinguish epileptic HFOs that could not be discerned by physical MEG sensors [51,52]. Leveraging seizure events detected by invasive electrodes, MEG demonstrates accuracy and sensitivity rates of 79.18 % and 68.88 %, respectively, for virtual electrode localization of epileptic foci [53], thereby aiding in the recording of HFOs and reducing the necessity for invasive electrode implantation.

HFOs during seizure periods also prove invaluable for pinpointing the epileptic focus. Research indicates that, by employing high-resolution, multi-frequency analysis on children with spasmodic epilepsy, it is feasible to establish spasmodic seizures as a form of localized seizure activity [54]. This study further reveals that pathological HFOs during seizure periods predominantly concentrate in the central sulcus area and frontal lobe (FL) of 80 % of the patients. Effective control of epilepsy can be achieved through localized resection of these epileptic cortical areas. However, this particular study did not compare HFOs with spike waves. Consequently, Miao et al. [55] utilized dynamic MSI (dMSI) to capture high-frequency signals during seizure periods in 10 children with absence seizures. Their findings highlight the greater significance of fast ripples over ripples in absence seizures, in comparison to spike waves, due to the precise localization of fast ripples.

Studies into MEG recordings of HFOs during seizure periods have unveiled that the left frontal and posterior cortical areas, encompassing the left anterior cingulate and medial occipital areas, assume a critical role in the initiation of epileptic activity in absence seizures. The propagation primarily transpires through the cortical–cortical pathway and the cortical–thalamo–cortical pathway. The cortex and the thalamus each play key roles during onset and excitatory stages, respectively [56]. The interaction between the frontal and parietal cortical–thalamic networks may foster a pathological state, contributing to the generation of spike waves and slow-wave discharges [57]. The shift from interictal to ictal periods entails an increase in low-frequency brain activity, while the epileptic core area exhibits a significant upsurge in the dynamic intensity of HFOs. The intensity of HFOs in the epileptic core area directly correlates with absence seizure severity [58,59]. Consequently, HFOs serve as a swift and oscillatory non-invasive examination tool in clinical settings.

Despite the reliability of HFOs as a biomarker for epilepsy, Roehri et al. have observed that ripples can also manifest in the mesial temporal lobe and the occipital lobe without epileptic onset, whereas spikes only noticeably increase in the mesial temporal lobe of epilepsy patients [60]. Given the pivotal role these structures play in epilepsy onset, HFO, in comparison to spikes, still lacks specificity, and ripples cannot yet serve as a biological marker for epileptic foci. This study has also identified that, as specificity thresholds increase to 85 % or 90 %, fast ripples and fast ripples with spikes exhibit reduced sensitivity. This suggests that not all epileptic foci experience HFO occurrences, and as specificity increases, the sensitivity for localizing epileptic foci decreases. A multicenter study on refractory epilepsy investigated the prediction of surgical outcomes based on HFO through electrode implantation and intraoperative electrophysiological monitoring [46]. The results indicate that 69.2 % (36 cases) of patients align with the previous predictions, with only 15.6 % (3 cases) experiencing effective relief from epilepsy. Even when the area with the most significant HFO occurrence isn't entirely resected, epilepsy can still be alleviated. Hence, the specificity of HFO for epileptic tissue may not be as robust as suggested by early studies. Despite some studies questioning the reliability of HFO as a biological marker for epileptic foci, HFO remains less specific compared to spikes. The extensive HFO area often exceeds the resected area due to the inclusion of physiological HFO, which broadens the scope. As such, localization must rigorously differentiate between pathological and physiological HFO, considering factors such as the morphology, power spectrum value, and location of spikes and HFO waveforms for comprehensive analysis and assessment.

Studies have applied beamforming techniques and standard low-resolution electromagnetic tomography (sLORETA) to HFO source localization [53,61], enabling more precise non-invasive examination and localization of HFO. This, in turn, aids in preoperative planning and diminishes the necessity for invasive procedures.

4. Conclusion

MEG is playing an important role in the preoperative evaluation of epilepsy, especially in the accurate location of the onset brain area, which could not be replaced by other detection methods. As technology advances and costs decrease, MEG is poised to gain wider acceptance in clinical diagnosis and treatment.

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Statement

AI or AI-assisted technologies were not used in the writing process.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Qingyan Zhang: Writing – review & editing, Writing – original draft. **Chuanming Yin:** Project administration. **Xiujie Fang:** Project administration. **Yunwei Ou:** Project administration. **Danyue Ma:** Funding acquisition. **Shabier Tuerxun:** Writing – review & editing.

Declaration of competing interest

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