Clinical Neurophysiology 190 (2026) 2112333

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Electrophysiology–MRI integration for epileptogenic zone detection and surgical prediction – A narrative review

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ARTICLE INFO

Keywords:
Focal epilepsy
Drug resistant epilepsy (DRE)
Electrophysiology
Magnetic resonance imaging (MRI)
Epileptogenic zone
Multimodal integration

ABSTRACT

(Invasive) electrophysiology and magnetic resonance imaging (MRI) are central to the presurgical evaluation of patients with focal drug-resistant epilepsy (DRE), providing complementary but incomplete views of the epileptogenic zone (EZ). Although numerous studies combine these modalities, a comprehensive overview of how electrophysiology and MRI can be systematically integrated across MRI modalities is currently lacking. This narrative review synthesizes state-of-the-art methods for integrating electrophysiology with MRI in epilepsy research. Rather than focusing solely on spatial overlap or comparative performance, we highlight approaches in which each modality informs the other. We outline key principles, advantages, and limitations of existing strategies, discuss epilepsy-specific and multimodal integration challenges, and describe methodological directions to address them. Importantly, despite the breadth of proposed approaches, only a small number of integration strategies are currently used in routine clinical practice, whereas many others remain confined to the research domain. We consider emerging opportunities and remaining barriers for clinical translation toward improved localization of the EZ and better prediction of surgical outcomes.

Introduction: Localization of epileptogenic zone

Epilepsy is one of the most prevalent chronic neurological disorders, affecting approximately 1% of the global population (Banerjee et al., 2009). While anti-seizure medication (ASM) effectively control seizures in most patients, 30% to 40% of patients suffer from drug-resistant epilepsy (DRE) (Kwan et al., 2010; Xue-Ping et al., 2019). For patients with focal DRE, surgical resection is an evidence-based, curative treatment (Engel, 2012; Wiebe et al., 2001). Minimally invasive treatments, such as MRI-guided laser interstitial thermal therapy (MRgLITT), stereo-EEG radiofrequency thermocoagulation (SEEG-RFTC), stereotactic radiosurgery (SRS), or high-intensity focused ultrasound (HIFU), also offer potential curative options (Winter et al., 2024) with varying success rates (Kohlhase et al., 2021; Shamim et al., 2022). Accurate identification of the epileptogenic zone (EZ) is critical prior to any intervention to maximize the likelihood of therapeutic success.

A network hypothesis (Bartolomei, 2024) distinguishes EZ, propagation zone (PZ), and non-involved zone (NIZ) based primarily on seizure propagation dynamics and recruitment delay. In contrast, Lüders conceptualized the EZ as an abstract, modality-independent construct rather than a directly measurable anatomical structure (Lüders et al., 2006). Several related zones are commonly described in epilepsy research, including the structural lesion, the seizure onset zone (SOZ), and the irritative zones (IZ). The SOZ corresponds to the region where seizures originate. Although sometimes used interchangeably with the EZ, the SOZ may represent only a portion of the EZ, and its removal alone does not necessarily guarantee seizure freedom (Lüders et al., 2006). Because the "ground truth" of the EZ can ultimately be established only through successful surgical outcome, many studies focus on SOZ detection as a practical surrogate. The IZ generates interictal

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https://doi.org/10.1016/j.clinph.2026.2112333
Accepted 30 June 2026
Available online 3 July 2026

epileptiform discharges (IEDs or spikes) and may extend beyond the EZ, including but not limited to the SOZ. Thus, the EZ is not equivalent to the structural lesion, SOZ, or IZ alone; rather, it is a theoretical construct inferred from their relationships.

Detecting the EZ involves the use of multiple modalities, including non-invasive techniques such as video-electroencephalography (video-EEG), high density EEG (HD-EEG), structural MRI, EEG-fMRI, positron emission tomography (PET), SPECT and MEG (for details, see Table 1). When non-invasive methods are insufficient, invasive approaches like stereo-electroencephalography (SEEG), extraoperative subdural registrations or intraoperative electrocorticography (ECoG) may be employed. The choice of modalities depends on the patient's specific needs and the resources available at the medical center (van Mierlo et al., 2020; Zijlmans et al., 2019).

Each of the aforementioned modalities has unique advantages and limitations. For instance, MRI provides good spatial resolution but lacks temporal precision, whereas MEG and EEG offer superior temporal resolution but poorer spatial accuracy. SEEG addresses many of the limitations of EEG, delivering both high temporal and spatial resolution, albeit with limited spatial sampling due to its invasive nature. For patients with data available from multiple modalities, combining these approaches offers a promising strategy to maximize diagnostic potential.

Multiple studies have demonstrated that concordance among different modalities is a strong predictor of successful surgical outcome and an effective indicator of EZ (Fiallo Arroyo & Leon-Rojas, 2025; Jin et al., 2021; Lapalme-Remis & Nguyen, 2022). For example, patients with concordant findings from structural MRI and high-density electrical source imaging were shown to have a significantly higher likelihood of favorable postsurgical outcomes (92.3%) compared to those with discordant results (63%) (Lascano et al., 2016). Similarly, concordant findings from MEG and T1-weighted MRI (W. Wang et al., 2024) or ictal SPECT (El Tahry et al., 2018) have been associated with seizure freedom following surgery. Concordance among PET, MEG, high-resolution EEG, and EEG-fMRI has been shown to localize the EZ, as defined by SEEG, with 80% accuracy (Rossi Sebastiano et al., 2020) Additionally, the combination of magnetic source imaging and EEG-fMRI has proven effective in identifying the EZ (Berger et al., 2021). In challenging non-lesional cases, overlapping results from electrophysiology and MRI data has been successfully used to localize the EZ (Biagioli et al., 2025; Gong et al., 2024).

However, the above-mentioned studies primarily focused on demonstrating overlapping results from independently analyzed modalities. In clinical practice, many challenging epilepsy cases still show discordant findings across modalities when identifying the EZ. This aligns with reports that, despite an increasing number of pre-surgical evaluations, the rate of epilepsy surgeries remains stable, often due to difficulties in localizing the EZ (Cloppenborg et al., 2016; Jehi et al., 2015). If we assume that surgical outcomes are shaped by complex interactions between electrophysiological, anatomical, and functional aspects of the EZ, then integrating multimodal data in more sophisticated ways should enhance both EZ identification and outcome prediction. Multimodal analysis could go beyond comparing or correlating independently derived results. For example, incorporating structural connectivity can guide and constrain functional connectivity analyses, ultimately improving their interpretive power (Jones, Beall, et al., 2014). This way, multimodal integration can serve two aims: improving EZ localization to support resective surgery or guide invasive exploration, and maximizing information gained from invasive explorations by accounting for their inherent biases.

To date, only two approaches are widely used in clinical practice to integrate electrophysiological data with MRI. The first involves simultaneous EEG-fMRI (Arafat et al., 2026; Gotman & Pittau, 2011; Ikemoto et al., 2022, 2024; Sadjadi et al., 2021) and the emerging method of simultaneous intracranial EEG-fMRI demonstrates potential (Jones, Zhang, et al., 2014; Wilson, Pittman, et al., 2024; Wilson, Tehrani, et al., 2024). The second approach uses individual structural MRI data, typically T1-weighted images, often complemented by T2-weighted and diffusion-weighted imaging (DWI), to build patient-specific head models for source localization in EEG or MEG analyses (section 4.3).

This narrative review presents state-of-the-art methods for integrating electrophysiological and MRI data to delineate the epileptogenic zone (EZ) and/or predict surgical outcomes in patients with focal DRE. These modalities are highlighted because of their complementary characteristics and widespread use in presurgical epilepsy evaluation. To our knowledge, this is the first review to provide a comprehensive overview of integration strategies across multiple MRI modalities. We first provide a brief overview of the modalities discussed, including their principles, limitations, and current applications in epilepsy presurgical evaluation. The subsequent sections are organized by MRI modality and outline their integration with electrophysiology, along with the relevant literature. A dedicated section addresses the role of machine learning (ML) approaches. Particular emphasis is placed on identifying challenges associated with multimodal integration and on strategies to reconcile the inherent differences between electrophysiological and MRI data.

2. Methods

The literature search was conducted between May 2024 and February 2026 on PubMed, Google Scholar and Scopus. Search terms included combinations of "epilep*", "EEG", "SEEG", "MEG", "electrophysiology", "MRI", "ASL", "DWI", "DTI", "fMRI", "MRSI", "single voxel

Table 1
Overview of the most common techniques used to detect the epileptogenic zone in the presurgical workup.

non-invasive	Video-EEG	Video-electroencephalography: the simultaneous recording of brain electrical activity and synchronized video to correlate seizures or abnormal EEG events with behavior (section 3.1)
	HD-EEG	High density EEG: recording of brain electrical activity with high number of electrodes (typically 64, 128 or 256) used to localize interictal epileptic discharges and identify the epileptogenic zone (section 3.1)
	Structural MRI	Structural magnetic resonance imaging: used to detect potential epileptogenic lesions (section 3.2)
	EEG-fMRI	Simultaneous electroencephalography and functional magnetic resonance imaging: used to localize generators of interictal epileptic discharges (section 4.2)
	PET	Positron emission tomography: used to measure brain metabolism (most commonly using ^{18}F-fluorodeoxyglucose tracer) and identify hypometabolic regions associated with the epileptogenic zone
	SPECT	Single-photon emission computed tomography: used to detect regions of increased cerebral blood flow during seizure corresponding to the ictal and propagation zones. Subtraction ictal SPECT coregistered to MRI (SISCOM) compare ictal and interictal perfusion.
	MEG	Magnetoencephalography: recording of magnetic fields generated by neuronal activity, used to localize interictal epileptic discharges and identify the epileptogenic zone (section 3.1)
invasive	SEEG	Stereo electroencephalography: recording of electrical activity directly from the brain using depth electrodes, used to localize epileptic activity (section 3.1)
	extraoperative subdural registrations	Long-term recording of electrical activity of the cortex using subdural electrodes, including grids and strips, placed directly on the cortical surface (section 3.1)
	intraoperative ECoG	Intraoperative electrocorticography: recording of electrical activity of the cortex using subdural electrodes, including grids and strips, placed directly on the cortical surface during resective surgery (section 3.1)

MRS", "multimodal", "fusion". Results of the search were screened based on titles and abstracts. The references of selected papers were screened for additional relevant literature. Only papers combining electrophysiology and MRI imaging were included. Animal research, publications in languages other than English, case studies and papers validating MRI imaging by comparing them with intracranial EEG as a gold standard were excluded.

3. Electrophysiological and neuroimaging modalities used in EZ detection and surgical outcome prediction

3.1. Electrophysiology

Electrophysiological techniques in epilepsy measure local field potentials arising from synchronized neuronal activity. Scalp EEG provides non-invasive recordings predominantly reflecting activity from superficial cortical layers, with high temporal but limited spatial resolution due to volume conduction. High-density EEG (HD-EEG) and MEG offer improved spatial resolution, although MEG is less widely used because of its high cost and technical demands. In contrast, intracranial EEG (iEEG), including extra- and intra-operative subdural registrations and SEEG, enables direct, high-resolution recording from both cortical and deep brain structures. Clinically, EEG is used to capture seizures and interictal epileptiform discharges (IEDs) which assist in the lateralization and localization of the seizure onset zone (SOZ). iEEG remains the gold standard for SOZ localization through recordings of spontaneous and stimulated seizures, interictal epileptiform discharges (IEDs), and high-frequency oscillations (HFOs). iEEG is also essential for mapping the eloquent cortex during presurgical evaluation.

3.2. Anatomical MRI

T1-weighted (T1w) MRI plays a central role in the presurgical evaluation of epilepsy due to its high spatial resolution. The primary utility of structural MRI lies in the detection of malformations of cortical development (MCDs) (Hoeberigs & Tousseyn, 2025). Complementary sequences, such as fluid-attenuated inversion recovery (FLAIR), enhance sensitivity to other pathological changes (Olson & Perry, 2013; Yoganathan et al., 2023). T2 Turbo spin echo and susceptibility-weighted images (SWI) are useful for imaging the subfields of the hippocampus and for identifying vascular abnormalities (Duncan & Trimmel, 2022; Lapalme-Remis & Nguyen, 2022). Although the detection of a lesion on MRI is a major predictive factor for successful outcome, not all lesions are epileptogenic, and the EZ may be located outside the visible anatomical abnormalities (Lapalme-Remis & Nguyen, 2022; Olson & Perry, 2013; Zijlmans et al., 2019). Additionally, T1w imaging with double contrast is commonly used for planning depth electrode trajectories for SEEG and in the differential diagnosis of tumors.

3.3. Functional MRI (fMRI)

Functional magnetic resonance imaging (fMRI) measures changes in the blood-oxygen-level-dependent (BOLD) signal. BOLD indirectly indicate neuronal activity via neurovascular coupling. Although fMRI provides high spatial resolution, its temporal resolution is limited primarily by the slow hemodynamic response and secondarily by the repetition time, which constrains the sampling rate of the BOLD signal. Task-based fMRI captures localized increases in energy consumption evoked by specific stimuli or actions, while resting-state fMRI (rs-fMRI) detects spontaneous fluctuations in brain activity. In clinical practice, task fMRI is used for mapping eloquent cortex prior to resective surgery or ablation, especially for language and motor cortices.

3.4. Diffusion weighted imaging (DWI)

Diffusion-weighted imaging (DWI) enables the characterization of water molecule diffusion within brain tissue, providing insight into its microstructural organization. From the DWI, several scalar metrics can be derived to assess tissue integrity, the most commonly used being mean diffusivity (MD) and fractional anisotropy (FA). MD represents the average water diffusivity within a voxel, while FA quantifies the degree of diffusion anisotropy, with higher values associated with well-organized axonal tracts. Tractography estimates the main direction of diffusion in each voxel and then traces the probable paths of white matter tracts. Clinically, tractography is used for presurgical planning, such as delineating the optic radiation with the aim to reduce risk of visual field deficits following surgery or RFTC (Song et al., 2024). However, whether the use of tractography reduces the risk of injury has not yet been systematically examined.

3.5. Proton magnetic resonance spectroscopic imaging (^{1}H-MRSI)

Proton Magnetic Resonance Spectroscopic Imaging (^{1}H-MRSI) can be used to quantify metabolite concentrations across brain tissue. Spectra acquired at each voxel display peaks at resonances specific to individual metabolites, enabling the generation of spatial metabolite maps. Commonly analyzed metabolites include N-acetylaspartate (NAA), creatine (Cr), and choline-containing compounds (Cho).

4. Integration of MRI and electrophysiology

4.1. Anatomical MRI

Quantitative metrics derived from T1w imaging, such as cortical thickness and grey matter volume, have been identified as strong predictors of the EZ (Říha et al., 2022). Sahlas et al. (Sahlas et al., 2025) reported structural alterations, including cortical thickness and quantitative T1, along with mean diffusivity from DWI, between patients and healthy controls. These changes were observed within the spike sources identified by HD-EEG and in regions functionally connected to those sources, but not in their anatomical neighbors. Structural MRI–derived features are also widely incorporated into multimodal machine-learning models for improved EZ localization and predicting surgery outcome (Marecek et al., 2021; Memarian et al., 2015; Mo et al., 2022; Moser et al., 2000; Nejedly et al., 2025), see section 5.

4.2. Functional MRI (fMRI)

Simultaneous EEG-fMRI (and more rarely, iEEG-fMRI) represents one of the few clinically applied multimodal imaging methods. Recent reviews (Arafat et al., 2026; Ikemoto et al., 2022; Sadjadi et al., 2021) have summarized the application and limitations of this technique in epilepsy. In brief, IEDs recorded during rs-fMRI are used as events in fMRI analysis. After convolution with a canonical hemodynamic response function (HRF), these events are used as regressors in a general linear model (GLM) to localize IEDs generators. While scalp EEG can only detect superficial cortical activity, fMRI may reveal deep or distant epileptogenic regions, beyond the detection capacity of EEG. Although rare, ictal EEG-fMRI analyses have also been reported (Ikemoto et al., 2022). EEG-fMRI can improve diagnostic confidence in epilepsy syndrome classification, EZ localization, and surgical candidacy assessment (Ikemoto et al., 2024).

Studies published after the aforementioned reviews have continued to address key limitations of EEG-fMRI (see Table 2), including the reliance on a space- and subject-invariant HRF. For example, Eyndhoven et al. (Van Eyndhoven et al., 2021) proposed a blind source separation (BSS) technique based on structured coupled matrix-tensor factorization (sCMTF) to detect SOZ based on IED related fMRI components. The method also enables to estimate HRF and its variability, which they argue provides informative insights. Chatzichristos et al. (Chatzichristos et al., 2022) similarly introduced BSS approaches, namely flexible and soft-coupling tensor models, as alternatives to an invariant HRF,

Table 2
List of studies discussed in this review combining electrophysiology and functional MRI.

Paper	Modality	Epilepsy	Number of subjects	Goal
Van Eyndhoven et al., 2021	Interictal EEG-fMRI	Focal DRE	12 patients	Structured coupled matrix-tensor factorization of EEG-fMRI to identify IED-related components
Chatzichristos et al., 2022	Interictal EEG-fMRI	TLE	10 patients	Two tensor models for EEG-fMRI coupling (soft and flexible) to identifying IED-related components
Wirsich et al., 2024	Interictal EEG-fMRI	TLE	35 healthy controls 34 patients	Comparison of correlations of EEG and fMRI connectivity matrixes in healthy controls and patients

EEG: Electroencephalography; fMRI: functional magnetic resonance imaging; TLE: temporal lobe epilepsy; DRE: drug resistant epilepsy; IED: interictal epileptic discharges; BOLD: Blood Oxygenation Level Dependent; HFO: high frequency oscillations; iEEG: intracranial EEG

demonstrating good performance in localizing IEDs. However, they noted that applying tensor-based methods in multi-subject studies requires the SOZ to be located in similar brain regions across patients. Moreover, the optimal choice of model parameters depends heavily on a priori knowledge of the problem.

Rather than modeling IED-related responses, Wirsich et al. (Wirsich et al., 2024) examined correlations between resting state EEG and fMRI connectivity matrices. They suggested that altered EEG-fMRI connectivity correlations in temporal lobe epilepsy (TLE) patients, compared to controls, highlight the value of multimodal analysis despite incomplete understanding of the link between metabolic and electrical brain activity. Specifically, right TLE showed increased correlations across multiple EEG bands (delta to beta) across the whole brain, while left TLE exhibited decreased beta-band correlations localized to the default mode network. These results indicate lateralized, modality-specific brain network alteration in TLE.

Although there is growing evidence supporting the usefulness of rs-fMRI in localizing the EZ and predicting surgical outcomes (Doss et al., 2024; Tracy & Doucet, 2015), few studies have combined separately acquired fMRI and (i)EEG data. rs-fMRI–derived metrics such as regional homogeneity and (fractional) amplitude of low-frequency fluctuations were identified as part of an optimal combination of imaging markers for EZ localization in MRI-negative patients (Říha et al., 2022; ; Uher et al., 2023). In parallel, the utility of rs-fMRI and independent component analysis (ICA) for detecting the SOZ was demonstrated in a *meta*-analysis (Chakraborty et al., 2020). These findings underscore the potential of rs-fMRI as a stand-alone tool, but its integration with (i)EEG remains largely unexplored. The lower temporal resolution of fMRI poses challenges for direct alignment with electrophysiological data, although emerging multimodal approaches may help bridge this gap. Two studies applied machine learning algorithm to combine separately acquired rs-fMRI and EEG data for EZ detection (Hosseini et al., 2020) and seizure recurrence (Drenthen et al., 2021), see section 5.

4.3. *Diffusion weighted imaging (DWI)*

Diffusion tensor imaging (DTI) can be integrated into personalized head models for the forward modeling step in EEG/MEG source analysis (Güllmar et al., 2010; Rullmann et al., 2009). For example, Aydin et al. (Aydin et al., 2017) incorporated DTI-derived conductivity tensors into their head models to account for anisotropic white matter. Subsequently, they used the resulting source localization (combined EEG and MEG) to guide a targeted, high-resolution ZOOMit MRI sequence, which enabled the detection of a subtle focal cortical dysplasia that was not visible on conventional imaging. Similarly, Zwick et al. (Zwick et al., 2022) used DTI to classify tissue type at the voxel level and to estimate patient-specific conductivity values in a source analysis framework that also accounted for brain deformations resulting from ECoG implantation.

Fractional anisotropy and mean diffusivity can be integrated into multimodal machine learning frameworks, combining neuroimaging, electrophysiological, and clinical variables (Marecek et al., 2021), see section 5. The following section describes the rationale behind combining tractography with electrophysiology. The summary of discussed papers is presented in Table 3.

In the context of epilepsy research, the combination of tractography with electrophysiological data is typically applied in three main ways: (1) identifying structural white matter connections between regions of interest (ROIs) defined by electrophysiology recordings, (2) assessing structure–function coupling, i.e., the correspondence between structural and electrophysiological connectivity, and (3) modelling epileptic activity using patient specific structural connectivity.

4.3.1. *Electrophysiologcally defined ROI for structural connectivity analysis*

4.3.1.1. IEDs propagation and source localization. ROIs in epilepsy research often include areas associated with the SOZ, propagation zone (PZ), irritative zone (IZ), and non-involved zone (NIZ). These ROIs are typically defined by experienced clinicians using SEEG as the gold standard, supported by evidence from non-invasive methods. Sometimes some quantitative metrics are used to objectively measure SOZ, like epileptogenicity index (EI) (Bartolomei, 2024; Bartolomei et al., 2008). Studies utilizing tractography within this framework aim to describe the role of white matter tracts in the propagation of seizures and IEDs, providing insight into the organization of epilepsy networks. This line of research addresses a question in epilepsy: whether such propagation occurs via grey matter (travelling wave) or is mediated by white matter tracks.

To answer this question, Azeem et al. (Azeem et al., 2023) classified ROI around SEEG contacts as source or sinks based on IEDs latency. Their findings showed that regions involved in spike propagation were more likely to be structurally connected through white matter pathways. However, they also observed instances of propagation between distant regions that lacked direct white matter connections, suggesting that long-range propagation may occur indirectly, either through grey matter or via a series of intermediate, structurally connected regions.

In another study, a unified model of IED propagation that accounts for both traveling wave through grey matter and spread along white matter tracts demonstrated equal or superior accuracy in predicting surgical outcomes compared to localization based solely on the leading electrode (Withers et al., 2023).

Mitsuhashi et al. (Mitsuhashi et al., 2021) introduced a new approach to modeling IED sources, using also spikes' latency to differentiate ROIs into leading and lagging sites. By incorporating tractography, they estimated IED propagation velocity, which was subsequently used to model potential sources along the white matter tracts from leading regions outside regions sampled by SEEG. In patients with mesial temporal lobe epilepsy (mTLE) who achieved ILAE Class 1 surgical outcomes, the modeled sources were more often located within the resected zone and within the medial temporal lobe compared to those with less favorable outcomes.

4.3.1.2. Seizure propagation. Azeem et al. (Azeem et al., 2024) investigated the role of white matter tracts in seizure propagation comparing structural connectivity between SOZ, propagation (PZ) and non-involved zones (NIZ). The study found that the SOZ was more tract-

Table 3
List of studies discussed in this review combining electrophysiology and diffusion weighted images.

Paper	Modality	Epilepsy	Number of subjects	Goal
Azeem et al., 2023	**dMRI:** probablistic tractography **SEEG:** spike propagation networks	no structural malformations or abnormalities that significantly distort the anatomy including patients with FCD lesions or questionable FCD lesions	59 patients; dMRI from Human Connectome project	Determination of the role of white matter tracts in spike propagation
Withers et al., 2023	**iEEG (ECoG and SEEG):** IED **DTI:** connectome	Focal DRE	38 patients	Model of IED propagation incorporating both travelling wave and white matter
Mitsuhashi et al., 2021	**ECoG:** source of spikes **DWI:** streamline length	TLE excluding multifocal mass lesions on MRI, malignant tumor suspected on MRI, previous resective surgery	19 patients (iEEG) 1065 individuals participating in the Human Connectome Project (DWI)	Dynamic tractography framework for mapping interictal spike sources and visualization of their spread through white matter
Azeem et al., 2024	**SEEG:** seizure propagation map **dMRI**: probabilistic tractography	DRE, excluding structural malformations or abnormalities that significantly distort the anatomy (atrophy, nodular heterotopia or surgical cavities). Including patients with circumscribed focal cortical dysplasia or questionable focal cortical dysplasia lesions.	26 patients, dMRI from Human Connectome project	Determination of the role of white matter tracts in seizure propagation
Gleichgerrcht et al., 2021	**SEEG:** directionality of seizure spread **DTI:** FA connectome	TLE	33 patients	Determination of the role of white matter tracts in directionality of seizure propagation
Besson et al., 2017	**SEEG:** definition of zones (EZ, PZ, NIZ) based on ictal signal (EI) **DWI:** high-resolution structural connectome framework	Focal DRE	15 patients; 36 healthy controls	Determination of structural connectivity changes in relation to epileptic activities
Chang et al., 2023	**SEEG:** ictal and rest, coherence in beta frequency range **DTI:** tractography	TLE	13 patients	Prediction of resective surgery (or laser ablation) outcome based on functional-structural coupling
Parker et al., 2018	**SEEG:** CCEP **DWI:** streamline density	Focal DRE	7 patients	Comparison of the effective and structural connectivity
Shah et al., 2019	**iEEG (ECoG and SEEG):** time-varying functional connectivity during preictal and ictal state **HARDI:** streamline count	Unilateral, focal DRE	9 patients	Determination of the role of structure–function coupling in seizure propagation
Sinha et al., 2023	**iEEG (ECoG and SEEG):** interictal frequency specific Pearson correlation in sliding window **DWI:** number of tracts between electrodes	Focal DRE	39 patients	Predictive value of structure–function coupling for surgery outcome
Johnson et al., 2023	**DWI:** patient-specific structural connectivity metrics obtained from SWiNDL, **SEEG:** interictal resting-state connectivity: ImCoh and PDC	uni and bilateral mTLE, unilateral lateral TLE, unilateral frontal lobe epilepsy, unilateral parietal lobe, multiple presumed foci	26 DRE patients	Evaluation of the structure–function coupling effects on connectivity
Rigoni et al., 2023	**HD-EEG:** IEDs source reconstruction **DSI:** tractography	TLE	17 patients (HD-EEG) 70 individuals from Human Connectome Project: DSI	Structure-function coupling during IED
Proix et al., 2017	**dMRI:** connectivity matrix **SEEG:** visually recognized SOZ and PZ and quantified PZ based on spectral changes during seizure	Focal DRE	15 patients	Improvement of the diagnosis and surgery outcome by using personalized virtual brain
Wang et al., 2023	**dMRI:** tractography **SEEG:** ictal signal	Focal DRE	53 patients	Determination of the SOZ and predict virtual surgery outcome
Vattikonda et al., 2021	**dMRI:** tractography **SEEG:** log power and total power in each sensor of the ictal signal	Focal DRE	25 patients	Delineation of the SOZ
Makhalova et al., 2022	**dMRI:** connectome **SEEG:** SOZ determined by visual inspection and EI score	Focal DRE	53 patients	Delineation of the SOZ and prediction of seizure outcome
Lopez-Sola et al 2025	**dMRI**: connectome **SEEG**: ictal signal (functional connectivity)	Focal DRE	6 patients	Simulation of patient-specific seizure propagation pattern and its changes due to intervention (surgical, pharmacological and stimulation)
Sip et al., 2021	**DTI:** connectome **SEEG:** ictal signal: seizure onset	Focal DRE	50 patients	Prediction of seizure activity and onset in regions unsampled by SEEG based on model of seizure spread

dMRI: diffusion MRI; SEEG: stereo-EEG; FCD: focal cortical dysplasia; DRE: drug resistant epilepsy; iEEG: intracranial EEG; HARDI: high angular resolution diffusion imaging; TLE: temporal lobe epilepsy; EZ: epileptogenic zone; PZ: propagation zone; NIZ: not involved zone; FA: fractional anisotropy; DSI: diffusion spectrum

imaging; IEDs: interictal epileptic discharges; CCEP: cortico-cortical evoked potentials; SOZ: seizure onset zone; EI: epileptogenicity index; SWiNDL: subsampling whole-brain tractography with iEEG near-field dynamic localization; ImCoh: imaginary coherence; PDC: partial directed coherence.

connected to PZs than to NIZs. However, PZs were not more interconnected with each other than with NIZs. These results imply that the SOZ may act as the main source of seizure propagation across the brain, rather than spreading through intermediary regions. Tract connectivity was also linked to surgical outcome: connectivity between the SOZ and propagation zone was higher in seizure-free patients than in those not seizure-free, and in seizure-free patients, connectivity could distinguish the SOZ from the PZ.

Gleichgerrcht et al. (Gleichgerrcht et al., 2021) focused on the directionality of seizure spread. Seizures were described by clinicians as either anterior-posterior (AP) or medial–lateral (ML) spread based upon SEEG evaluation. Patients with ML seizures had higher fractional anisotropy (FA) along the corpus callosum and, to a lesser degree, some portions of the bilateral cingulate tracts. In contrast, patients with AP seizures had higher FA along several anterior-posterior white matter projections bundles, including the cingulate and the inferior longitudinal fasciculus, with significantly less involvement of the corpus callosum compared with ML seizures.

While the above-mentioned studies demonstrated structural changes that may underlie spike and seizure propagation, Besson et al. (Besson et al., 2017) reported decreased white matter fiber tract density between EZ–NIZ and between PZ–NIZ, but not between or within EZ. Widespread changes in structural connectivity were observed across major functional networks, including the salience, default mode, and frontoparietal networks, while connectivity within the epileptogenic network was relatively preserved. Besson argued that these findings suggest the relatively normal connectivity observed between pathological brain regions may, in fact, represent pathologically hyperconnected areas, potentially at the expense of connectivity with the rest of the brain.

4.3.2. Structure-function coupling

Seizures in focal epilepsy are thought to arise from structurally altered brain regions, where anatomical abnormalities drive functional disruptions. Since surgery targets these structural changes to alter brain function, structure–function coupling is an interesting, but still underexplored focus in epilepsy research.

Most of studies assess structure–function coupling by comparing structural (derived from DTI) and functional (both resting state (intracranial) EEG and cortico-cortical evoked potentials (CCEPs)) connectivity matrices, often using similarity metrics such as the Jaccard or Dice indices for binarized matrices, or correlation. For instance, Chang et al. (Chang et al., 2023) employed the Jaccard index to evaluate structure–function coupling both at rest and during ictal events. They found that patients who did not achieve seizure freedom after surgery exhibited greater coupling recruitment than responders, both at rest and during early and mid-seizure phases.

The Jaccard index was also used by Parker et al. (Parker et al., 2018). While Chang et al. focused on SEEG functional connectivity based on beta-band coherence, Parker et al. analyzed effective connectivity derived from CCEPs. Interestingly, although the overlap between structural and effective connectivity was higher than anticipated, the correlation between the two modalities remained low.

Pearson correlation between structural and functional connectivity matrices was employed by Shah et al. (Shah et al., 2019) to investigate changes in structure–function coupling from pre-ictal to ictal periods, as well as to assess the consistency of coupling patterns across seizures within individual patients. They observed a significant increase in structure–function coupling during the ictal phase compared to the pre-ictal state. Using a virtual edge resection approach, where individual edges were systematically removed and the resulting change in structure–function correlation was evaluated, they demonstrated that this coupling increase was primarily driven by short-range structural connections. Furthermore, they found that the spatiotemporal patterns of structure–function coupling were highly consistent between seizures within each patient.

Correlation and virtual edge resection was also employed by Sinha et al. (Sinha et al., 2023) to predict postsurgical seizure outcomes. In their analysis, they assessed the change in structure–function correlation following the removal of each node, categorizing nodes as “boosters” or “dumpers” depending on whether their removal increased or decreased structure–function coupling during interictal period. These features were then incorporated into a support vector machine (SVM) model, which also included 16 clinical variables. Their results suggested that patients whose structure–function coupling increased after surgery were more likely to achieve seizure freedom.

Two studies moved beyond similarity indexes. Johnson et al. (Johnson et al., 2023) focused on Interictal Suppression Hypothesis, which posits that SOZ is actively suppressed by the broader brain network during interictal periods. While their primary analysis relied on SEEG data, they also analyzed structure–function coupling. They introduced a novel contact-specific structural connectivity framework termed SWiNDL (‘subsampling whole-brain tractography with iEEG near-field dynamic localization’) to construct of a patient-specific SEEG contact-to-contact structural connectome. The structure–function coupling was evaluated by calculating the ratio of structural to resting state functional connectivity for each SEEG edge in a patient.

Rigoni et al. (Rigoni et al., 2023) applied graph signal processing (GSP) to investigate the role of structural connectivity in the temporal dynamics IEDs. In GSP, the structural connectivity matrix is decomposed into Laplacian eigenvectors (graph harmonics). Low-eigenvalue components reflect integrative processes constrained by structural architecture, whereas high-eigenvalue components capture segregative, localized dynamics. Functional time-series, such as source-projected EEG, can be expressed as linear combinations of these components, allowing assessment of whether integration or segregation dominates. Using this approach, Rigoni found that, at the whole-brain level, IEDs are characterized by a shift from segregative to integrative dynamics. Locally, areas typically implicated in the TLE network exhibited increased alignment with long-range structural connectivity during IED events.

4.3.3. Whole-brain modelling

Whole-brain modeling in epilepsy emerged with tractography, enabling the integration of white matter pathways into simulations of seizure propagation (D’Angelo & Jirsa, 2022; V. Jirsa et al., 2023). Virtual brain models, constrained by individual structural connectivity, aim to reproduce functional dynamics across imaging modalities (V. K. Jirsa et al., 2017; Lopez-Sola et al., 2025; Makhalova et al., 2022; Proix et al., 2017; Vattikonda et al., 2021; H. E. Wang et al., 2023). Structural connectomes are defined using tractography, with nodes based on anatomical atlases and edges representing white matter tracts. Neural mass models, system of nonlinear differential equations, are employed at each node to estimate average neural activity, with parameters informed by empirical data, clinical hypotheses about the SOZ, PZ and validated against empirical data, including SEEG. Virtual brain models provide a framework for testing hypotheses about the location of the EZ and the potential effects of surgical intervention.

While personalized brain models hold promise for improving surgery planning in future and is undergoing clinical trial (V. Jirsa et al., 2023), complex models with multiple parameters require expertise and may therefore be difficult to implement in clinical settings. Moreover, the use of many parameters may reduce interpretability and make inversion the model difficult even if possible. Sip et al. (Sip et al., 2021) developed a simplified model of seizure spread using a single regional excitability parameter. This approach allowed for efficient model inversion and the

estimation of brain activity in regions not sampled by SEEG. The model was individualized using weighted structural connectivity and trained on SEEG-determined seizure onsets to predict seizure versus non-seizure states and onset timing.

4.4. Proton magnetic resonance spectroscopic imaging (^{1}H-MRSI)

Although ^{1}H-MRSI is not routinely used in current epilepsy research or clinical workups, early studies explored its potential to link metabolic and electrophysiological data (Table 4). Bernasconi et al. (Bernasconi et al., 1999) investigated a possible correlation between interictal delta EEG activity (<4 Hz) and NAA levels in the lateral and posterior temporal lobe in temporal lobe epilepsy, but found no significant relationship. Serles et al. (Serles et al., 1999) reported higher IED frequencies on surface EEG in regions with pronounced metabolic dysfunction. Subsequent studies demonstrated reduced NAA in epilepsy patients, particularly within the SEEG-defined EZ and propagation compared to non-involved zones (Azilinon et al., 2023; Guye et al., 2005).

5. Machine learning

Artificial Intelligence (AI) and its subfield ML have gained significant attention in recent years within biomedical science, including epilepsy research (Abbasi & Goldenholz, 2019; Lucas et al., 2024; Mirchi et al., 2022; Sone & Beheshti, 2021; Yuan et al., 2022). ML algorithms excel at identifying patterns within vast datasets that may be difficult or impossible to discern using traditional methods due to the complexity and volume of the data. The automation of large-scale data analysis holds great potential for streamlining clinical workflows. Although this capability makes ML particularly well-suited for multimodal analysis, it is surprising that the majority of research in this area has focused on either MRI or electrophysiology independently, with studies combining both remaining relatively rare (Lucas et al., 2024).

A limited number of studies have utilized ML models trained on both EEG and MRI data to advance epilepsy research. These include models to predict epileptogenic networks (Hosseini et al., 2020; Mo et al., 2022), lateralization of seizure (Moser et al., 2000), localize and differentiate SOZ, PZ, and NIZ (Johnson et al., 2023; Xiao et al., 2025), forecast seizure outcomes (Memarian et al., 2015), automate surgical planning (Nejedly et al., 2025), and prediction of seizure recurrence (Drenthen et al., 2021). The summary of cited papers is shown in Table 5.

When compared to unimodal classifiers, multimodal classifiers demonstrated superior performance (Drenthen et al., 2021; Johnson et al., 2023; Memarian et al., 2015; Moser et al., 2000; Xiao et al., 2025). Even when feature selection for training was automated, rather than determined by researchers, the combination of electrophysiological and MRI features emerged as part of the most optimal feature set (Memarian et al., 2015).

In supervised ML model training, defined classes are essential. For predicting seizure outcome, the class is typically clear, with patients grouped according to the ILAE classification (seizure-free ILAE = 1 vs non-seizure-free) (Memarian et al., 2015). For EZ detection, manually labeled brain regions may be required (Johnson et al., 2023), or models can be trained using T-value statistical maps that quantify deviations from a normative model based on healthy control cohorts (Marecek et al., 2021). Nejedly et al. (Nejedly et al., 2025) used the resection or ablation status of each SEEG contact as the classification label. Unlike other studies in this section, Mo et al. (Mo et al., 2022) did not use both neuroimaging and electrophysiology but instead aimed to predict SEEG based epileptogenicity mapping (EM) values (Yan et al., 2020) in patients with focal cortical dysplasia type IIIa (FCD IIIa). EM values, calculated from SEEG signals, reflect brain regions with higher frequency activities (80–250 Hz), helping identify EZ. Their goal was to predict EM values in areas unsampled by SEEG data, using MRI and PET surface metrics. The resulting epileptogenicity map was correlated with surgical outcomes, showing that in seizure-free patients (7 patients, ILAE = 1), most high-epileptogenicity regions were resected. In contrast, non-seizure-free patients exhibited high-epileptogenicity regions outside the surgical cavity.

While ML analysis addresses some limitations of traditional statistical methods, it also introduces new challenges, both in scientific validation and practical implementation (Lucas et al., 2024). ML models perform best when trained on large datasets, but the highly specific inclusion criteria used in many studies result in relatively small datasets, which can lead to overfitting and poor generalizability. Strategies applied in the cited studies to mitigate these issues include (nested) cross-validation (Johnson et al., 2023; Mo et al., 2022; Moser et al., 2000; Nejedly et al., 2025), feature selection (Drenthen et al., 2021; Memarian et al., 2015) and regularization (Drenthen et al., 2021). In addition, well-balanced datasets are essential to reduce bias in clinical applications (Loushy & Sperling, 2025).

Moreover, the 'black box' nature of many ML models raises issues of trust in clinical settings and questions about medical responsibility. Consequently, explainable AI is a crucial direction for translating research into clinical practice and enhancing interpretability and applicability (Reyes et al., 2020; van der Velden et al., 2022). Notably, as Reyes et al. pointed out, interpretability is influenced not only by model architecture, but also by the complexity of input features; even a linear model can be difficult to interpret if its features are complex (Reyes et al., 2020).

Table 4
List of studies discussed in this review combining electrophysiology and Proton Magnetic Resonance Spectroscopic Imaging.

Paper	Modality	Epilepsy	Number of subjects	Goal
Bernasconi et al., 1999	**^{1}H-MRSI:** level of NAA **Interictal EEG:** delta (< 4 Hz) power	TLE	34 patients 10 HC	Association of background delta activity with NAA
Serles et al., 1999	**EEG:** spike frequency **^{1}H-MRSI:** NAA/Cr ratio	TLE and FLE	14 patients	Association of frequency of interictal spikes with NAA/Cr ratio
Guye et al., 2005	**SEEG:** EZ/PZ/NIZ definition based on both ictal and interictal signals **^{1}H-MRSI:** NAA/Cr, NAA/(Cho + Cr)	FLE	12 patients 12 HC	Characterization of metabolic changes in epileptogenic network to evaluate the usefulness of ^{1}H-MRSI in the presurgical assessment of FLE
Azilinon et al., 2023	**SEEG:** ROI definition based on ictal signal (EI) **^{1}H-MRSI:** level of NAA, Cho, tCr	Focal DRE	MRSI: 19 patients MRSI: 25 HC	Characterization of metabolic changes within epileptogenic networks

ROI: region of interest; TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; HC: healthy control; TSC: total sodium concentration; DRE: drug resistant epilepsy; ^{1}H-MRSI: proton magnetic resonance spectroscopic imaging; NAA: N-acetyl aspartate; Cho: choline compounds; tCr: and total creatine; Cr: creatine; EI: epileptogenicity index.

6. Discussion

In this review, we examined electrophysiological and MRI-based techniques used for EZ detection and surgical outcome prediction. Our focus was on approaches that integrate these modalities, based on the premise that their distinct yet complementary strengths can help overcome the limitations inherent to each when used in isolation. It is worth

Table 5
List of studies discussed in this review combining electrophysiology and MRI using machine learning.

Paper	Modality	Type/Etiology	Number of subjects	Goal	Model	Success
Mo et al., 2022	**T1:** cortical thickness, GM/WM boundary blurring, surface area, cortical folding complexity, **FLAIR**: midsurface intensity, signal gradient, **PET**: midsurface intensity, signal gradient **SEEG:** changes during seizures compared to baseline (EM)	FCD IIIa	9 patients	Whole-brain epileptogenicity (SEEG) prediction	Support vector regression model	mean-squared error = 13.8 ± 9.8
Hosseini et al., 2020	**EEG:** DDCG **rs-fMRI**: connectivity	Temporal and extratemporal epilepsy	9 patients	Estimation and prediction of the epileptogenic network	LSTM deep learning	Accuracy 98%, Sensitivity 96%, Specificity 97%
Moser et al., 2000	**Ictal EEG:** seizure lateralization index **T1w MRI:** difference in hippocampal volume	Unilateral TLE	44 patients after successful anterior temporal lobectomy	Prediction lateralization of the seizure	Discriminant function analyses	93% correct lateralization
Johnson et al., 2023	**DWI:** patient-specific structural connectivity metrics obtained from SWiNDL, **SEEG:** interictal resting-state connectivity: ImCoh and PDC	uni and bilateral mTLE, unilateral lateral TLE, unilateral frontal lobe epilepsy, unilateral parietal lobe, multiple presumed foci	26 DRE patients	SOZ, early PZ and NIZs identification	SVM	Overall accuracy: 92.0 ± 2.2% SOZ detection accuracy: 92.5 ± 7.5% Propagation zone: 93.0 ± 5.3% Not-Involved zones: 71.2 ± 2.0%
Xiao et al., 2025	**SEEG:** ictal signal **DTI:** structural connectivity between SEEG contacts	TLE	15 patients	EZ localization	ST-CAN	Accuracy: 97.9% Sensitivity: 97.33% F1-score: 96.98%
Memarian et al., 2015	Family history, age*, epilepsy duration** **SEEG:** proportion of seizures that first appeared in ipsilateral amygdala to total seizures **MRI**: gray matter thickness reduction in the hemisphere ipsilateral to seizure onset *only SVM-RBF and LS-SVM **only LS-SVM	Suspected mTLE	20 patients	Prediction of seizure outcome of anteromesial temporal lobectomy	mRMR feature selector + 5 different classifiers: LDA Naïve Bayes SVM-RBF SVM-MLP LS-SVM	Accuracy: 80% 80% 90% 85% 95%
Nejedly et al., 2025	**SEEG:** interictal signals: power in bands, spectral features, spike rate, spike propagation, and phase-amplitude coupling **MRI:** Euclidean distance between electrode contacts, MNI coordinates, white matter, and grey matter distribution of contacts	Focal DRE	80 patients	Automatic suggestion of target for surgery. Estimating the role of SEEG implantation topology and MNI coordinates in model prediction.	GGN	Best model trained on all SEEG features and MNI coordinates: AUPRC = 0.6897
Drenthen et al., 2021	**EEG:** hyperventilation and resting-state: PLI, coherence, SL averaged across time and channels in different frequency bands **fMRI:** fALFF, ReHo, characteristic path length, clustering coefficient, small worldness	Not specified	26 epilepsy patients 17 subjects with single seizure	Prediction of seizure recurrence after first-ever seizure	logistic regression model with L2 regularization	Sensitivity: 74 ± 19% Specificity: 82 ± 18% AUC = 0.75 ± 0.12
Marecek et al., 2021	**T1:** GMC, GMV, JUN; **ASL**; **DWI**: FA, MD, MK **HDEEG:** IED, **PET, SPECT**	Focal DRE; MRI negative or inconclusive	137 DRE patients; 110 HC	Presurgical evaluations of MR-negative epilepsy patients; identification of epileptogenic grey matter tissue	Gaussian mixture model	AUC = 0.82 ± 0.14 in validation group, higher than a chance ($p < 0.001$)

SEEG: stereo-EEG; ECoG: electrocorticography; DDCG: directed differential connectivity graph; rs-fMRI: resting state fMRI; LSTM, long short term memory; GM: grey matter; WM: white matter, FLAIR: Fluid-Attenuated Inversion Recovery; PET: Positron Emission Tomography; EM: epileptogenicity mapping; FCD: Focal cortical dysplasia; TLE: temporal lobe epilepsy; DWI: diffusion weighted imaging;; SWiNDL: subsampling whole-brain tractography with iEEG near-field dynamic localization; ImCoh: imaginary coherence; PDC: partial directed coherence; DRE: drug resistant epilepsy;; SOZ: seizure onset zone; SVM: support vector machine; LDA: Linear Discriminant Analysis; SVM-RBF: SVM with radial basis kernel function; SVM-MLP: SVM with multilayer perceptron kernel; LS-SVM: least square SVM; mTLE: mesial temporal lobe epilepsy; mRMR: maximum relevance minimum redundancy; GMC: local gray matter intensity changes; GMV: local gray matter volume changes; JUN:

junction, gray-white matter boundary blurring; ASL: arterial spin labelling; FA: fractional anisotropy; MD: mean diffusivity; MK: mean kurtosis; HDEEG: high density EEG; IED: interictal epileptic discharges; SPECT: Single Photon Emission Computed Tomography; HC: healthy control; AUC: Area Under the curve; GGN: graph neural network; AUPRC: area under the precision-recall curve; PLI: phase Lag Index; SL: synchronization likelihood; fALFF: fractional amplitude of low-frequency fluctuation; ReHO: regional homogeneity; EZ: epileptogenic zone; ST-CAN: spatiotemporal co-attention deep neural network.

noting that studies combining electrophysiology with other modalities have also been conducted, e.g., SEEG–SPECT (Krishnan et al., 2021, 2024; Tousseyn et al., 2017) or MEG-SPECT (El Tahry et al., 2018).

Clinically, the most established fusion methods are simultaneous EEG-fMRI and personalized head models for source localization. In research, SEEG-defined ROIs (seizure onset, propagation, irritative, non-involved zones) are commonly used to investigate their properties and relations between them which can provide an insight into EZ (sections 4.3.1, 4.4). Structural connectivity has also been used to model functional dynamics (e.g., SEEG activity; section 4.3.3), and structure–function coupling can be assessed through connectivity matrix comparisons or graph signal processing analysis (section 4.3.2). Finally, features from multiple modalities can be integrated using machine learning (section 5). However, the very differences that motivate multimodal integration also present challenges for combined analyses.

6.1. Different modalities capture different phenomena and scales

Electrophysiology captures fast neural activity, primarily reflecting postsynaptic currents of synchronized pyramidal cells. Scalp EEG and MEG provide whole-head coverage of activity from superficial cortical layers, albeit with limited spatial precision, whereas iEEG offers higher spatial resolution at the cost of sampling only selected brain regions. MRI, by contrast, images the entire brain, providing structural, metabolic, and perfusion information.

Differences in the spatio-temporal resolution of fMRI and electrophysiology make their combined analysis challenging, which likely explains the relatively small number of studies integrating separately acquired fMRI and (i)EEG. Although correlations between neural and metabolic activity have been demonstrated (Kucyi et al., 2018; Logothetis et al., 2001; Wirsich et al., 2017, 2021) their relationship is not fully understood. Within a simultaneous EEG-fMRI framework, fMRI can detect deep or small IED generators that are impossible to capture using EEG or iEEG alone. However, although peak BOLD responses to IEDs often localize within the SOZ (Heers et al., 2014; Khoo et al., 2017), fMRI frequently overestimates the SOZ, showing broader activation beyond the SOZ (Grova et al., 2008; Heers et al., 2014; Tousseyn et al., 2014a; Wilson, Tehrani, et al., 2024). Integrating both modalities requires models linking neural activity to hemodynamic changes, typically via the HRF. Yet, HRF shape varies across individuals, brain regions, and is altered in epilepsy (Arafat et al., 2026; Ikemoto et al., 2022; Sadjadi et al., 2021) prompting methods that account for this variability (Cai et al., 2023; LeVan et al., 2010; Lu et al., 2007; Storti et al., 2013; Van Eyndhoven et al., 2021). EEG-fMRI analyses are also limited by the number of IEDs recorded during scanning, highlighting the need to address cases with few or absent IEDs (Ebrahimzadeh et al., 2019; Grouiller et al., 2011; Laufs et al., 2006; Rodionov et al., 2007; Tousseyn et al., 2014b). Using simultaneous EEG-fMRI, Mostame et al. (Mostame et al., 2025) showed that while EEG and fMRI functional connectivity share spatial similarities, they operate on different timescales and reflect distinct, yet parallel, network dynamics. Wirsich et al. (Wirsich et al., 2024) proposed that EEG-fMRI connectivity divergence itself may be a marker of epilepsy, even if the exact relationship remains unclear.

Structural data, in contrast, offers a more interpretable link between electrophysiology and connectivity (section 4.3), allowing investigation of the role of white matter tracts in seizure and spike propagation as well as structure–function coupling. However, challenges remain in accurately translating electrophysiological signals into MRI space or accounting for gray matter cortical spreading in seizure and spike propagation.

6.2. iEEG as a gold standard

ECoG and SEEG remain the gold standard for SOZ detection, forming the basis for ROI analyses and machine learning approaches. Their strength lies in high temporal resolution and direct neural measurement. However, sparse spatial sampling, limits full coverage of the potential EZ and propagation zones. Although iEEG is implanted based on the previous non-invasive investigation, there is no guarantee that EZ is fully sampled. Moreover, the process of delineating EZ based on iEEG is not trivial and depends on expertise and varies between centers. Consequently, (i)EEG should be regarded as gold standard with caution. To address this issue, some studies report resection or ablation zone in patients who achieved seizure freedom postsurgically as a gold standard which should be regarded as best practice.

6.3. The implantation problem

Each iEEG implantation is tailored to the individual patient, making group-level analyses challenging. A common strategy to address this issue is to use SEEG-defined ROIs (seizure onset, propagation, irritative, non-involved zones) to investigate their features and inter-regional relations. Most studies rely on clinically defined ROIs, some have used quantitative metrics like the epileptogenicity index (EI) to define epileptogenic regions (Besson et al., 2017). However, there is no universally accepted method to quantify the EZ. These approaches generally assume that SEEG-defined ROIs follow consistent activation patterns regardless of anatomical location. Another strategy is to analyze contacts located within overlapping brain regions across patients (Chang et al., 2023; Trotta et al., 2018) and same etiology (Chang et al., 2023) although this is less feasible in small cohorts.

Regardless of approach, accurate electrode localization in MRI space is essential yet non-trivial (Trotta et al., 2018). The spatial contribution of SEEG contacts depends on multiple factors, including impedance, contact size, volume conduction properties of surrounding tissue, and signal strength (Lachaux et al., 2003). As a result, different studies have used varying radii around electrode contacts (or midpoint between contacts in bipolar montage) to define ROIs in MRI space, typically ranging from 4 mm (Mitsuhashi et al., 2021), to 5 mm (Azeem et al., 2023, 2024; Azilinon et al., 2023; Ridley, Marchi, et al., 2017) up to 10 mm (Abdallah et al., 2022; Besson et al., 2017; Lachaux et al., 2003). In case of the scalp EEG, signal can be interpolated on the same surface when combined with MRI (Sahlas et al., 2025). Additionally, in simultaneous iEEG-fMRI recordings, electrodes can cause local signal dropout (Lachaux et al., 2003).

Sparse sampling in SEEG is a recurring issue in epilepsy practice and studies. Mitsuhashi et al. (Mitsuhashi et al., 2021) attempted to estimate the probability distribution of observed sources using IED propagation speed and white matter tractography. Sip et al. (Sip et al., 2021) used a simplified virtual brain model to predict seizure state and onset, while Mo et al. (Mo et al., 2022) applied a machine learning model trained on surface-level MRI and PET features to predict epileptogenicity mapping in brain regions unsampled by SEEG.

Finally, in network analyses, the tendency to implant electrodes primarily in suspected SOZ areas introduces sampling bias. In ECoG studies, short-range connections might be overrepresented.

6.4. Multiple features and limited number of patients

Each discussed modality offers numerous metrics, making feature selection challenging. Říha et al., (Říha et al., 2022) used hierarchical clustering based on mutual similarity for this purpose. Epilepsy studies

often involve small patient cohorts, so careful feature selection is critical, yet difficult. Additionally, epilepsy encompasses diverse underlying pathologies, where different biomarkers may predict EZ or surgical outcomes depending on etiology, potentially biasing or obscuring results when combined (Ryvlin, 2025). Restricting analyses to a single etiology is difficult due to small sample sizes. These challenges also limit machine learning studies, reducing generalizability by biasing training sets and constraining the number of usable features. This underscores the need for studies comparing different etiologies and biomarkers, as well as for multicenter studies including larger patient cohorts.

6.5. *Future directions of multimodal research and clinical implementation*

Despite the challenges discussed above, multimodal approaches offer considerable promise, particularly in complex or ambiguous cases. Numerous studies have demonstrated variability across modalities (Bettus et al., 2011; Centeno & Carmichael, 2014; Jones, Beall, et al., 2014; Mostame et al., 2025; Ridley, Wirsich, et al., 2017). While different techniques may identify different EZ when analyzed separately, combining them could yield more robust and conclusive insights.

Multimodal analysis may also reveal new insights into epilepsy, such as analyses of structure–function coupling either by comparison of connectivity matrices (structural and functional) or by graph signal processing analysis. Even without a full understanding of how these modalities relate, shifts in their intermodal correlations between patients and controls may carry diagnostic or prognostic value.

Machine learning, particularly explainable methods, given the clinical context, is another promising tool for integrating multimodal features to predict the EZ or surgical outcomes. It also facilitates feature selection when datasets are large enough. Yet, despite growing interest, relatively few studies have applied machine learning to multimodal data. Promising combinations which include for example fMRI and ASL remain underexplored in ML frameworks, pointing to a key opportunity for future research.

The main goal of multimodal analyses for detecting the EZ is to improve patient treatment and achieve higher rates of seizure freedom following surgical intervention. A major challenge in implementing newly proposed analytical techniques is that most studies analyze relatively small patient groups, highlighting the need for collaboration to create larger databases for more robust validation. This is particularly important in epilepsy, as the condition can arise from many different underlying causes, and patient selection can heavily bias results, potentially leading to incongruent findings (Ryvlin, 2025; Zijlmans et al., 2019). Additionally, prospective research is missing. Finally, as in many other cases of translating scientific research into clinical practice, open science with well-documented codes and protocols is essential, as are solutions that are easy to implement and accessible not only to a narrow group of specialized scientists but also to a broader range of clinicians.

Conclusions

Electrophysiology and MRI are central to the diagnosis and treatment of epilepsy, each offering distinct and complementary perspectives on brain function. Their integration can enhance EZ detection and delineation, surgical planning, and seizure outcome prediction. In this review, we outlined the current state of multimodal approaches combining electrophysiology and MRI. While some methods, such as simultaneous EEG-fMRI and personalized source analysis, are already in clinical use, many promising techniques remain under active investigation.

Emerging strategies include structure–function coupling analyses, virtual brain models, machine learning–based predictions, and non-invasive estimation of activity in brain regions not sampled by iEEG. These approaches hold potential for clinical translation, particularly in complex cases. However, further research is needed to identify optimal features from each modality, account for variability across etiologies, and address patient-specific factors such as anatomical variation in EZ location and seizure patterns.

Declarations

The authors would like to acknowledge that this research was supported by EpilepsieNL grant 23-08.

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