

A Review of EEG-based Localization of Epileptic Seizure Foci: Common Points with Multimodal Fusion of Brain Data

Abstract

Unexpected seizures significantly decrease the quality of life in epileptic patients. Seizure attacks are caused by hyperexcitability and anatomical lesions of special regions of the brain, and cognitive impairments and memory deficits are their most common concomitant effects. In addition to seizure reduction treatments, medical rehabilitation involving brain-computer interfaces and neurofeedback can improve cognition and quality of life in patients with focal epilepsy in most cases, in particular when resective epilepsy surgery has been considered treatment in drug-resistant epilepsy. Source estimation and precise localization of epileptic foci can improve such rehabilitation and treatment. Electroencephalography (EEG) monitoring and multimodal noninvasive neuroimaging techniques such as ictal/interictal single-photon emission computerized tomography (SPECT) imaging and structural magnetic resonance imaging are common practices for the localization of epileptic foci and have been studied in several kinds of researches. In this article, we review the most recent research on EEG-based localization of seizure foci and discuss various methods, their advantages, limitations, and challenges with a focus on model-based data processing and machine learning algorithms. In addition, we survey whether combined analysis of EEG monitoring and neuroimaging techniques, which is known as multimodal brain data fusion, can potentially increase the precision of the seizure foci localization. To this end, we further review and summarize the key parameters and challenges of processing, fusion, and analysis of multiple source data, in the framework of model-based signal processing, for the development of a multimodal brain data analyzing system. This article has the potential to be used as a valuable resource for neuroscience researchers for the development of EEG-based rehabilitation systems based on multimodal data analysis related to focal epilepsy.

Keywords: *Electroencephalography, epilepsy, localization, multi-modal fusion*

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Introduction

Epilepsy is one of the most common neurological diseases, which causes recurrent seizures. It is a chronic noncommunicable brain disorder, affecting people of all ages worldwide. According to the latest study by the World Health Organization, epilepsy affects about 50 million people worldwide among them between 4 and 10 per 1000 people have active epilepsy (continuing seizures) which needs treatment.^[1]

Based on identifying features of seizures, two primary types of epilepsy are known.^[2] Focal epilepsies, also known as partial epilepsies, are the most popular kind of adult-onset epilepsy, which represent seizure disorders originating within unifocal

or multifocal neuronal networks limited to one hemisphere. Nonfocal epilepsies are other types, which, in contrast, have no specific origins, and seizures may rapidly become generalized. Structural brain abnormalities are conventionally known to be the underlying cause of focal epilepsies, while other causative factors often remain of unknown etiology.

Anti-epileptic drugs are ordinarily prescribed to control epileptic seizures. In addition, surgical removal of epileptic foci is another treatment to provide the chance for seizure freedom in patients with focal epilepsy, in particular when the seizures are drug-resistant. In epileptic patients with drug resistance, so-called refractory patients, surgery is done to resect epileptogenic tissues of the brain that contain seizure foci. Surgery is an invasive treatment and cannot be prescribed

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for all patients due to overlap with the important areas of the cortex.^[3] Therefore, extended presurgical evaluation must be done to precisely determine the part of the brain to be removed. In addition, postsurgical rehabilitation is usually recommended to increase the quality of life in the patients.^[4] In this regard, cognitive and behavioral functions of the brain must be considered because the neurobiological mechanism is shown to be dependent on seizure localization and directly underpins changes in mood and behavior.^[5] Exact localization of epilepsy helps predict the risk of cognitive difficulties after surgery and for planning postsurgical rehabilitation.^[6,7] Meanwhile, less invasive or noninvasive neurostimulation techniques such as vagus nerve stimulation, transcranial magnetic stimulation (TMS), transcranial electric stimulation (tES), and deep brain stimulation have recently received progressive attention for epilepsy treatment, while there is strong evidence that the efficacy of these methods can be improved when epileptogenic zones are exactly localized.^[8]

Despite existing various neuroimaging modalities, electroencephalography (EEG) recordings are the first-line method to define epileptogenic cortex.^[9-11] When exact localization cannot be performed using the results of noninvasive methods, intracranial EEG (iEEG) recordings must be supplemented using subdural electrodes.^[12,13] Indeed, iEEG is the gold standard for determining the surgical plan in patients with refractory epilepsy. An iEEG study can be done by placing electrodes in the cortex of the brain through invasive surgery and recording brain electrical activity. The placement of iEEG electrodes is done through surgical operation and is an expensive procedure imposing definite risks itself. Since epileptic activity happens rarely, long-length of EEG recordings (either scalp or iEEG) shall be acquired and processed to detect such activities. This is time-consuming and skill-dependent process requiring intensive review and discussion of clinicians and can lead to erroneous decisions. In this regard, automatic methods can potentially improve the localization of epilepsy foci. In addition, these methods usually provide a fast, accurate treatment plan for early-onset seizures by differentiating between focal and nonfocal seizures. Automatic systems for epilepsy detection usually include three main steps.^[14,15] First, the recorded EEG signals are preprocessed utilizing appropriate signal processing methods.^[16] Then, lots of features are extracted from the preprocessed signals^[17,18] to discriminate them. At last, the extracted features are classified by various methods including simple thresholds to complex machine learning algorithms.^[19-21] The studies are still ongoing and several new signal-processing methods have been investigated in the last years for identifying epileptic focus. The final aim is to design computer-aided diagnosis systems for the localization of epileptic seizures using EEG signals. Although there are many studies in this field, few review works have been conducted on the automatic localization of epileptic foci so

far. Hussein *et al.*^[14] summarized the methods which have been applied to a variant of datasets for focal and nonfocal channel selection. They provided a comprehensive review of the features and classifiers. Islam *et al.*^[22] limited their survey to the iEEG signals and drew their attention to the artificial intelligence (AI)-based methods developed in the detection of the epileptic seizure focus. However, as far as we know, in both studies, no particular categorization has been provided for reviewing the methods in particular from a signal modeling point of view. Here, from a “signal modeling point of view,” we mean every mathematical model, which can justify the procedure of the feature extraction and describe the processing procedure. As an example, when ordinary statistical features including mean, variance, skewness, etc. are used as EEG features, a stochastic model with a specific probability distribution is considered the core of assumptions even if it is not explicitly declared. Therefore, the stochastic model can provide distinctive statistical features as much as it provides goodness of fit to the distribution of data. However, using models to justify the feature extraction performance of a processor is proposed here to help the researchers find whether the inclusion of models can introduce *a priori* information to improve the performance of feature extraction.

On the other hand, the brain’s structural and functional information is required for the exact localization of epileptogenic zones. To provide such information noninvasively, based on clinical guidelines, results of several neuroimaging modalities such as video EEG monitoring, magnetoencephalography (MEG)^[23] recordings, magnetic resonance imaging (MRI),^[24] positron emission tomography (PET), and single-photon emission computed tomography (SPECT) scans are precisely surveyed.^[25] However, there is no definite method to localize focal epilepsy, and a multidisciplinary team is usually formed to investigate the concordance of EEG recordings with brain imaging. Based on the investigations, the epileptogenic zone is localized for epilepsy surgery such that it imposes minimum risk. Ideally, concordant results must be achieved from various localizing examinations of mentioned neuroimaging modalities and a single region must be identified as the epileptogenic zone. However, in most cases, due to inconclusive imaging data, extensive manual data analysis, and eye fatigue, incorrect localization occurs causing approximately 20%–30% of patients to suffer from seizures despite resection surgery. To overcome this failure, multimodal/multisensor image fusion techniques have become of great interest. In these techniques, images from various imaging modalities are combined to obtain complementary information about the images and increase the accuracy of localization.^[26] The fusion integrates critical information from various modalities for health specialists to make accurate decisions.

Toward developing accurate noninvasive diagnosis techniques, the main objective of this survey is to abstract a modeling-based pipeline for the localization of epileptogenic foci utilizing neuroimaging modalities. This abstraction further facilitates the development of new methods for the accurate detection of the epileptic seizure foci. To this end, in this review article, first, we present a review of AI-based methods developed for the localization of epileptogenic zones in EEG signals and categorize these methods considering modeling approaches. Then, based on the model-based categorization provided for EEG signals, we survey and summarize the key parameters and challenges of processing, fusion, and analysis of multiple source data for the development of a multimodal brain data analyzing system. This helps the researchers achieve a general model-based approach for information fusion and overcome the shortcomings of the previous works and move toward minimally invasive and accurate localization of epileptogenic tissue for surgical resection, rehabilitations, and new nonsurgical treatments. Indeed, the main impact of this work is to provide a review for identifying the nature and extent of previous studies in the localization of epileptic foci, by creating a profile of existing (EEG-based and multimodal fusion) studies with emphasis on study methodological features. The studies are reviewed to answer the following questions:

What signal-modeling methods are ordinarily employed as the underlying core of feature extraction from EEG data? Are these methods applicable to multimodal fusion of neuroimaging data?

What classification approaches are currently utilized to localize the epileptic foci in the EEG signals? Can the multimodal fusion of neuroimaging data be categorized as a classification task?

Are there common points in EEG-only studies and multimodal fusion research?

The rest of the article is organized as follows. In section 2, the semiology of focal epilepsy is briefly explained and AI solutions for the localization of foci are reviewed. In section 3, various neuroimaging modalities are introduced and their fusion methods are surveyed. AI solutions for multimodal disease-based fusion are reviewed in this section. In section 4, reviewed studies are discussed and research problems are determined.

EEG for Seizure Foci Localization

Many underlying factors contribute to epilepsy, which leads to a wide range of patient presentations. Epilepsy can be broadly manifested into two types: focal and generalized (nonfocal) seizures.^[2] Generalized seizures are distinguished by simultaneous manifestations of epileptic activity throughout the cortex, despite the variety in their presentations. Focal seizures, on the other hand, originate from a single spot in the brain. Local rhythmic activities

are frequently used to identify the onset of focal epilepsy. Generalized secondary seizures can result from this epileptic activity spreading to nearby brain areas or even to the entire brain.

The cortex area in the brain where the seizure originates is typically referred to as the epileptic seizure focus which is somehow conceptually defined as the epileptogenic zone.^[27] Resection of epileptogenic tissues is one of the most effective treatments for patients with drug-resistant focal epilepsy in managing epileptic seizures. Thus, it is crucial to identify the seizure focus before surgical therapy. Despite it is likely appropriate to equate the epileptogenic zone with the seizure focus, no diagnostic procedure can currently define the boundaries of this region. Instead, cortical regions connected to, but not necessarily adjacent to, the epileptogenic zone are defined by neuroimaging and EEG recording techniques. These regions include functional and structural abnormalities and are defined as the location of seizure focus when they are spatially coordinated. Till now, diagnostic methods could not provide the precise localization of the boundary of the epileptogenic zone which is usually referred to as the seizure-onset zone.^[28] Therefore, a seizure may continue from the other potential zones after the resection of epileptogenic zones. Accordingly, the localization of the epileptogenic zones is the main issue to be solved, in particular when there are several potential zones.

Critical zones

EEG is currently the first-line method for clinical epilepsy follow-up and is consistently used to answer whether the patient suffers from epilepsy, where the location of the epileptogenic zone exists, and if the treatments are effective. Remarkably, electrocorticography and stereoelectroencephalography (SEEG) are two iEEG techniques that provide simultaneous recordings of the neocortex from tens to hundreds of electrodes.^[29] The spatiotemporal precision of these recordings is high enough to localize the seizure focus for further surgical operation in patients with refractory epilepsy, in particular when noninvasive techniques such as scalp EEG are not informative enough. EEG recordings are nonstationary signals which provide data from the neural activities of the brain and are normally composed of 5 frequency bands (rhythms), i.e., Delta (up to 4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–26 Hz), and Gamma (26–100 Hz). Two kinds of activities can be seen in the EEG signals of epileptic patients.^[30] (1) The burst of sharp and spiky wave complex that is called ictal EEG signals and occurs during the epileptic seizure. (2) Temporary waveforms that are called interictal and are seen in seizure-free activity. Since ictal signals are very rare, a longer recording of EEG signals is usually done for visual inspection required for the detection of ictal and interictal episodes. During the presurgical evaluations, the

epileptogenic zone is clinically localized by marking the seizure-onset zones by reviewing the scalp and iEEG.^[31] The seizure onset is defined as a sudden change of the neural activity in both frequency and amplitude, which is distinct from the background. However, it has been observed that epileptic seizures can be generated from other brain areas after resection of the localized epileptogenic zone. This means there are potential seizure-onset zones to be completely resected to have complete seizure treatment.

To utilize possible seizure-onset zones for localization of the boundaries of the epileptogenic zones, epileptologists usually consider five cortical zones, namely, the irritative zone, the seizure-onset zone, the symptomatogenic zone, the epileptogenic lesion, and the functional deficit zone.^[28] Recently, it has been shown that the high-frequency oscillation (HFO) zone is another possible seizure onset zone.^[32] These zones must be evaluated to understand their spatial relationship with the epileptogenic zone. Since these zones cannot be merely described through EEG recordings, presurgical evaluation requires multiple sources of information provided by extra neuroimaging techniques. In this way, the complete elimination of the epileptogenic zones can be done and successful surgical treatment of epilepsy is achieved. Figure 1 schematically represents seizure-onset zones, their overlapping, and the neuroimaging modality to detect them.

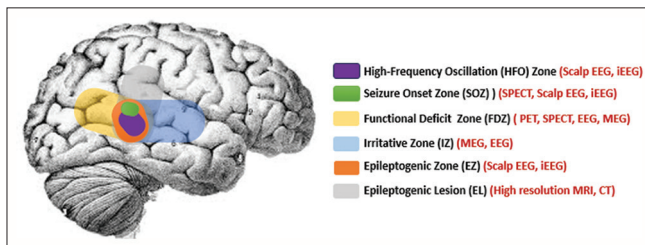


Figure 1: Schematic representation of critical zones and neuroimaging modality to detect them. EEG – Electroencephalography; iEEG – Intracranial EEG; MRI – Magnetic resonance imaging; CT – Computerized tomography; PET – Positron emission tomography; SPECT – Single-photon emission computerized tomography; MEG – Magnetoencephalography

EEG-based localization of epileptic foci: Artificial intelligence solutions

Nowadays, extensive research has been done on the automatic localization of seizure foci using EEG signals. The automatic localization of seizure-onset zones can reduce the required visual inspection of the long-term multichannel EEG and additionally help to make accurate and fast decisions for epilepsy management. However, automatic localization requires precise automatic pipeline which includes several stages:^[15] preprocessing, feature extraction, classification, and evaluation. Figure 2 illustrates the currently available automatic pipeline for localization of epileptic foci.

EEG signals acquired from scalp EEG and iEEG are nonstationary signals, which are recorded by electrodes fixed on the subject scalp, implanted on the subdural space, and deeper sites, respectively. During acquisition, several measurement artifacts, arising from measuring instruments, may contaminate EEG signals. These artifacts, usually referred to as noise, are greater in scalp EEG recordings and can be limited by developing precise recording tools and even invasive recording methods such as iEEG, though they cannot be avoided completely. In addition, there are some physiological artifacts such as eye movements, eye blinks, cardiac activity, and muscle activity, requiring complicated methods to be limited. Therefore, the first stage is preprocessing where signal acquisition, segmenting, averaging, and artifact removal are done.^[33] Preprocessing of EEG signals requires solving forward and inverse problems and research is still ongoing in this field.

The second stage of the automatic localization pipeline is feature extraction. A feature, indeed, can be considered any measurement or component of a signal extracted from its pattern. Feature extraction methods try to provide informative features from the signals to help discriminate and characterize their pattern. Regardless of feature type and from a signal-processing point of view, the conventional features are usually derived from the signal original domain or transform domain through a modeling method. Indeed, modeling in its general

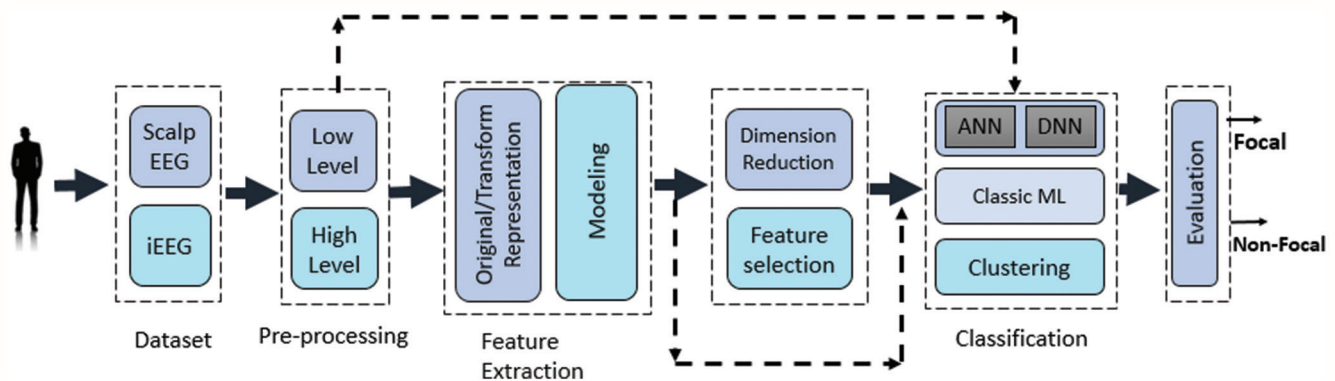


Figure 2: Illustration of block diagram of available automatic pipelines for localization of epileptic foci. EEG – Electroencephalography; iEEG – Intracranial EEG; ANN – Artificial neural networks

sense is the core of signal processing and analysis, whereas parameters and specifications of the models are potential discriminative features for consequent classification.^[26] The extracted features can be generally referred to as model-based features. These features do not necessarily have explicit clinical diagnostic value and are usually obtained through mathematical analysis. Meanwhile, clinically distinguishable features are generally called biomarkers. Indeed, those model-based features, which are essential for the detection of seizure onsets in clinical systems and can be manually detected by epileptologists through visual inspection of EEG signals, can be usually referred to as biomarkers. The most important biomarkers to identify epileptic seizure foci are HFO,^[34] phase-amplitude coupling (PAC),^[35] and interictal epileptiform discharges (IEDs).^[36] Research is still ongoing regarding the detection of new biomarker-type features for the localization of seizure foci. While experts can visually inspect these features, they may become hidden even in patients with a clear diagnosis of epilepsy, due to different reasons. To tackle this issue, several automatic feature extraction methods have been developed which can be included and reviewed in the proposed model-based approach as well. Several automatic methods for the extraction of biomarkers have been reviewed in.^[37,38]

In addition, extracted features can be either directly entered in the classification step or after dimensionality reduction or feature selection procedure. Classification of the extracted features is the next stage of the automatic pipeline and is conventionally done by classic (feature-based) machine learning algorithms or deep learning methods, which are another powerful subcategory of machine learning methods. However, in the case of sufficiently uncorrelated biomarkers and features, simple thresholding algorithms can classify the features. Finally, the performance of the classification is evaluated and modification in any previous stages is done if needed.

While feature extraction and classification are traditionally done in separate consequent steps, deep learning methods can do these steps all at once. Indeed, deep algorithms can be employed in two different methods. In the first method, feature extraction and classification are all performed by the deep network through an end-to-end model. In the second method, the deep algorithm is just a classifier, and feature extraction is separately done by an extra algorithm that may be another deep method itself.^[39] Therefore, here we categorize deep methods in both steps of feature extraction and classification.

Feature extraction and classification are two main steps in seizure foci localization and we review their corresponding methods in the following. We first elaborate on the sub-blocks of the feature extraction block from a modeling point of view. Then, we review classification methods applied in the localization of seizure foci.

Model-based feature extraction for localization of seizure foci

Model-based feature extraction includes two steps. While it is not necessary, data transformation is usually done in the first step to provide a better representation of data. Data modeling which leads to the feature extraction is done in the next step. To have a better visualization of the model-based feature extraction, we provided the categorization of models as a tree structure in Figure 3. It must be mentioned that several branches of the tree structure can be simultaneously applied to the data, which is usually called hybrid models.

Data transformation

Based on the signal processing domain, the features can be extracted either from preprocessed EEG signals in the time domain (TD) or after applying the specific transform on the signal.^[26,40] A transform can be simply considered every mathematical function, which is applied to the signal and may change the representation of the signal to the new form. However, here we consider those transforms, which are specifically applied to project the signal on a set of basis functions. Utilizing such transforms, the EEG signal is decomposed into scaled versions of basis functions whose weights are known as transform coefficients. According to the type of basis functions, transforms can be divided into two main groups: data-adaptive, and nondata-adaptive. In nondata-adaptive transforms, apart from data characteristics, fixed basis functions are applied to data. In addition, transformed signals may have TD, frequency domain (FD), and time-FD (TFD) representations depending on the properties of applied basis functions. Discrete Fourier transform (DFT)^[41] with a fixed exponential-shaped basis function has been traditionally used to transform EEG signals to the FD. Fast Walsh–Hadamard Transform,^[42] which is the multidimensional generalization of DFT and is usually interpreted as the Fourier transform on the Boolean group, has been recently used for EEG data in foci localization applications. Hilbert transform^[43] is another widely used nondata-adaptive transform which is indeed calculated by Fourier transform and retains the TD representation of the EEG signal.

However, due to the nonstationary properties of EEG signals, time–frequency analysis such as short-time Fourier transform has been one of the first-line methods to represent biomarker features such as HFO.^[44] Wavelets, on the other hand, provide a better representation of signals through a multi-scale basis. This multi-scale property allows the signal to be decomposed into several scales, from coarse to fine scales, each one representing a particular coarseness of the EEG signal. Several wavelets such as complex Morlet wavelet,^[45] discrete, tunable-Q wavelet transformation,^[46] and flexible analytic wavelet transform^[47] have been used in this regard.

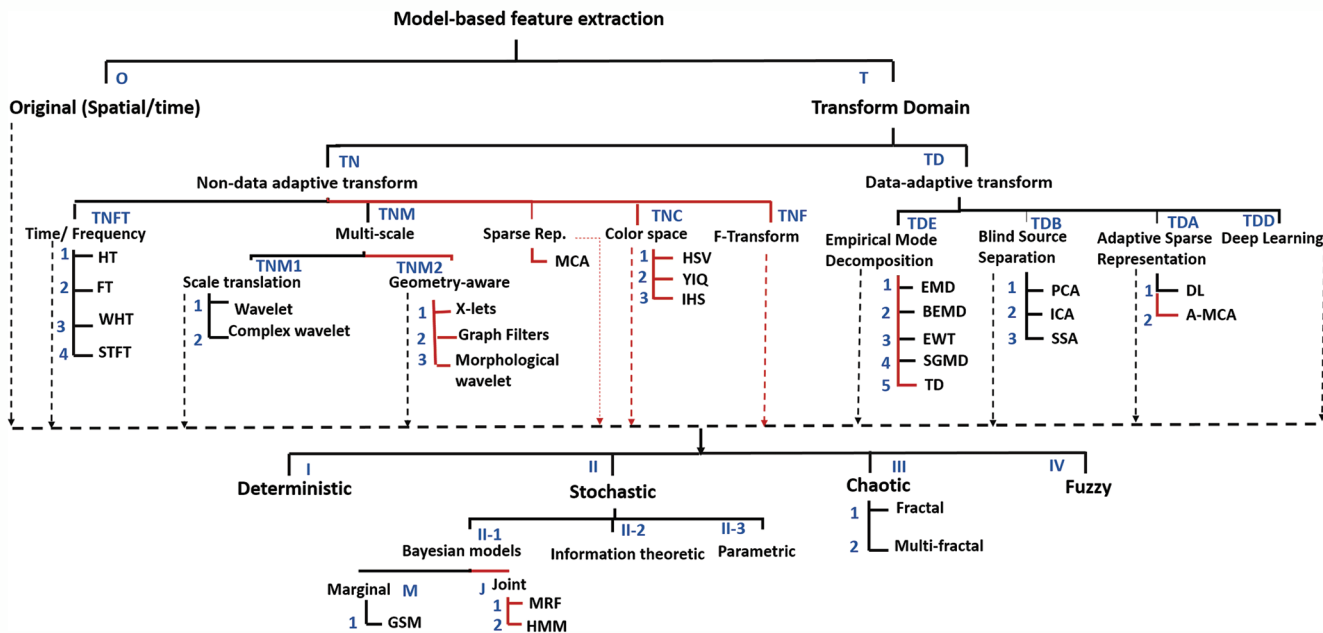


Figure 3: Categorization of the model-based feature extraction methods. EEG-based features are extracted including, but not restricted to these categorizations. Red lines indicate the methods specifically used in multimodal neuroimaging fusion. HT – Hilbert Transform; FT – Fourier Transform; WHT – Walsh–Hadamard Transform; STFT – Short Time Fourier Transform; HSV – Hue, Saturation, Value; YIQ – Y, Inphase, Quadrature; HIS:; EMD – Empirical Mode Decomposition; BEMD – Bivariate Empirical Mode Decomposition; EWT – Empirical Wavelet Transform; PCA – Principal Component Analysis; ICA – Independent Component Analysis; SSA – Singular Spectrum Analysis; SGMD – Symplectic Geometry Mode Decomposition; TD – Tensor Decomposition; DL – Dictionary Learning; A-MCA – Adaptive Morphological Component Analysis; GSM – Gaussian Scale Mixture; MRF – Markov Random Field; HMM – Hidden Markov Model

In data adaptive transforms, the basis functions are derived from the data itself. Empirical mode decomposition (EMD) and variational mode decomposition (VMD) are two multiresolution data-adaptive transforms that decompose the signal into several components. The created components, so-called intrinsic mode functions (IMF), and band-limited IMF, have the same time scale as the EEG signal, and the decomposition algorithm recursively extracts different resolutions without a fixed basis function. EMD,^[48] bivariate EMD,^[49] empirical wavelet transform,^[50] adaptive discrete cosine transform,^[51] and VMD^[52] are some examples in this regard. Blind source separation (BSS) includes multiple kinds of techniques, which are very useful for retrieving the underlying sources of EEG signals. In these techniques, data are represented in a statistical domain rather than a TFD. That is, some statistical criteria such as independence are considered and the data are projected onto axes to attain the statistical conditions. Principal component analysis (PCA) and independent component analysis (ICA) are two well-known methods in BSS techniques, which attempt to find a set of independent sources of data (data projected onto new independent axes). For this purpose, some measure of independence/de-correlation is defined and is optimized for projections of data onto each axis of the new space. Since the components are determined by data, BSS can be categorized in the data-adaptive transform domains. Rather than multi-scale PCA^[53] and ICA,^[54] neighborhood component analysis,^[55] singular spectrum analysis,^[56] and

symplectic geometry mode decomposition^[57] have been used as BSS techniques for foci localization. Furthermore, due to their ability to represent the interdependencies among various dimensions of EEG data including channels, and time; tensor decomposition techniques have been widely investigated in the BSS problem, in particular for EEG source localization.^[58-60]

Another data-adaptive transformation of data includes an adaptive sparse representation of data. In these methods, signals are represented with as few as possible significant coefficients. These coefficients are usually learned employing a dictionary of learned basis functions (atoms) and through algorithms such as k-singular value decomposition. During dictionary learning (DL), the most well-known method in this area, the data are transformed to an over-complete space where the basic functions of this space are learned adaptively from data. DL has been recently used in epileptic foci localization for extracting HFO features.^[61] The main advantage of DL-based methods is their ability to simultaneously learn and classify the features.

Data modeling and extracting features

After applying the appropriate transform to the EEG signals, they are usually modeled to extract efficient features based on the model parameters and specifications. Depending on assumptions about the nature of EEG signals, deterministic, chaotic, stochastic, and fuzzy models have been widely

used to extract discriminative features from EEG data for the localization of seizure foci.

When the random nature of EEG signals is not involved in the calculation of the features, the underlying assumption is that the signals are generated by a deterministic system and can be described by deterministic models. These models are simple and easy to understand, however, the mathematical representation of the system, features, and their relationships are assumed to be fixed over all EEG signals. Therefore, these models are not representative enough to extract distinct features from EEG patterns. Due to their simplicity, root mean square,^[62] band power spectra,^[63] phase lock value,^[64] zero crossing, and Teager energy^[65] have been used as accessible deterministic features.

However, EEG signals have a random nature that must be considered during modeling and feature extraction. When their randomness is assumed to be generated from a nonlinear dynamic system that behaves as a deterministic chaotic attractor, they can be described by chaotic models.^[66] These models characterize randomly fluctuated patterns that were caused by the sensitivity of deterministic systems on initial conditions where no probabilistic component is required to describe them. The main advantage of these models is that they can well describe underlying patterns, fractal, multi-fractal,^[67] and self-organization behavior of EEG signals.^[68] Katz fractal dimension,^[69] fractal dimension,^[70] recurrence qualitative analysis, mean diagonal line length, laminarity, trapping time, longest vertical line, longest diagonal line, and recurrence times are some of the features that have been extracted from these models of focal EEG signals.^[71]

While randomness in a chaotic system is due to its sensitivity to initial conditions, a stochastic system results in various possible final states, with even a unique initial condition, which usually follows a probability distribution.^[72] Stochastic models, which consider the inherent random nature of the EEG signals, have been widely used in the automatic localization of foci. The underlying assumption of these models is a probability density function, which is used to compute simple statistical features such as statistical moments to more sophisticated ones. Based on the complexity of features, the stochastic models applied for foci localization are subdivided into Bayesian models, information-theoretic, and parametric models.

In Bayesian models,^[73] a set of assumptions is considered for the probability distribution of EEG signals and the moments, order statistics, etc. are estimated to determine how the probability mass of EEG data is distributed. Gaussianity is the simplest assumption in this regard and, mean, variance, standard deviation, coefficient of variation, mean absolute value, modified mean absolute value, mean frequency, skewness, kurtosis, different types

of quartile, log detector median frequency, mean frequency, Hjorth parameter: (activity, mobility, and complexity), and moments of 1st and 2nd derivative are samples of features extracted from the statistics-based models.^[69]

Information-theoretic models^[74] are based on information theory and define some measures for the information of the data using maximum likelihood estimates. These measures that provide discriminative features are generally called entropy and sample entropy, permutation entropy, delay permutation entropy, approximate entropy, Renyi's entropy, Shannon entropy, Tsallis entropy, phase entropy (S1 and S2), wavelet entropy, k-nearest neighbors (KNN)-entropy, centered correntropy, Stein's unbiased risk-estimate entropy, log-energy entropy, and multi-variate entropy are some widely used features in this regard. Kolmogorov complexity and Lempel–Ziv complexity are two features that are also calculated based on information theory but are conceptually different from the entropy features.^[42,56,75,76]

Parametric models,^[53,52] such as autoregressive (AR), moving average (MA), and ARMA methods, are mathematical models that characterize EEG data as the outputs of filters whose inputs are some kind of noise. Parameters of these models can either be used as distinct features themselves or be utilized for better representation of EEG signal for accurate estimation of EEG spectrum and higher order spectra such as bispectrum.^[77]

Feature classification

The feature classification step finds the boundaries between the classes and contains a wide variety of algorithms from defining simple feature thresholds to complicated methods, which are used in machine learning algorithms. Earlier automatic classification methods tried to establish a simple threshold-based relationship between the biomarker-type features for the selection of the events from the background. For instance, HFO-based localization of seizure foci depends on the classification of pathological HFOs and physiological-induced HFOs.^[78] Statistical thresholds which identify significant variations from the background have been widely used and were also implemented in RIPPLELAB to be more examined.^[79] However, nonstatistical thresholding including methods such as thresholding the time–frequency map of a Morelet wavelet transform^[80] and moving thresholding related to the signal level (adaptive thresholding)^[81] were developed to increase the performance of the HFO classification task. Noorlag *et al.* provided a review of HFO detection methods and assessed their clinical potential.^[82] Furthermore, statistical thresholds have been widely used for PAC classification. Synchronization between low and high-frequency bands of the EEG signals is measured by PAC and the statistical thresholds are usually used to determine the significant changes in the amplitude and phase of coupled bands. In this way, epileptogenic couplings can be classified.^[83-85] Meanwhile, fewer studies have been done to detect IEDs by

thresholding,^[86] or adaptive thresholding methods,^[87] since threshold-based detector was taught to be insufficient to accurately classify IEDs (single spikes, generalized spikes, and multiple spikes) arose from nonepileptiform activities such as eye blink, and electrode artifacts.^[38] However, Palepu *et al.*^[88] recently developed a preprocessing step to obtain an optimal threshold for automated IED detection that improved the detection performance. Apart from the aforementioned methods, which are usually used for the classification of biomarker-type features; other model-based features usually need more complicated approaches such as machine learning-based classifiers. From here on, from a classifier, we mean a mathematical algorithm that is used to categorize data into various classes through supervised, semi-supervised, and unsupervised learning. Few unsupervised methods such as K-means, fuzzy c-means clustering,^[89] Gaussian mixture model (GMM),^[62] and non-nested generalized exemplars classifier^[90] have been studied to localize seizure foci. However, supervised classification is much easier than unsupervised methods, as the class labels are known. In this regard, machine learning algorithms, which are usually categorized into classic algorithms and neural networks (NN), have been widely used in the supervised learning of focal and nonfocal EEG signals which we will review in the following. To have a better visualization of the machine learning-based classification methods, we provided the categorization of methods in Figure 4.

Classic machine learning algorithms

Machine learning algorithms have been widely used for the localization of seizure foci. However, their performance has highly depended on extracting discriminative and independent features from EEG data. Through the learning process, these algorithms try to find decision boundaries that divide input feature space into several regions, which correspond to the output labels. Based on the linearity of

the decision boundary, the classic classifiers can be divided into linear/nonlinear methods.^[91]

Linear classification methods are useful when the features are linearly separable and may have poor performance for complex nonlinear data. Linear discriminant analysis (LDA),^[92] naive Bayes (NB),^[90] Logistic Regression (LR),^[62] and support vector machine (SVM)^[47,46,55,67] with a linear kernel are examples of linear methods which have been used in automatic localization of seizure foci. LDA, indeed, is a dimensionality reduction technique that projects data to lower dimension space in such a way that within-class variation is minimized and the distance between the mean of classes is maximized. However, it has poor performance for features with the same class mean. NB is based on the Bayes theorem and determines the likelihood of a class utilizing conditional probabilities. The independence of the features is essential for this classifier to have good performance. LR is a very popular algorithm that builds a regression model and finds the probability of a given feature coming from a specific class. SVM with linear kernel is a powerful accessible classifier, which provides a linear decision boundary (hyperplane) to have the largest distance from the nearest feature. It works very well for small linear datasets.

Nonlinear classification refers to categorizing the features by curvature shape boundaries. Decision trees (DT),^[90] random forest (RF),^[48] KNN,^[90,93] and neighborhood component analysis^[55] are examples of the nonlinear methods utilized in the localization of seizure foci. DT, indeed, is one of the most powerful and robust classifiers, which starts from the tree's root node and recursively partition the data, moving down the branches of the tree. RF, as a flexible classifier, is a collection of DTs that combines their outputs to reach a single result. KNN analyses the K-nearest data points to the newly entered point and based on the label of the majority of the KNN determines the label of the new point.

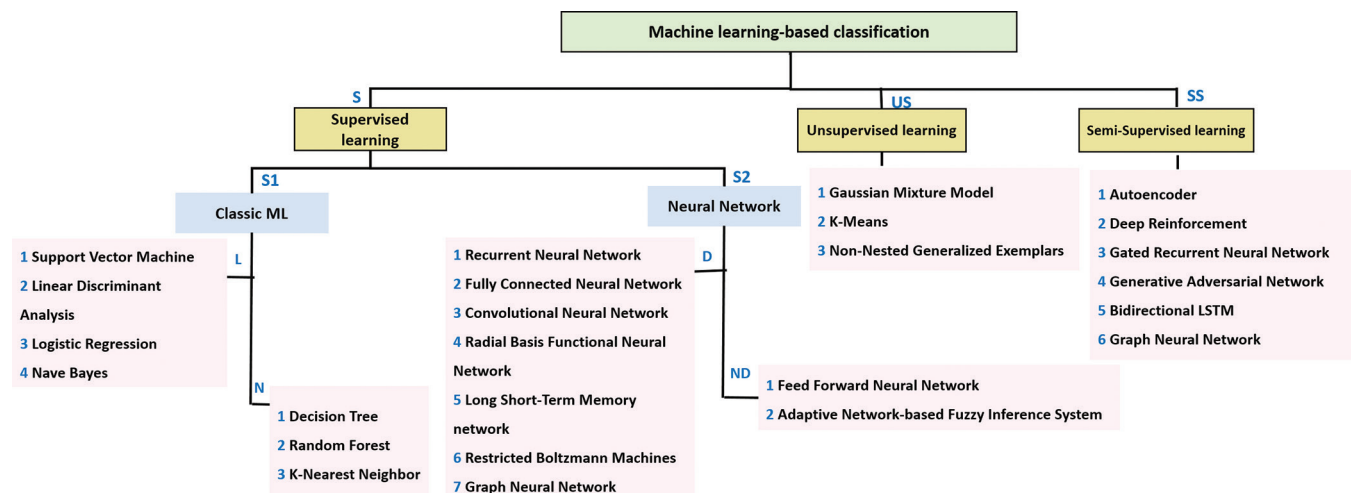


Figure 4: Categorization of machine learning-based classification methods used in the localization of the epileptic foci. L – Linear; N – Nonlinear; D – Deep learning structure; ND – Nondeep learning structure

This classifier is sensitive to outliers and needs all data to make a new decision.

Neural networks

NN or artificial neural networks (ANN) are a subset of machine learning methods, which are constructed from a huge number of interconnected artificial neurons or nodes.^[94] When multiple neural layers are stacked, a deep network is constructed and a deep learning method is created. NN algorithms typically do not require feature engineering and learn the pattern of data by forward propagating the input and adjusting the weights and biases through backward propagation. In this way, during training, the NN learns what features of the input data are required to generate the proper output or label. New unseen inputs will then be conducted to their corresponding output if the network is trained with a sufficient number of data. Since data are hierarchically passed through several layers, in deep learning methods, many complex features are simultaneously extracted and classified. Therefore, a well-trained deep NN can be used for feature extraction. Due to their efficient representation of raw data, deep learning methods are powerful tools for the analysis of EEG data, in particular for seizure localization. There are various types of NNs available that can be categorized based on their structure, learning process, data flow, basic neurons, number of layers, and depth, etc. However, depending on structure and data flow categorization, feedforward neural network (FFNN),^[42,95] multi-layer perceptron (MLP) or fully connected neural network (FCNN),^[96] convolutional neural network (CNN),^[97,98] radial basis functional neural network (RBFNN),^[56] recurrent neural network (RNN),^[99] long short-term memory network (LSTM)^[77,100] adaptive network-based fuzzy inference system (ANFIS),^[101] graph neural network (GNN),^[102] and restricted Boltzmann machines (RBM)^[57] are ANN tools which have been used for the localization of seizure foci.

FFNN is the simplest structure of a neural network which has just forward propagation and learns the pattern of data. Based on the complexity of the data, a number of layers can change. These networks are fast, robust to data noise, and efficient for simple classification. However, they cannot be used for deep learning structures.

An MLP has an FCNN structure, in which each node connects to all possible nodes in the surrounding layers. In MLP, weights and biases are modified in back-propagation to reduce the loss between true outputs and predicted ones. Despite their complexity, they are widely used in deep learning methods for various tasks such as classification.

In CNNs, neurons are arranged in three dimensions and each neuron in the convolutional layer only connects to a few surrounding neurons learning local information. Each neuron has a local receptive field. This means input neurons learn the features of small sections of the input

data and when taken together, a feature map is built for the whole image. CNNs have fewer parameters than FCNNs, and since they provide both uni/bidirectional propagation, they can be used in various deep structures.

RBFNN is constructed from a layer of RBF neuron, which measures the similarity between inputs and data points existing in training data through Euclidean distance and stores a prototype assuming a Gaussian distribution for data. However, they have training challenges in particular in deep models.

In RNNs, nodes can create cyclic connections, and the output from some nodes can affect the subsequent input to the same nodes. In this way, they have an internal state (memory) and can learn temporal or sequential data. Although short-correlated sequential data can be well represented by these networks, they have challenges in the training process. LSTM networks are a developed version of RNN that includes a memory cell for maintaining information of longer sequences, thereby they can model long-term dependencies as well.

ANFIS is a kind of NN that integrates NN and fuzzy logic principles in a single framework. It is constructed from several adaptive nodes with different functions, which are adaptively affected by the inputs and parameters. Hybrid methods are used for adjusting parameters in ANFIS which is different from back-propagation in ordinary NN. ANFIS is robust to complex nonlinear data and can be generalized such as other kinds of NN, however, the computational cost is one of its main drawbacks.^[103]

GNN is a class of NN that provides a graph representation of data. They are designed based on pairwise message passing, and the representation of corresponding graph nodes is iteratively updated by passing information with their neighbors. They are widely used for modeling complex interactions of data for node-level, edge-level, and graph-level prediction tasks. However, a limited number of nodes may be one of their drawbacks.^[102,104]

RBM is a class of ANN that can learn the probability distribution of its input data. They are categorized as generative stochastic NNs that are made of symmetrically connected hidden layers. Deep belief networks are deep architectures constructed from RBM networks. The main advantage of RBMs is that they can be trained in an unsupervised manner thereby are widely used for learning high-level features from data. However, the computational complexity is their current limitation.^[105]

Recently, due to the fast development of deep learning-based methods, semi-supervised classification has received great attention. Deep convolutional autoencoder (AE),^[106] deep reinforcement learning,^[107] gated RNN,^[108] generative adversarial networks (GAN)-based semi-supervised learning,^[109] bidirectional LSTM RNN,^[110] and graph CNN^[111] are some examples of unsupervised methods proposed for localization of seizure foci.

In Table 1, we summarized some recent methods in automatic localization of epileptogenic zones developed between 2016 and 2022 and categorized them with specific letter/number notations corresponding to tree structure illustrated in Figures 3 and 4. We have elaborated the method, feature type, and evaluation index as well.

EEG-based localization of epileptic foci: Model-driven methods

In addition to AI solutions which are usually based on EEG measurements through signal processing techniques, several studies have been done to localize epileptic foci by solving forward/inverse problems.^[117,118] Traditionally, the use of model-driven signal processing had an important role in the

field of inverse problems, in which the goal is to extract information concerning the medium or certain of its contents. In such problems, the model plays the role of the structure in which the unknown parameters lie. EEG inverse problem is a good example of this where a forward model structure is considered to explain the source of the EEG signal. Since brain activity is often modeled as a current dipole, in this approach, the scalp measurements (recorded potentials) are considered to be generated by a current distribution inside the head, which is transferred by the head volume conductor model or a forward model. Consequently, the inverse problem refers to finding the current distributions (the sources of measurements) from the recorded potentials.^[119] A forward model is often specified by a set of equations and parameters.

Table 1: Some recent artificial intelligence solutions for electroencephalography-based epileptic foci localization

Author	Year	Feature extraction approach	Classifier	Modality	Biomarker		Benefits	Limitations
Elahian <i>et al.</i> ^[64]	2017	O-I	S-S1-N3	iEEG	PAC	Original	Quick,	Noise and
Arunkumar <i>et al.</i> ^[90]	2017	O-II2	US3	iEEG	-	time	computationally	artifacts
Chatterjee <i>et al.</i> ^[67]	2017	O-III-2	S-S1-NL3	iEEG	-	domain	efficient, and	Nonstationary
Gagliano <i>et al.</i> ^[77]	2019	O-II3	S-S2-D5	iEEG	-		faster	property of EEG
Sciaraffa <i>et al.</i> ^[65]	2020	O-I, O-III	S-S1-L2	iEEG	HFO		Fairly simple	signals
Sharma <i>et al.</i> ^[112]	2020	O-II-1S	S-S1-L1	iEEG	-			Low
Jrad <i>et al.</i> ^[113]	2017	T-TN-TNM11-I	S-S1-L1	iEEG	HFO	Nondata	Provide	Computational
Deivasigamani <i>et al.</i> ^[101]	2016	T-TN-TNM1-IV	S-S2-ND2	iEEG	-	adaptive	time-frequency	complexity
Varatharajah <i>et al.</i> ^[114]	2018	T-TN-TNM11-I	S-S1-L1	iEEG	HFO, PAC	transform	localization	Fixed predefined
Zhao <i>et al.</i> ^[98]	2018	T-TN-TNFT2-II-2	S-S2-D3	iEEG	-	domain	Require less	basis functions
Dalal <i>et al.</i> ^[70]	2019	T-TN-TNM-TNM11-III1	S-S1-L1	iEEG	-		preprocessing	Requires
Subasi <i>et al.</i> ^[48]	2019	T-TN-TNM11-II-2	S-S1-NL1	iEEG	-		Tackle	feature selection
You <i>et al.</i> ^[115]	2020	T-TN-TNM-TNM11-II-2	S-S1-L1	iEEG	-		nonstationary	methods
Sui <i>et al.</i> ^[97]	2019	T-TN-TNFT4-I	S-S2-D3	iEEG	-		properties	
Gupta and Pachori ^[47]	2020	T-TN-TNM11-II-2	S-S1-L1	iEEG	-		Provide	multi-resolution
Najafi <i>et al.</i> ^[99]	2022	T-TN-TNM11-II-1M1	S-S2-D15	EEG/iEEG	-		features	
Rai <i>et al.</i> ^[89]	2015	T-TD-TDE1-I	US2	iEEG	-	Data	Provide	Typically
Abdelhameed and Bayoumi ^[110]	2018	T-TD-TDD	SS5	iEEG	-	adaptive	data-adaptive	complex and
Raghu and Sriraam ^[55]	2018	T-TD-TDB1-I	S-S1-L1	iEEG	-	transform	basis functions	time-consuming
Siddharth <i>et al.</i> ^[56]	2019	T-TD-TDB3	S-S2-D4	iEEG	-	domain	Require less	Require large
Daoud and Bayoumi ^[96]	2020	T-TD-TDD	S-S2-D2	iEEG	-		preprocessing	amount of
Daoud and Bayoumi ^[106]	2019	T-TD-TDD	SS1	iEEG	-		Tackle	balanced, labeled
Jukic <i>et al.</i> ^[53]	2020	T-TD-TDB1-II-3	S-S1-NL1	iEEG	-		nonstationary	training data
Daoud and Bayoumi ^[108]	2020	T-TD-TDD	SS4	iEEG	-		properties	Fine-tuning
Daoud and Bayoumi ^[109]	2021	T-TD-TDD	SS4	iEEG	-		Tackle the	of a lot of
Besheli <i>et al.</i> ^[61]	2022	T-TD-TDA1	-	iEEG	HFO		feature	hyper-parameters
Grattarola <i>et al.</i> ^[102]	2022	T-TD-TDD	S-S2-D7	iEEG	-		engineering	
Johnson <i>et al.</i> ^[116]	2023	T-TD-TDD	S-S2-D3	iEEG	-		problem	
Liu <i>et al.</i> ^[111]	2022	T-TD-TDD	SS6	EEG/iEEG	-		Can provide	sparse features
Visalini <i>et al.</i> ^[57]	2023	T-TD-TDD	S-S2-D6	EEG/iEEG	-		Typically do not	need subsequent
Liu <i>et al.</i> ^[107]	2023	T-TD-TDD	SS2	EEG/iEEG	-		classifier	

PAC – Phase-amplitude coupling; EEG – Electroencephalography; iEEG – Intracranial EEG; HFO – High-frequency oscillation

Similar to supervised learning, the parameters are optimized such that a cost function between the measured EEG and the model output is minimized. Spatiotemporal prior knowledge of ictal EEG can be used as a constraint in the inverse problem, which is the main advantage of this approach. In addition, noise can be minimized while solving the inverse problem and direct spatial interpretation of clinical EEG. However, many modeling methods including head modeling, modeling the activity of the brain, and instrumental/biological noise models affect the accuracy of source localization in this approach. In this regard, simple spherical head models to realistic head models such as boundary element model,^[120] finite element model,^[121] and finite difference model^[122] have been investigated in ictal EEG source localization. In addition, EEG inverse problem is an ill-posed problem with nonunique and nonstable solutions. Therefore, several parametric and nonparametric optimization methods including the regularization techniques, such as minimum norm estimates, mixed-norm estimate, low-resolution brain electromagnetic tomography (LORETA), and ANN, and their modified variants have been proposed to solve it^[120-123] is the most recent method employed for solving the EEG inverse problem. In this regard, previous works^[10,124] provided a comprehensive review of ictal EEG source localization in focal epilepsy.

Multimodal Neuroimage Fusion

Neuroimaging methods have been widely used in the diagnosis of brain disorders. Each of these methods has its pros and cons to help diagnosis diseases and provides specific types of structural, functional, and temporal information. The diagnosis decisions usually need whole complementary information at once, usually not provided by one modality alone. The main objective of the multi-modality fusion of neuroimaging modalities is to combine different diagnostic modalities and provide a single representation of these modalities to improve the diagnosis process and decision-making in various diseases.^[125] Several algorithms have been proposed for this purpose and new approaches are still ongoing. In the following, first, we briefly introduce neuroimaging modalities and available AI solutions for the fusion of their information and mention the benefits and limitations of methods in general. Then, we review the methods from a modeling point of view and generalize our categorization for EEG signals to cover fusion methods as well.

Additional neuroimaging techniques for seizure foci localization

As it was aforementioned, in addition to EEG, other imaging modalities such as MRI, functional MRI (fMRI), PET, SPECT, and MEG can be used to measure potential seizure onset zones.

Since high-quality structural MRI can visualize epileptogenic lesions, it has been officially recommended

for the clinical evaluation of epilepsy patients. Indeed, T1-weighted images, fluid-attenuated inversion recovery images, and T2-weighted images protocols have been considered standard routines to provide better visualization of previously invisible lesions.^[126] In addition, MRI can identify the anatomical epileptogenic zone as well. Meanwhile, advanced structural MRI sequences are developed for the localization of epileptogenic zones. In the recent era of advances, the advantages of diffusion tensor imaging and MR spectroscopy and arterial spin labeling are noninvasive techniques that are still being examined.^[127,128]

However, in 15%–30% of patients, focal epilepsy is nonlesional and when structural lesions are not found, functional imaging neuroimaging can be helpful. fMRI is an imaging modality that can provide visualization of blood oxygen level-dependent (BOLD) signals during ictal and interictal activities. Simultaneous EEG and fMRI recording have been shown to be effective for the localization of epileptic zones.^[129,130] However, the exact relationship between discharge activities and BOLD signals is not known and needs more studies.

PET is an imaging technique that applies radioactive materials to reveal the metabolism of tissues and can be used to find potential seizure onset zones. Interictal reduction of glucose metabolisms (hypometabolism) which occurs in the onset zones can be visualized by Fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging. Although the zones indicated by PET imaging are typically wider than the seizure focus itself, PET is still a popular imaging technique in addition to MRI for the detection of the seizure focus.^[131]

Dynamic changes of the cerebral perfusion that occur during an epileptic seizure can be detected by ictal SPECT. During the seizure, the area of hyperperfusion which corresponds to high brain activity can determine the epileptogenic zone.^[132] However, the low temporal resolution of ictal SPECT imaging usually complicates the acquisition of true ictal imaging.

MEG is another modality that measures magnetic fields produced within the brain. Unlike EEG signals, which are usually attenuated by the brain, skull, and scalp, magnetic fields are less attenuated and MEG signals have high temporal and spatial resolution. Therefore, MEG is widely used as expletory information for the localization of seizure foci.^[133] However, mathematical modeling is required to measure the neuronal activity of the patients from MEG and the spatial localization is dependent on the precision of the employed mathematical models.

In Figure 5, we illustrate the spatial and temporal resolutions for the most popular functional neuroimaging methods for the detection of epileptogenic zones.

The fMRI has the highest spatial resolution while suffering from low temporal resolution (typically a few seconds). In

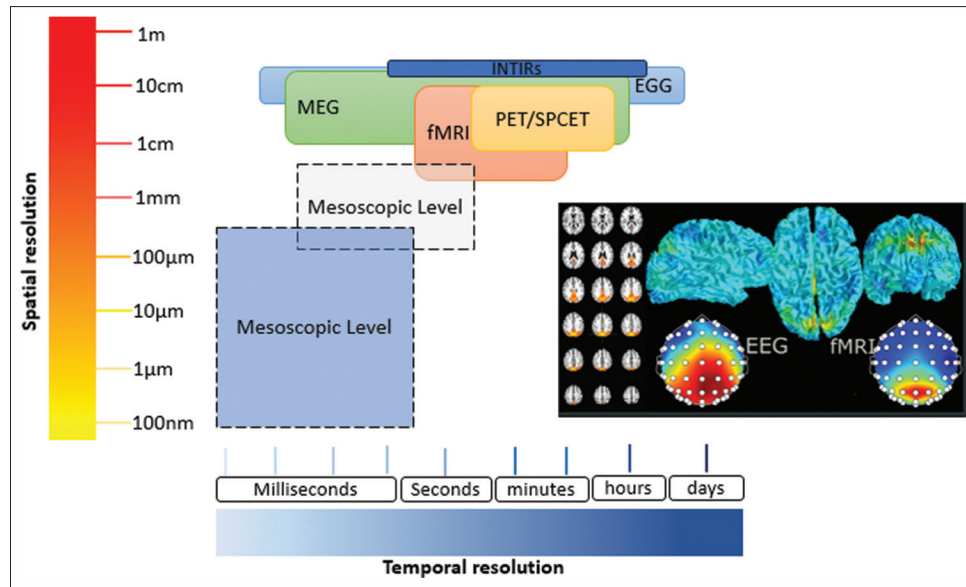


Figure 5: Illustration of the spatial and temporal resolutions for the most popular functional neuro-imaging methods for detection of epileptogenic zones. EEG – Electroencephalography; MRI – Magnetic resonance imaging; PET – Positron emission tomography; SPECT – Single-photon emission computerized tomography; MEG – Magnetoencephalography; fMRI – Functional magnetic resonance imaging

contrast, EEG and MEG have a temporal resolution of a millisecond order with a spatial resolution of at least several millimeters. The microscopic and mesoscopic level imaging of neuroscience is now an invasive imaging technique and is currently under investigation. It must be mentioned that multimodal fusion takes advantage of this spatiotemporal diversity and aims to improve the spatiotemporal resolution of information acquired from the brain by combining various modalities. Therefore, the first guess is to fuse a modality with superior temporal resolution with one, which has superior spatial resolution. In this regard, the fusion of M/EEG-fMRI^[134] and EEG-PET^[135] has been investigated. A combination of imaging modalities with a similar spatiotemporal resolution, which is called validation, has also been investigated in the combination of data.^[136,137]

Fusion of neuroimaging modalities: Artificial intelligence solutions

So far, several algorithms have been investigated for multimodal fusion of imaging techniques. Similar to AI solutions of EEG data, these algorithms can be done in both representation domains of data: the original (spatial) domain and the transform domain in data-adaptive and nondata-adaptive manner. Basically, multimodal image fusion consists of two main steps: choosing regions or pixels of data in spatial or transform domain according to activity level measurements, then, merging with a specific fusion rule which can be a linear or nonlinear operation. Therefore, fusion methods have three main issues, i.e., type of image transform, activity-level measurement, and fusion rule design.^[138] Activity level measurement is performed to extract quantitative information from different modalities, and the fusion rules determine the weight distribution of extracted information to be merged. Due to the crucial

role of the last two steps, most studies of multimodal image fusion have tried to find out such activity level measurement and fusion rule that can preserve more information of source data. However, the activity level measure can be considered a feature extraction step and the design of the fusion rule can be considered a classification step. This consideration can be well generalized under the proposed categorization as follows.

Preprocessing

In every neuroimaging modality, several challenges often occur during data acquisition that can degrade the quality of images and cause problems at different fusion levels of image fusion. Unwanted information caused by various types of noise, including impulse noise, speckle noise, and Poisson noise, reduces the fusion performance. The movement of patients, in particular, unavoidable movements such as breathing and heart beating can blur the acquired images. Inappropriate field of view, artifacts occurring in image reconstruction, and even can change the information of data in each modality. Therefore, rather than general state-of-the-art algorithms, there are several modality-specified methods available for denoising,^[139,140] artifact removal,^[141,142] and movement correction^[143] as a preprocessing step to be applied to the datasets to achieve reliable results. In addition to intrinsic artifacts of each modality, some sources of artifacts occur during the simultaneous recording of multimodal data. In particular, in the simultaneous recording of EEG-fMRI, large sources of noise inside the MR environment contaminate the recorded EEG signals and induce artificial artifacts in the EEG recording. Gradient artifacts, motion artifacts, ballistocardiogram artifacts, and environmental artifacts are the four main sources of noise in the simultaneous recording

of EEG-fMRI. A systematic review of methods and contemporary usage of artifact reduction in simultaneous EEG-fMRI is presented.^[144] In particular, EEG-fMRI data preprocessing can be performed using available software such as Net Station Software and the EEGLAB toolbox.^[145] Through the Net Station Software, gradient artifacts can be removed by employing an average artifact subtraction algorithm. Ballistocardiogram artifacts can also be reduced through an optimal basis set algorithm by Net Station Software. Further artifacts such as environmental artifacts can be rejected by visual inspection and a zero-reference transformation. Secondary denoising is often done by EEGLAB to remove the residual noise component in the recorded EEG signal. fMRI data preprocessing commonly includes slice timing correction, realignment, normalization, spatial smoothing, and filtration which can be performed using the statistical parametric mapping toolbox.^[146]

In addition, registration may be required, as a preprocessing step, to reduce spatial or temporal in-homogeneities between samples in various modalities. In the registration process, two medical images are aligned to become spatially matched, mapping the same anatomical structures on the two images. The main purpose of the registration is to incorporate the details, and complementary information of multimodal data, acquired at different times and positions. The registration can be performed either extrinsically or intrinsically. In the extrinsic registration methods, markers, implantations, and frames are rigidly attached to patients. Since the external objects are more visible in the acquired images, they can be used as references for the registration. In the intrinsic registration, which we mention as a common preprocessing step, the inherent information of the images such as the vessels, and the edges of the bones are considered mapping references. Intrinsic medical image registration methods contain a wide variety of image processing algorithms, which can be divided into pixel-level (intensity-based) or feature-level algorithms. More details about the medical registration methods and studies can be found in.^[147,148] In addition, a comprehensive review of advances in data preprocessing for biomedical data fusion has been recently done by Wang *et al.*^[149]

Modeling generalization

From a modeling point of view, our proposed categorization can be generalized to multimodal neuroimage fusion methods as well [Figure 3, red branches]. Being loyal to the basic idea, this generalization is required for sub-branches of the categorization tree due to the intrinsic difference between signals and images. In particular, rather than the ordinary wavelet transform,^[150] multiscale decomposition branch can be extended to a wide variety of X-let transforms such as pyramid,^[151,152] curvelet,^[153] ridgelet,^[154] contourlet,^[155] and shearlet^[156] transforms. These transforms are geometric aware and can specify a special geometric feature of an image during decomposition. In addition, graph-based

decomposing filters,^[157] multi-level edge-preserving filtering,^[158] morphological multiscale analysis such as multiscale top-hat transform,^[159] morphological towers,^[160] and morphological wavelets^[161] also be categorized as geometry-aware transforms. Sparse representation methods, which separate features in an image based on different morphological aspects, such as morphological component analysis (MCA) have been widely used in medical image fusion.^[162] Color space transform is another nondata adaptive transform that transforms the image's color, usually RGB, to other color systems such as HSV,^[163] YIQ,^[164] IHS^[165] for neuroimaging modality fusion. Inspired by fuzzy logic, fuzzy transform, as a nondata adaptive transform which transforms data into a reduced set of real samples, thereby, making complex computations easier, has been successfully applied in multimodal image fusion.^[166,167]

In data adaptive transforms, DL^[151] and adaptive MCA,^[168] which are samples of adaptive sparse representation have also been used for multimodal fusion. BSS methods, such as PCA, ICA^[169] tensor decomposition,^[60,170,171] and singular value decomposition,^[172,173] have been frequently used in combination with other nondata adaptive transform for component decomposition in biomedical image fusion.

As can be seen from Figure 2, modeling is the second step in the feature extraction block. Except for parametric models, all categorized modeling methods have been applied in neuroimaging modality fusion as well. Zhang and Blum^[174] reviewed some pixel, window, and region-based activity level measurements which have been generally used in image fusion based on deterministic assumptions. Bayesian-based methods such as Markov random field^[175] have been used in modality fusion to provide prior distribution of data as measurement level activity. Bayesian decision methods such as maximum likelihood^[176] or maximum a posteriori^[177] and Kullback–Leibler distance^[178] were then applied as fusion rules. Entropy^[179] as an exemplar measure provided by information theoretic models and fractal dimension,^[180,181] as a sample feature from chaotic models have been used in the multimodal fusion of images. While multimodal image fusion is usually performed in an end-to-end manner through deep learning-based methods, deep features which are usually extracted from trained deep neural network layers have been used for this purpose as well. Such a study has been conducted and a deep Boltzmann machine was used to extract informative features for fusion of MRI and PET.^[182]

Meanwhile, fuzzy models achieved significant growth in image fusion. In this regard, a fuzzy logic model has been applied either in the feature extraction step as an underlying model such as fuzzy,^[183] neuro-fuzzy,^[184] type-2 near fuzzy,^[185] or as a fusion rule in the classification part.^[186]

Classification issues

As it was aforementioned, after feature extraction, a fusion

rule is employed to determine significant complementary features. This has been traditionally done by simple methods such as choosing maximum value, passing high/low bands, averaging, gradient-based to complex methods such as maximum likelihood, optimization rules, and local energy-based measures, and search algorithms.^[187,188] Correspondingly, from the classifier, here we refer to any algorithm that classifies the significant features from the insignificance ones. By this definition, a broad range of algorithms can be employed as fusion rules (classifiers) in particular for lower levels of diffusion. However, when multimodal fusion is performed for a classification purpose, the information of various modalities can be combined to help feature learning to better classification. Therefore, machine learning algorithms including, but not restricted to, SVM,^[189] fuzzy clustering, and KNN^[190] can be more efficient than classic methods. Pulse-coupled neural networks are a recent type of neural network which have been proposed by modeling cats' visual cortex and used for medical image fusion with several modifications.^[191] Thanks to great improvements in deep learning methods, several fusion techniques have been investigated in an end-to-end manner. RBM,^[182] GAN,^[192] AE,^[193] RNN,^[194] and CNN^[195] are the most applicable methods in this regard.

Fusion of neuroimaging modalities: Model-driven methods

In addition to AI solutions, the multimodal fusion of neuroimaging methods can be considered the solution to the inverse problem.^[196] In this consideration, the forward models of neuroimaging modalities can be combined with each other for a joint analysis of multimodal data. The combination of appropriate forward models makes the information of neuroimaging modalities be brought together. This can be done by asymmetric and symmetric approaches for data fusion. In the symmetric approaches, the modalities are analyzed simultaneously, while in the asymmetric approaches, features from one modality are used to improve the performance of another modality. In the

asymmetric approaches, one modality biases the estimate of another modality by selecting exclusive features that are not revealed in the other modality at all. EEG, MEG, and fMRI are four modalities that have received more attention in this regard. As we have aforementioned, the EEG inverse problem is ill-posed and various spatiotemporal prior constraints can be added to the problem to make it well conditioned. EEG signals have high temporal resolution and any spatial or temporal information, provided by other neuroimaging modalities such as fMRI^[197] and MEG,^[198-200] can help improve the inverse problem solution. The review study on the application of the inverse problem in EEG-fMRI fusion is conducted in.^[201] The forward model complexity for each modality and solutions for model inversion have a crucial effect on the performance of multimodal fusion.

Toward diagnosis of brain diseases

While multimodal neuroimage fusion can be done to construct more informative images from the brain for human visualization and machine perception, it has been shown to be of great significance in diagnostics and treatments of diseases as well.^[115] By combining the anatomical, structural, and functional information acquired from different modalities, complete information is provided through a single representation of multimodal data, thus, manual/automatic diagnosis performance is greatly improved. Therefore, the fusion of neuroimaging modalities can promisingly provide improvement in the diagnosis process and decision-making in various diseases. This can be achieved when multimodal fusion is done to diagnose a particular disease and the information of various modalities is combined to highlight that disease. This approach is called disease-based multimodal fusion and recently has become of great interest.

On the other hand, multimodal fusion has been traditionally categorized to be performed in three levels: pixel (low), feature (middle), and decision (high) levels, as shown

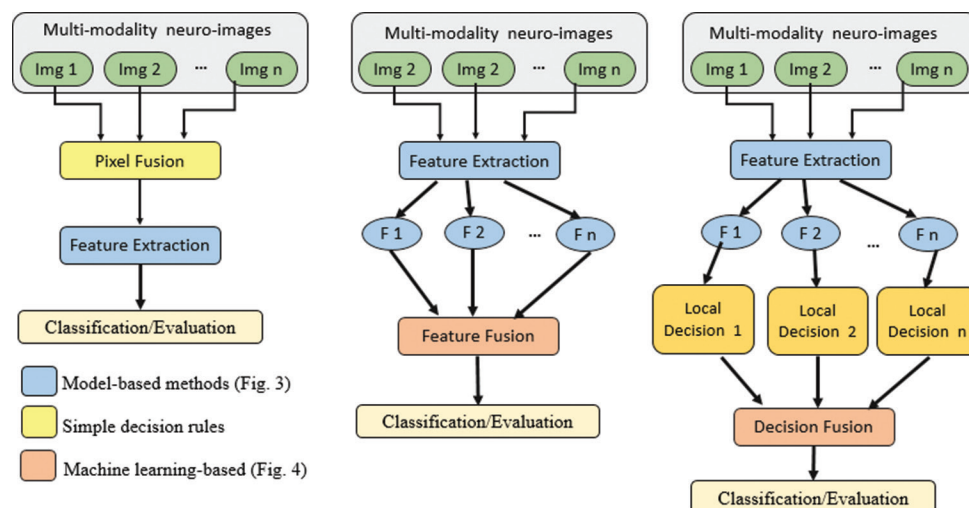


Figure 6: Block diagram of three-level fusions currently utilized in multimodal fusion of neuroimages

in Figure 6. All levels can be applied disease-based multimodal fusion approach.

Low-level image fusion is directly done on details of an original pixel of the image in both spatial and transform domains. In this way, the values and features of each pixel contribute in the fused image. Multi-scale decomposition, sparse representation, component analysis, and hybrid models have been widely used to develop low-level fusion methods.^[138] In addition, the classification step is done based on simple fusion rules, such as average selection, maximum selection, and minimum selection rule, to more complicated methods such as machine learning-based algorithms. Low-level fusion has been examined in the fusion of neuroimaging modalities such as MRI-computed tomography (CT) scans,^[202] PET-MRI,^[203] and MRI-CT-PET^[204] to provide better visualization of images. Low-level fusion is the easiest type of multimodal fusion and preserves much information on modalities, however, the sensitivity of low-level fusion to blurring effects, noise, and registration accuracy are existing challenges to be handled.

Middle-level fusion algorithms are done on the features extracted from informative objects or regions of modalities' data. This means segmented informative regions of source modalities must be determined and their features, varying from simple ones such as the intensity of pixels, edges, and textures to aforementioned model-based features must be extracted. Machine learning approaches, region-based algorithms, and similarity-matching methods have been studied in middle-level fusion.^[205] The machine learning method exactly matches the classification approach. In the region-based method, informative regions are extracted from the input images through segmentation algorithms and model-based features are extracted from corresponding regions, and suitable fusion rules or classification algorithms are used to fuse the features. The similarity-matching salient contents of an image are first extracted through various representation methods such as geometric-based decomposition, and color space transform and then relevant fusion rules are applied to get the fused image.^[206] Middle-level fusion has overcome the challenges of low-level fusion, however, they have still shortcomings such as sensitivity to the segmentation of informative regions. Middle-level fusion has been investigated in the

fusion of neuroimaging modalities such as MRI-CT^[207] and fMRI-MRI.^[208]

The high-level image fusion, also referred to as interpretation or symbol fusion level, has been performed under the following framework: feature extraction from each source modality, classification using first-level local classifiers, and final classification to get fused modalities. In this level, prior information of data must be available and specific criteria are optimized to get maximum matching to this information after fusion. DL and Bayesian techniques are mostly investigated methods used for decision-level fusion. Indeed stochastic modeling methods including information-theoretic, and Bayesian models are usually integrated for image fusion. Bayesian classification techniques, hybrid methods, voting, and fuzzy rules are mostly prevalent fusion rules.^[209] Complexity, correct prior assumption, and information loss are current challenges of this fusion level. High-level fusion has been investigated in the fusion of neuroimaging modalities such as PET-T1 MRI,^[210] fuzzy method for MRI-CT fusion,^[211] and Alzheimer diagnosis based on sparse representation SPECT-MRI fusion.^[212]

In Table 2, we summarized some recent methods in AI solutions for disease-based multimodal neuroimaging fusion developed in recent years and categorized them with specific letter/number notations corresponding to tree structure illustrated in Figures 3 and 4.

As it was aforementioned, epilepsy surgical planning requires localization of the seizure foci using structural and functional data acquired from multiple neuroimaging modalities. Conventionally, disease-based multimodal fusion for localization of epileptogenic zones has been done by first extracting modality-specific features and then fusing their complementary information during classifier learning. So far, several multimodal fusion methods have been investigated to improve localization performance. In this regard, EEG-fMRI fusion has been widely investigated whose recent methods have been reviewed.^[218] These methods have mostly involved deep features and ANN classifiers. For instance, Hosseini *et al.*^[219] extracted deep features from independently acquired EEG and rs-fMRI data and applied them to multimodal data analysis for

Table 2: Some recent artificial intelligence solutions for disease-based multimodal neuroimaging fusion

Author	Year	Feature extraction approach	Evaluation (%)	Modality	Disease/abnormality
Lei <i>et al.</i> ^[213]	2016	O-III + S-S2-D2	Acc=97	MRI-PET	Diagnosis of Alzheimer's and MCI
Kaur <i>et al.</i> ^[214]	2019	T-TN-TNM11-TD-TDB1 + maximum criteria	-	CT-MRI-SPECT	Brain tumor
Algarni <i>et al.</i> ^[215]	2020	T-TN-TNM21 + S-S2-D2	Acc=91	CT-MRI	Tumor detection
Hao <i>et al.</i> ^[216]	2020	OI + S-S1NL1 + S-S1-L1	Acc=97	MRI-PET	Diagnosis of Alzheimer's disease
Song <i>et al.</i> ^[217]	2021	T-TN-TNM21 + search algorithm	Acc=98	MRI-PET	Mild Alzheimer's disease
Jia and Lao ^[208]	2022	T-TD-TDD-II-1M + S-S1-L1	Acc=99	fMRI-MRI	Diagnosis of Alzheimer's disease

Acc – Accuracy; MRI – Magnetic resonance imaging; PET – Positron emission tomography; SPECT – Single-photon emission computed tomography; fMRI – Functional MRI; CT – Computed Tomography

predicting the epileptogenic network using an LSTM classifier. However, few studies have been conducted to explore the benefits of other modality fusion for focal localization. Chowdhury *et al.*^[220] proposed an entropy-based method (MEM-fusion) to take advantage of the complementarities between EEG and MEG to improve localization accuracy from 50% for EEG and 71% for MEG to 90% for fused data. Tang *et al.*^[221] proposed a machine learning-based multimodal neuroimaging to predict seizure outcomes after epilepsy surgery by fusion of F-FDG PET/CT and iEEG modalities. They used a deep residual network (DRN) to extract and transfer deep features, and then a multi-kernel SVM was used to integrate feature sets and to predict seizure outcomes. The accuracy of the classification performance of the DRN-MKSVM model was reported as 91.5%. Multimodal fusion of EEG-fNIRS was investigated in^[222] using LSTM-RNN for feature extraction and fusion rule. A comprehensive review of MRI and CT fusion to sEEG is done by Perez *et al.*^[223] where various metrics, registration, and fusion methods have been surveyed. Mareček *et al.*^[224] investigated the multimodal fusion of MRI-PET-SPECT using GMM as unsupervised feature learning and classification. More investigation is required to assess these methods and develop effective multimodal techniques.

In Table 3, we summarized some recent methods in AI solutions for epileptic foci localization based on multimodal neuroimaging fusion developed in recent years, their benefits and limitations, and categorized them with specific letter/number notations corresponding to tree structure illustrated in Figures 3 and 4.

Multimodal fusion pitfalls

Despite several promising research studies that have been conducted on multimodal image fusion, there are still multiple challenges and limitations that affect the performance of the fusion process and cause erroneous conclusions. Some of these limitations are due to data availability, quality, compatibility, resolution, dimension, and characteristics of different modalities. Defining new clinical protocols for data recording, data augmentation through synthesis data, and adding extra preprocessing steps

to enhance the quality and resolution of the images can be some steps to deal with these challenges. In addition, there are inherent trade-offs between the information available in temporal, spectral, and spatial domains. For instance, spatial domain fusion may produce spectral degradation of modalities. Conversely, transform-based fusion methods such as wavelet transform may outperform in terms of minimizing the spectral distortion, however, they induced spatial distortions. Thus, finding the multisource data, which meets the desired condition and the appropriate fusion technique, is a challenging issue.

While pixel-level fusion has received great attention in recent years, it suffers from certain pitfalls. During image fusion, different levels of blurriness and contrast reduction are imposed on the results. In addition, transform domain methods cause color artifacts that need to be reduced. An inappropriate fusion rule may cause inconsistent illumination in the fused images due to the nonuniform detail enhancement of darker/brighter images during fusion. The presence of noise, which degrades the quality of fused images, is unavoidable, and noise reduction is still important. It seems that hybrid image fusion approaches and multi-level fusion techniques which employ multiple transformations, before extraction of model-based features and application of fusion rules, can provide improvement in visualization, quality enhancement, and suitable processing time of fused images.^[226] In these methods, fused images contained both high spatial resolution with high-quality spectral content, but the computational complexity, hardware requirement, and processing time of these models are the most limiting factors. Optimization techniques can be used to modify the parameters of the fusion algorithm for best performance and visualization.^[227] In this regard, new evaluation metrics should be developed to give correct assessment measures for fusion performance.

The major limitation is that the practical implementation of multimodal fusion methods is still limited to software applications, which are not real-time. They are useful for ready datasets that have been acquired from different modalities previously and asynchronously at different times. Multimodal imaging devices and simultaneous capturing can be a solution to these problems. While

Table 3: Some recent artificial intelligence solutions for epileptic foci localization based on multimodal neuroimaging fusion

Author	Year	Feature extraction approach	Classifier	Modality	Benefit/limitation
Hosseini <i>et al.</i> ^[217]	2020	T-TD-TDD	S-S2-D5	EEG-rs-fMRI	High performance, customizable/require large data, computational complexity, large amount of hyperparameters
Tang <i>et al.</i> ^[219]	2021	T-TD-TDD	S-S1-L1	F-FDG PET/CT iEEG	
Sirpal <i>et al.</i> ^[220]	2019	T-TD-TDD	S-S2-D5	EEG-fNIRS	
Kyathanahally <i>et al.</i> ^[225]	2017	T-TD-TDB	-	EEG-fMRI	
Chowdhury <i>et al.</i> ^[218]	2018	O-II2	-	EEG-MEG	Simple, fast/spectral degradation, blurring effect, low spatial resolution, low performance
Mareček <i>et al.</i> ^[222]	2021	O-II-1S	US1	MRI-PET-SPECT	

MRI – Magnetic resonance imaging; PET – Positron emission tomography; SPECT – Single-photon emission computed tomography; fMRI – Functional MRI; EEG – Electroencephalography; iEEG – Intracranial EEG; MEG – Magnetoencephalography, fNIRS – Functional near-infrared spectroscopy; rs-fMRI – Resting state fMRI; F-FDG PET – 8F-Fluorodeoxyglucose Positron Emission Tomography

simultaneous data acquisition helps capture the same brain condition, synchronous acquisition of data, in particular EEG-fMRI,^[228] is still challenging and the recordings have large artifacts due to the scanning procedure. In this context, a wide variety of research is expected to keep this matter growing in the future.

Discussion

In refractory epileptic patients, resection of the epileptogenic tissue is the best treatment, which requires precise localization of epileptogenic zones. In addition, other alternative treatments, such as TMS and TES, as well as post-surgical rehabilitation, have been shown to be highly dependent on accurate localization. However, the exact localization of the epileptogenic zone is currently a clinical challenge due to the lack of clarity regarding the crucial zones necessary for determining the boundaries of the epileptogenic tissue. Scalp EEG video monitoring is currently the primary diagnostic method for epilepsy, and iEEG is the preferred neuroimaging technique for localizing focal epilepsy, despite being a costly and invasive procedure. However, other noninvasive imaging techniques can be utilized as new diagnostic tools if their complementary information is combined.

In this article, we aim to provide a comprehensive review of current software-based localization methods that investigate EEG signals. The purpose of this review is to assist researchers in developing new EEG-based computer-aided systems for epileptic focus detection. In additionally, we

conduct a survey on various multimodal neuroimage fusion methods to achieve accurate and noninvasive diagnosis. The survey aims to introduce current multimodal image fusion techniques that can be applied in epileptic focus localization. Despite the inherent differences between EEG and other modalities, this work introduces a joint localization pipeline based on signal processing modeling. This allows for the duplication, merging, and evaluation of localization methods based on underlying models. The summary of sections covered in this article is highlighted in Figure 7.

According to the various reviewed studies in this article, both EEG-based localization and diagnosis-based multimodal fusion depend on the extracted features, which can be categorized under the modeling framework. Modeling can be done in both the original and transform domain of each modality. Accordingly, deterministic, stochastic, chaotic, and fuzzy features can be extracted. The schematic of such categorization is elaborated as a tree structure in Figure 3. The studies listed in Tables 1 and 2 provide evidence justifying this model-based approach and this may give the researchers a technical overview for developing new methods in these areas. An advantage of this modeling perspective is that it can legitimize biomarkers in EEG signals and may help discover new ones. The next superiority of this categorization is that it provides a unique framework for feature extraction in various modalities. This framework is helpful in middle-level and high-level fusion methods due to investigating common discriminative features of modalities. In addition, the proposed framework provides the possibility to classify different methods to

Table 4: Performance comparison between the studied methods in the localization of foci regions based on the applied feature extraction approach

Feature extraction approach	Number of research article	Accuracy range	Sensitivity range	Specificity range
Time domain-based models	[62,63,65,75,88,110]	83%–98%	85%–90%	87%–92%
Nondata adaptive transform models	[45,46,68,95-97,99,111-113]	90%–99%	95%–98%	96%–100%
Data adaptive transform models	[51,53-55,59,87,94,100,104-109,114]	90%–100%	94%–98%	97%–99%

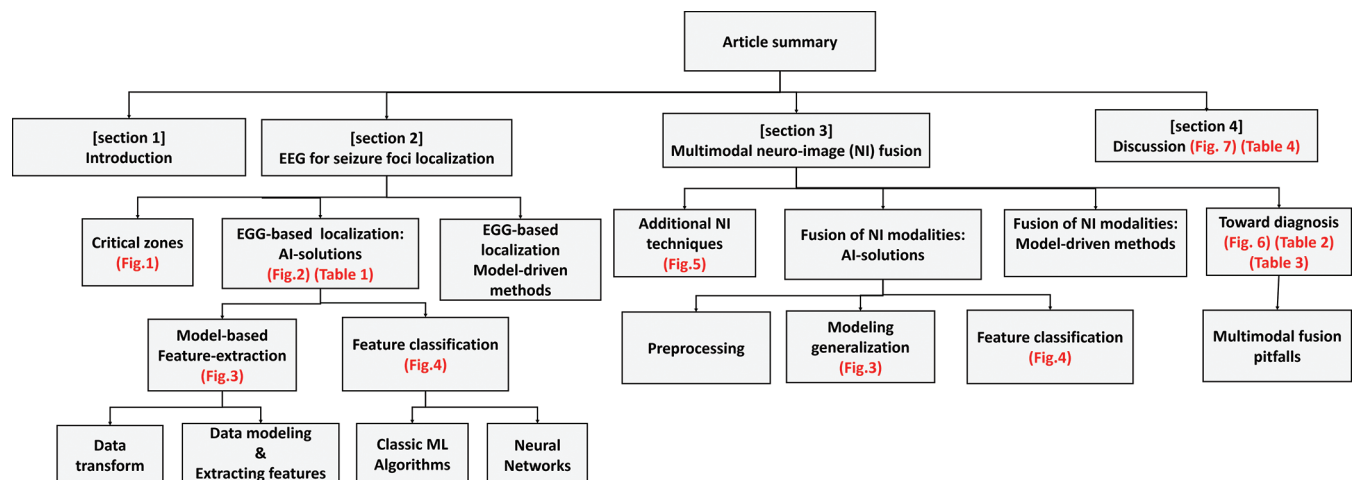


Figure 7: Summary of sections encompassed in this article

show which of them is more effective and applicable in the localization of foci regions based on the applied feature extraction approach. In Table 4, we provided a performance comparison between the studied methods in the localization of foci regions based on the applied feature extraction approach. It can be seen that the data-adaptive models, particularly deep learning-based methods, have become of more interest in recent years and have relatively higher performance than other methods.

In addition, in this review, both EEG-based localization and diagnosis-based multimodal fusion are considered classification tasks. According to various reviewed studies reported in Table 1, the crucial role of machine learning algorithms for the classification of epileptogenic zones in neuroimaging modalities is determined. It can be seen that while classic machine learning algorithms still have an important role in EEG-based localization, most diagnosis-based multimodal fusion methods take advantage of deep learning methods in both feature extraction and selection.

Despite the significant benefits of AI methods, they have several limitations: supervised learning requires a large amount of labeled data while providing such huge data is a basic challenge. Therefore, investigation of new unsupervised methods should be of great priority. In addition, to develop a subject-independent computer-aided system, machine learning algorithms require being trained by a large variety of data. Therefore, a challenge is to collect and build new datasets from various modalities.

Overall, there is a large variety of automatic localization methods based on EEG signals. However, the review shows that multimodal fusion of neuroimaging modalities, in particular EEG and other modalities, is still at the beginning and extensive studies can be done in the future to improve it. Correct selection of modalities to be fused, and fusion method including extracted features and classifier are important challenges in this regard.

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Conflicts of interest

There are no conflicts of interest.

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