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Advances in epilepsy

Artificial intelligence applied to epilepsy imaging: Current status and future perspectives

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ABSTRACT

In recent years, artificial intelligence (AI) has become an increasingly prominent focus of medical research, significantly impacting epileptology as well. Studies on deep learning (DL) and machine learning (ML) – the core of AI – have explored their applications in epilepsy imaging, primarily focusing on lesion detection, lateralization and localization of epileptogenic areas, postsurgical outcome prediction and automatic differentiation between people with epilepsy and healthy individuals. Various AI-driven approaches are being investigated across different neuroimaging modalities, with the ultimate goal of integrating these tools into clinical practice to enhance the diagnosis and treatment of epilepsy. As computing power continues to advance, the development, research integration, and clinical implementation of AI applications are expected to accelerate, making them even more effective and accessible. However, ensuring the safety of patient data will require strict regulatory measures. Despite these challenges, AI represents a transformative opportunity for medicine, particularly in epilepsy neuroimaging. Since ML and DL models thrive on large datasets, fostering collaborations and expanding open-access databases will become increasingly pivotal in the future.

1. Abbreviations

AI	artificial intelligence
CNN	convolutional neural network
CT	computed tomography
DL	deep learning
DTI	diffusion tensor imaging
DRE	drug resistant epilepsy
FCD	focal cortical dysplasia
FLAIR	fluid-attenuated inversion recovery
HARNESS-MRI	harmonized neuroimaging of epilepsy structural sequences
ILAE	International League Against Epilepsy
MELD	Multi-centre Epilepsy Lesion Detection
ML	machine learning

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MRI	magnetic resonance imaging
PET	positron emission tomography
ROI	region of interest
SPECT	single-photon emission computed tomography
T	Tesla
T1w	T1-weighted
T2w	T2-weighted

2. Background

In France, more than 680,000 people were identified as having epilepsy in 2020 [1]. Globally, approximately 50 million people are affected, resulting in epilepsy being one of the most common neurological diseases as well as a significant burden on healthcare systems worldwide [2]. Artificial intelligence (AI), through machine learning (ML) and specifically deep learning (DL), has started to influence diagnosis, treatment and research across medical fields [3], and is playing an increasingly important role in epilepsy specifically. With its growing influence, AI holds the potential to improve care for millions of people with epilepsy while also transforming the daily work of healthcare professionals in neurology and beyond.

2.1. *Neuroimaging in epilepsy*

Neuroimaging plays a crucial role in the management of people with epilepsy, beginning with the first seizure. At least one imaging study is recommended at this stage to allow early detection of potential acute intracranial pathologies, such as hematoma, stroke, vascular malformations, trauma, tumors, or infections [4]. To maximize the sensitivity of lesion detection, the International League Against Epilepsy (ILAE) recommends performing a standardized magnetic resonance imaging (MRI) scan within the first days after a first seizure. The harmonized neuroimaging of epilepsy structural sequences (HARNESS-MRI) protocol including isotropic, millimetric 3D T1-weighted (T1w) and fluid-attenuated inversion recovery (FLAIR) images, and high-resolution 2D submillimetric T2-weighted (T2w) images should be acquired on a 3 Tesla (T) Scanner if available, alternatively on a 1.5T scanner [5]. While computed tomography (CT) is less sensitive and less specific than MRI for the detection of most intracranial pathologies, it is still commonly used to rule out intracranial bleeding after a first seizure due to its advantages in availability, shorter scanning duration and lower costs. In cases of drug resistant epilepsy (DRE) requiring surgical evaluation, additional imaging techniques, such as functional MRI, diffusion tensor imaging (DTI) or tractography, EEG-fMRI (electroencephalogram-functional MRI), magnetic source imaging, positron emission tomography (PET), and single-photon emission computed tomography (SPECT), are widely utilized [4].

The integration of AI models into neuroimaging modalities was only a matter of time. More than a decade ago, initial attempts were made to apply simple ML models to various research questions in epilepsy neuroimaging.

In this review, we provide a brief overview of how research groups worldwide have integrated ML and DL approaches into their scientific studies and explored how these technologies could potentially be adopted into clinical practice for epilepsy imaging.

3. Artificial intelligence (AI) applied to epilepsy imaging

AI is often used as an umbrella term encompassing ML and DL models, which enable computers to analyze data, make decisions, generate predictions, and learn from the encountered data. In epilepsy imaging research different ML approaches, such as logistic regression, linear discriminant analysis and support vector machines were tested in several studies. Meanwhile, neural networks – the basis of DL – have evolved from single-layer to dual-layer and multi-layer neural networks to more complex architectures like deep neural networks, which are increasingly being applied in epilepsy imaging research. To achieve optimal performance of ML models, a major requirement is high data quality demanding extensive manual data preparation. In contrast to classic ML approaches, DL can process data more effectively due to its multi-layered neural network architecture. However, due to increasing complexity and more than a million trainable parameters of DL approaches, larger datasets are required to not overfit the training data and produce meaningful and robust (generalized) outcomes for unseen new data [5].

MRI is the gold standard diagnostic tool for detecting epileptogenic lesions after a first seizure and during the presurgical evaluation of DRE. T1w, FLAIR and T2w images are crucial for detecting epileptogenic brain abnormalities with the highest possible sensitivity [6]. Common abnormalities include mesial temporal sclerosis, focal cortical dysplasia (FCD), and tumors. As a result, most AI approaches in the field of epilepsy imaging developed so far have focused on detecting epileptogenic brain abnormalities – primarily FCD [5].

3.1. *FCD detection*

More than a third of histologically confirmed FCD are reported as MR-negative before surgery. Even for experienced specialists, detecting FCD on MRI can be challenging [7]. Assisting specialists in this task enhancing sensitivity while maintaining the highest possible specificity in FCD detection has been a key objective for many research teams worldwide. In 2014, Hong et al. published a study on the automated detection of FCD type II. The proposed classifier (Fisher linear discriminant analysis [LDA]) was trained on 3 morphologic and 2 intensity-based brain tissue surface features extracted from 3T MR images of 19 patients to identify lesions in previously MR-negative patients. The approach achieved a sensitivity of 74% and a specificity of 100%, validated [leave-one-out cross-validation (LOOCV)] on the 3T MRI dataset of 19 patients of which 15 were histologically confirmed FCD and 24 controls. In LOOCV, a model is trained on all but one subject of a cohort and then tested on the excluded subject. This process repeats until each subject has been left out once, allowing the model's overall performance to be averaged. Cross-validation on a 1.5T MRI dataset of 14 patients and 20 healthy controls achieved a sensitivity of 71% and specificity of 95% [8]. In 2015, Ahmed

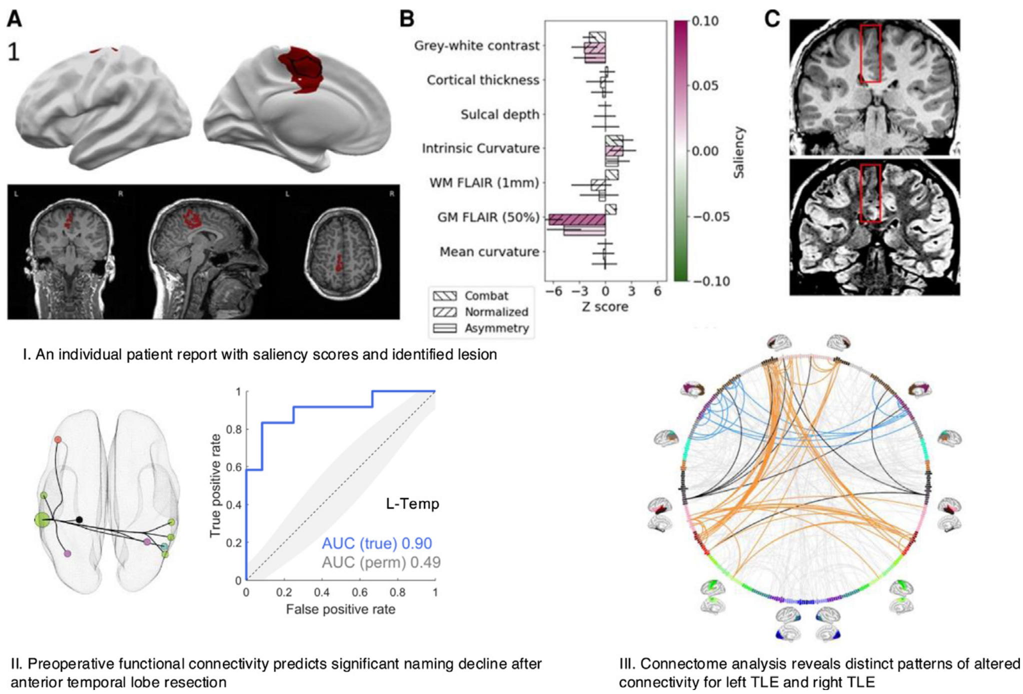

Fig. 1 – Different approaches of artificial intelligence (AI) in epilepsy imaging. I. Individual report of one patient with focal cortical dysplasia (FCD). I.A. Lesion mask in dark red. I.B. Saliency scores for several patient MRI features. I.C. Identified FCDs in coronal plane MRI. II. Predicting significant naming decline after anterior temporal lobe resection (ATLR). Seed-based connectivity of individual regions of interest (ROIs) showed the potential of functional connectivity patterns to preoperatively predict significant cognitive decline after ATLR. L-Temp = left temporal ROI; AUC = area under the curve. III. Connectome analysis: comparison of left TLE patients vs. healthy controls. Compared to controls, in left TLE widespread altered connectome structure involving multiple language relevant regions (orange) were observed. Modified from Spitzer et al. Interpretable surface-based detection of focal cortical dysplasias: a Multi-centre Epilepsy Lesion Detection study, *Brain* 2022 [12] and Nenning et al. The impact of hippocampal impairment on task-positive and task-negative language networks in temporal lobe epilepsy, *Clinical Neurophysiology* 2021 [13].

et al. developed a ML-model for FCD detection (consisting of 10 logistic regression classifiers with majority vote for predictions) using five cortical surface features extracted from 3T MR images as input. For evaluation LOOCV was used achieving a sensitivity of 58% on a cohort of 24 FCD patients [9]. Over the years, automated FCD detection has advanced significantly, evolving from classic ML approaches to deep learning-based strategies and more recently to increasingly complex DL classifiers, such as convolutional neural networks (CNN) [10]. A study with great impact on future studies was published by Adler et al. in 2016, utilizing a neural network classifier to identify FCD in a cohort of pediatric patients. In addition to well established features such as cortical thickness, blurring of grey-white matter, FLAIR signal intensity, curvature and sulcal depth, they implemented measurements of local cortical deformation, local variability in cortical morphometry and MRI signal intensity. The neural network was trained on these features extracted from MR images of 22 patients with focal epilepsy to enhance its ability to recognize complex patterns, marking a significant advancement in automated FCD detection [11]. A study conducted as part of the Multi-centre Epilepsy Lesion Detection (MELD) project showed that sensitivity and specificity of a neural network classifier declines amidst more real-life conditions [12]. While the study conducted in 2014 [8] on 35 patients reported a sensitivity of approximately 70% and a specificity of approximately 95–100%, the 2022 MELD-study, which analyzed a much larger cohort of 618 patients (training data: 278 patients, 180 controls; test data: 260 patients, 193 controls) from 22 epilepsy centers worldwide found a sensitivity of 59% and a specificity of 54%. They used surface-based morphological and intensity features as input for a simple neural network with two hidden layers (Fig. 1I) [12,13]. These findings highlight the challenges of translating AI models from controlled research settings to clinical practice. A different approach, requiring less time-consuming preprocessing and imaging data preparation, was tested in a multi-centre study involving 148 FCD patients. This study tested a deep learning approach for analyzing MRI data in a 3D voxel space. It consists of a cascade of 2 concatenated CNN (1) focusing on detecting lesional voxels and (2) reducing the number of misclassified voxels. LOOCV (8 sites in total) was used for evaluating the model's performance, which successfully detected FCD in 137 out of 148 patients, achieving a sensitivity of 93% and a specificity of 89% [14]. Helping specialists detect subtle lesions with high sensitivity and specificity is a shared goal of many research groups. In the era of AI, big data and rapidly advancing computing power, automatic FCD detection tools will continue to improve and are likely to become part of clinical practice in the coming years. Collaborative efforts, such as multicenter studies, will have an important role in accelerating this progress and enhancing detecting accuracy, underscoring the importance of such initiatives.

3.2. *Automated detection of lesions and outcome prediction in TLE*

Another approach to integrating AI – specifically ML or DL – into structural epilepsy imaging is to further refine automated lesion detection in TLE patients based on MRI. AI models can identify subtle structural and functional patterns characteristic of TLE that may be imperceptible by visual inspection, improving diagnostic accuracy. Recently, Gleichgerrcht et al. [15] published a study testing a 3D CNN model for distinguishing MRI-negative TLE patients from healthy controls using MRI data. They further compared their 3D CNN model against support vector machine models trained with 5-fold cross-validation on whole-brain volumetrics and hippocampal volumes (1178 scans from 12 different centers) and demonstrated the clear superiority of the 3D CNN model compared to other ML approaches. In an MRI-negative group, the 3D CNN model identified TLE patients with an accuracy of 82.7% and in an MRI-positive group with an accuracy of 89.5% [15]. In a pediatric cohort from Shenzen Children's Hospital, a support vector machine model based on grey matter volume in MRI was tested in a small group of 22 patients with TLE and hippocampal sclerosis and 15 healthy controls. The model achieved an area under the curve of 0.902, demonstrating strong discriminatory performance [16].

Another important application of AI will be to determine the extent of the epileptogenic area using advanced MR sequences such as DTI and 18FDG-PET imaging in surgical planning. Different AI approaches have already been applied to diffusion tensor imaging (DTI), which allows for the measurement and visualization of white matter tracts. This technique is widely used for surgical planning, helping to identify and preserve critical tracts during epilepsy surgery. Several studies have explored ML and DL models using DTI to lateralize the epileptogenic hemisphere in TLE patients compared to healthy controls and predict seizure or language outcomes after surgery. Automated differentiation of TLE patients from healthy controls based on structurally deviating white matter networks has been performed not only in adults but also in pediatric epilepsy patients [4,5].

Positron emission tomography (PET) imaging with the metabolite ^{18}F-fluorodeoxyglucose (FDG) is commonly used interictally for presurgical evaluation in people with DRE. FDG-PET, which is more sensitive in temporal lobe epilepsy than in extratemporal epilepsy, may help localize and lateralize the seizure onset zone by detecting hypometabolism in epileptogenic regions [4]. Studies applying AI approaches to this field primarily focused on ML classifiers, such as support vector machines, to assist in the lateralization of the seizure onset zone based on PET imaging. As with other neuroimaging modalities, more advanced approaches, such as CNN were later introduced – with the aim of fully automated seizure onset zone-localization in PET scans. In addition, several studies have pursued the use of presurgical PET imaging to predict postsurgical outcomes. However, the accuracies of these studies need to be carefully evaluated due to the complexity of this task. Furthermore, scientists are investigating AI-driven techniques to enhance PET scan quality, which could further improve detection rates [5].

Different research groups are exploring AI applications in functional MRI (fMRI) data. One approach involved a semi-supervised classifier based on logistic regression for left, right or bilateral language dominance [17]. Based on resting-state fMRI a support vector machine model was used in another study to distinguish people with TLE from healthy controls [18]. In a smaller cohort of pediatric epilepsy patients a 3D CNN approach was tested to differentiate children with epilepsy from healthy controls [19]. Similar to their use in PET imaging studies, ML and DL have been applied to functional connectivity analyses to lateralize or localize the seizure onset zone. Support vector machines have been implemented to predict seizure outcomes after epilepsy surgery and assess patients' responses to medication (Fig. 1II and III) [5]. A semi-automatic DL-based detector for interictal epileptic discharges was integrated into EEG-fMRI to enhance time efficient analyses in 2017 by Hao et al. and achieved a median sensitivity of 84% [20].

4. Conclusion

In the field of epilepsy imaging, as in many others, the application of AI, particularly ML and DL models, has gained significant interest and seen remarkable progress over the past decade. These advancements have been driven by the current era of big data and the exponent growth of computing power [5]. Various imaging modalities are routinely used in epilepsy particularly as part of the presurgical evaluation [2,4,6]. It was merely a matter of time before AI applications found their way into epilepsy imaging research, and it is likely only a matter of time before AI applications are integrated into clinical practice. In many commonly used epilepsy imaging modalities, research groups initially implemented ML tools such as support vector machines and linear discriminant analysis before adopting DL approaches like neural networks [5]. Computer-assisted or automated lesion detection – especially for FCD in MRI – is certainly one of the furthest developed AI applications in epilepsy neuroimaging. Since FCD often cannot be detected even by experienced specialists, identification of these subtle lesions assisted by AI is of great interest. Multicenter projects like MELD have made significant progress through global collaborations across multiple sites. This approach enabled the testing of FCD detection tools on large real-world datasets – a crucial factor in the breakthroughs achieved by the MELD project [8–14]. Attempts to automatically distinguish epilepsy patients from healthy controls have been performed using various imaging modalities, including DTI, fMRI and PET-imaging. This could help to train models to identify visually imperceptible lesions and abnormalities. In several studies, models have achieved accuracies comparable to experts in neuroradiology, which nevertheless requires careful interpretation in the light of missing real-world data. Studies often relied on pre-selected cohorts with small sample sizes and consequently were dependent on LOOCV [5,15,16]. This highlights the need for future studies under more realistic conditions. Advancing research on DL and ML models will foster establishing new collaborations and strengthening existing ones. Automatic or semi-automatic localisation and lateralisation of the seizure onset zone have been explored using PET-imaging and fMRI. Individual virtual brain models mapping a person's brain network to create a 'digital twin' could help clinical decision making by identifying epileptogenic areas more accurately, thereby improving the targeting of regions for epilepsy surgery [21]. To the best of our knowledge, none of the epilepsy imaging approaches based on DL and ML that we have cited have obtained *Conformité Européenne* (CE) or US Food and Drug Administration (FDA) approval to date. The major challenge in achieving an FDA and CE approved product will be the necessity of prospective real-world studies, which should include large, heterogeneous patient cohorts and ideally employ multimodal strategies. Various approaches to harness the potential of AI-models in epilepsy imaging have been attempted, some of which present a unique opportunity to improve diagnosis and treatment for people with epilepsy. Which of these approaches will ultimately translate into clinical practice – affecting the lives of both people with epilepsy and their clinicians – will likely become more apparent in the coming years.

Declaration of generative AI in scientific writing

In the process of writing and editing this review article, AI-based grammar checking and research tools have been utilized. We declare that we critically reviewed all information and results generated by AI-technologies and are aware of our responsibility for the whole content of this work.

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The authors declare that they have no competing interest.

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