Transforming Epilepsy Care through Artificial Intelligence and Machine Learning

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Abstract

It is imperative to focus on improving reliable methods to detect epilepsy in patients in order to manage this disorder appropriately. In today's world, machine learning is an active area of research and many new algorithms have been developed to assist scientists with further research discoveries. Successful machine learning models have been a favorable tool for doctors as they help them with potential diagnoses in their patients. The advancements in machine learning technology are beneficial in detecting and predicting seizures in an epileptic individual. This research paper answers the question of how doctors and scientists use machine learning models to improve the detection of epilepsy in a patient. In this review, we outline epilepsy and address the potential impacts of machine learning on patient care. We discuss recent literature regarding the application of such tools in epilepsy. Finally, we compare different machine learning models and methods and discuss the potential of artificial intelligence in the future.

Introduction

When a person experiences abnormal brain activity, it can result in seizures, loss of consciousness, and other unusual behaviors. Epilepsy is a central nervous system neurological disorder marked by recurrent seizures and sensory disturbances due to the excessive discharge of neurons. *[6]* Epilepsy can be associated with various transient brain dysfunction syndromes, which are a group of conditions characterized by abnormalities in brain function. Around the world, epilepsy affects approximately 50 million people, making it one of the most common neurological diseases today. *[7]* People living with epilepsy often face challenges in their lives due to recurrent seizures that can manifest in a variety of different ways, including speech impairments or motor symptoms.

Epilepsy diagnosis can be difficult as seizures are exhibited in a variety of ways and often occur outside of the medical settings when a healthcare worker is present. Suspected patients can undergo multiple diagnostic tests to help detect and potentially aid in the treatment of epilepsy, such as the electroencephalogram (EEG), magnetic resonance imaging (MRI), and positron emission tomography (PET). The EEG is a method scientists use to measure the electrical activity in the brain, while MRI and PET are types of neuroimaging techniques that can be used to detect potential epileptic brain lesions in a patient. *[25]*

There are a wide variety of treatments for patients with epilepsy. When possible epileptic patients are screened with noninvasive techniques and are diagnosed with epilepsy, they are treated with daily anti-seizure medications (AEDs). *[25]* AEDs are drugs that control abnormal electrical activity in the brain in order to treat and prevent seizures. Anti-epileptic medications can treat two-thirds of epileptic patients while the remaining one-third are considered to have drug-resistant epilepsy (DRE). A patient's epilepsy is considered to be drug-resistant if they try at least three anti-seizure medications without successful treatment of their symptoms. This drug-resistant epilepsy, or intractable epilepsy, is much harder to treat with medication so it has a high mortality rate and poor prognosis, requiring surgical treatment. *[25]*

There are two types of surgical treatments for epilepsy: Radical Surgery and Palliative Surgery. Radical surgery is used to remove the neurons in a patient's brain that are specifically causing seizures. Radical surgery is recommended for patients whose epileptogenic foci -the discrete area of the brain that generates electrical activity which leads to seizures- does not involve the eloquent cortex. Clinicians may have to use advanced screening techniques in order to accurately determine the epileptic source for radical surgery. *[25]* On the other hand, Palliative surgery is used when it is hard to identify the location of the epileptogenic focus, and this surgery will try to limit the number of seizures a patient experiences overall. Palliative surgery also includes cases having epileptogenic foci involved in the eloquent cortex.

When doctors perform these surgeries, neuroimaging tools are essential for the detection of epileptogenic foci, and to certify their size and range. When the epileptogenic foci are identified, there is a 2-3 times increased chance that there will be no seizures after radical surgery compared to no surgery. *[25]* This highlights the importance of the development of high-fidelity seizure detection devices and algorithms. This review paper will summarize the application and limits of current diagnostic and neuroimaging tools and discuss areas of ongoing research regarding utilizing machine learning algorithms to detect epileptic activity.

Neuroimaging Tools for Epilepsy

EEG

An electroencephalogram (EEG) is a non-invasive tool that measures electrical activity in the brain in order to detect and locate seizure activity. Electrodes are placed on the scalp to measure electrical signals in the brain. EEG can also determine the seizure type a patient is experiencing. For example, it can help identify whether the seizure disorder is focal, generalized, idiopathic, symptomatic, or part of any other epilepsy syndrome. *[20]* An EEG can be particularly useful for non-lesional patients, where the focus of the seizure cannot be seen on MRI or PET.

In certain cases, EEG can directly reflect abnormal neural activities associated with epilepsy. *[25]* However, there are still limitations for this tool. EEG has a low sensitivity for epilepsy that ranges from 25% to 56%. *[20]* EEG tests have an increased chance of generating more false negatives. This means that a doctor can put an EEG on a patient and may not even see a seizure when the patient is actually experiencing one.

It is crucial that a patient has a seizure during the EEG in order for doctors to collect data. Detection for an EEG takes a substantial amount of time and effort (Epileptic Seizure Detection). In the case of epilepsy monitoring, the longer the length of the test, the better it is because it increases the amount of time to sample the EEG. Long-term monitoring can include 2 hours, 6 hours, 24 hours, or even overnight. *[3]*

Another limitation of the EEG is that it uses 12 or 24 electrodes which only cover discrete points on the brain, making it hard to cover the entire region of the brain. As a result, it is often difficult for EEG to locate the accurate epilepsy lesion region in the brain. Often, it is hard to determine where specifically the seizure is coming from as electrical activity propagates through the electrodes.

ECoG

Electrocorticography (ECoG) is an electrophysiological recording method used for a patient undergoing surgery. For example, if a patient fails more than 3 anti-seizure medications, ECoG will most likely be used. Temporal lobe resection is the common process used where the temporal lobe, amygdala, and a part of the hippocampus is removed in order to expose the brain during epileptic surgery. The type of surgery involving ECoG typically takes 3 to 4 hours, and the patient must go through multiple diagnostic tests and evaluations by the doctor to understand the cognitive function of their brain. Moreover, the surgery is complex and can come with risks of bleeding, infection, or brain swelling. *[18]*

Unlike EEG, ECoG is invasive and records electrical brain activity from the cerebral cortex. ECoG requires the use of flat electrode contacts that are placed on a silicon sheet for seizure localization. This sheet will be under the brain's surface or within the sulcus. *[18]* ECoG has been used in the past to map epileptogenic regions in the brain for surgical management of drug-resistant epilepsy.

Today, ECoG is widely used in 80-84% of Epilepsy Centers globally. The recording and stimulating electrodes of ECoG can flexibly be placed and there is a direct electrical stimulation of the brain. Despite these advantages, there are still many limitations to this technology. Limited studies have been done on the effectiveness of ECoG. In the Maudsley Hospital in the United Kingdom, the group never used the spikes that were produced by ECoG because they were not useful when determining areas of epileptogenic anterior temporal lobe resection. *[13]*

MRI

Compared to diagnostic tools like EEG, neuroimaging tools are better for confirming the size and range of epileptogenic foci. The advancements in neuroimaging tools such as MRI and PET have greatly improved the processes of detecting epilepsy. These advancements include the use of machine learning models, which can be beneficial for computer-aided diagnosis and prognosis of neurological disorders. *[25]*

Magnetic resonance imaging (MRI) is a noninvasive neuroimaging technique used by scientists to produce images of internal structures in the body. A typical MRI procedure is safe and most patients can receive one without difficulty. An MRI scan usually takes about half an hour to produce an image of the patient's brain. *[4]*

MRI's application to epilepsy is important because it can highlight different brain tissues, detect potential lesions of the brain, and identify epileptogenic tissue in a patient. In one study, using an epilepsy protocol, the guidelines taken by doctors to standardize the diagnosis and treatment of epilepsy, MRI scans revealed focal lesions in 85% of patients who had nonlesional standard MRI previously. MRI detects the way hydrogen ions are spinning and by doing so, can map the direction of water molecule movement in the brain. fMRI is a type of functional MRI that can detect changes in cerebral blood flow and metabolism due to the paramagnetism of blood. fMRI can be beneficial from a surgical standpoint because it can show the parts of the brain that are active and used for motor control. That way, a surgeon has an advantage in surgical planning as they know which parts of the brain they should not interfere with during a surgery.

The main MRI sequences that are used in imaging different brain tissues are T1w, T2w, and T2w-FLAIR. T1w is used for the anatomical, gray matter structures of the brain. T2w identifies the aberrant zone in white matter and fluids. T2w can be used for seeing fluid in brain edema, while T2w-FLAIR depicts the high contrast between gray matter and cerebrospinal fluid.

Although MRI is non-invasive and does identify structural abnormalities in the brain, there are some limitations to the technology, such as slice thickness. In an MRI, pictures of the brain need to be taken in separate sections. These images are then collapsed to form a 3D image. Slice thickness can vary a lot based on what type of MRI is used. For example, if each slice is 4 mm, then information can be lost as a lesion that is less than 4 mm can easily be missed. Most MRI standard protocol is 4 mm. A 1 mm protocol is more optimal in terms of looking at lesions and understanding which ones are clinically relevant but there is also a time constraint because it requires a greater effort of making thinner slices. Additionally, an expert on staff should be required at all times to review the MRI scan clearly in order to detect epilepsy in a patient. For example, a "'standard' MRI read by a 'nonexpert' radiologist was much less likely to reveal a relevant epileptogenic lesion (39% detection rate) than an 'expert' reader reviewing images generated using a dedicated epilepsy protocol (91%)." *[21]* Another limitation is that at times, MRI examinations do not display therapeutically relevant epileptogenic lesions. *[21]* Another limitation is that scientists may not be able to see pictures of non-lesional epilepsy in patients from MRI scans, which can be too small. This circumstance emphasizes the importance of

Machine Learning Models, which can potentially solve this problem and detect lesions in the future.

Similarly, using new AI technology can potentially help scientists better diagnose lesions and even account for errors from patient head tilt. An example is Neosoma, a radiology company that focuses on neurooncology and brain tumors. Neosoma (HGG) produces accurate brain tumor analysis on MRIs which can help physicians come up with treatment decisions. *[11]* This technology can potentially be used in other neuro fields and epilepsy.

DTI/DWI

Diffusion tensor imaging (DTI) is a type of MRI technique that is used to detect water molecules in the brain. DTI is more sensitive and can measure the direction of white matter fibers. In multiple reports, patients with temporal lobe epilepsy have water diffusion abnormalities in white matter structures. *[16]* The ability of DTI to identify these white matter fibers helps scientists understand white matter tracts and learn about which parts of the brain are disrupted by these abnormalities which can lead to epileptic seizures. Diffusion-weighted Imaging (DWI) is an MRI utility that also shows white matter tracts in the brain and where neurons are running. Additionally, it can identify the parts of the brain that are not receiving enough oxygen or nutrients, as well as the parts that are affected by epilepsy. DWI and DTI are utilized in complex cases where additional topological information is required to inform medical decision-making.

PET

Positron emission tomography (PET) is a neuroimaging technique that can locate seizures in a patient with epilepsy. A radioactive drug tracer is injected into the vein and will go into areas where high levels of metabolic activity are present. *[15]* The PET scan shows the brain's use of oxygen and glucose, and the radioactive drug tracer is used in order to display both normal and abnormal brain activity in a patient. In a single session, PET can enable the simultaneous acquisition of functional images, and structural images, to improve the localization of anatomic and metabolic abnormalities in the body. *[8]* It can reflect abnormal metabolism in the brain by locating regional interictal hypometabolism, which helps neuroradiologists look for lesions. *[25]*

PET scans last for 45-60 minutes, and after the scan, patients are recommended to drink lots of water to flush out the tracer chemical from their bodies. There is only a very small risk of tissue damage from the PET procedure because there are only low amounts of radiation sent through the body.

Fludeoxyglucose F18 PET (FDG-PET) is the main type of PET used for epilepsy. FDG-PET can show areas of increased glucose metabolism during a patient's seizure which helps doctors identify the parts in the brain involved with seizure activity. In a study assessing the diagnostic accuracy of FDG-PET for epileptic zone detection, the sensitivity of FDG-PET/CT was

61.3-64.5%, which was similar to other reported sensitivities from 60-90%. Despite its common use, FDG-PET has limitations including low spatial resolution and low temporal resolution. It cannot accurately localize precise areas in the brain contributing to seizure activity. Additionally, it cannot define the surgical margin because the hypometabolism area extends beyond the epileptogenic zone. *[17]*

Machine Learning Overview

As the world continues to advance, artificial intelligence has the potential to play a significant role in our lives. Artificial intelligence is a broad category for all machines that are programmed to act like humans and perform tasks more efficiently. Machine learning falls under the branch of artificial intelligence. It focuses on training computers to analyze data without explicitly being programmed. Machine learning utilizes algorithms to imitate human understanding and improve accuracy in predictions.

Machine learning requires access to a large amount of data in order to continually improve the processes that analyze this data. Big data consists of extremely large datasets and can be used by machine learning algorithms to discover patterns and trends. The basic structure of a machine learning algorithm can be divided into three parts: the decision process, error function creation, and the optimization process. During the decision process (first step), the model takes in an input of data that represents a certain characteristic such as height. It outputs a pattern from analyzing the data. In the second step, an error function is initiated to determine whether the algorithm's prediction is accurate. This prediction may be compared with other available and known examples. In the optimization process (final step), the algorithm is adjusted to reduce errors between actual data points and the predicted values. *[23]* The algorithm consistently repeats the optimization process to reach accuracy as well as train the model to be attuned to any new data set.

Conventional machine learning is a statistically-based subset of artificial intelligence which consists of algorithms and techniques that are used to analyze data to come up with predictions and decisions. Conventional machine learning can be broken down into two main steps. The first step is feature engineering where hand-crafted features are extracted from brain images. Hand-crafted features are necessary to reduce data dimension as well as to prevent the overfitting of the model. The second step in the process is the machine learning step. During this step, features are inputted into a machine learning model to perform a certain task. Examples include regression to predict epilepsy or classification. Feature extraction can be utilized in neuroimaging tools. An example is with MRI, where feature extraction can be built into an MRI model to extract features from a medical image. MRI tools have billions of pixels so extracting a subset of features from these pixels can prevent the model from overfitting. Feature extraction can help scientists focus on certain important features in medical images.

After feature extraction, there are a variety of machine learning models that can be applied. Linear regression is a model that predicts the value of a variable based on the value of another variable. Linear regression requires a set of data points where a straight line is drawn through them to plot a graph. By analyzing the relationship between a dependent input variable and an independent output variable, machine learning models are able to make predictions regarding the data. An example of how linear regression would be used is with fMRI as it can show the relationship between brain activity and stimuli or tasks. Multivariate regression is also used in AI technologies. For example, it is used to “study the relation between fMRI spatial activation patterns and experimental stimuli or behavioral ratings”. *[22]*

Principal Component Analysis (PCA) is a dimensionality reduction method that transfers data from a high dimensional space to a low dimensional space but still keeps the information in the large set. *[25]* This process is commonly used for feature extraction. There is minimal information loss because the most distinguishable features are selected. PCA can be particularly useful for noise reduction. For example, a PCA algorithm could remove high-frequency noise in a wavelet analysis and process EEG signals to reduce data dimension.

It is important to note with the progressive advancements of machine learning, there are still limitations that need to be considered when diagnosing diseases and predicting prognosis in the healthcare field. Machine learning is heavily dependent upon input data to produce output data. If the input data is poor, then there will be a bad outcome. For example, during an EEG scan, if a patient moves, then the image produced is blurry which can alter the results of the scan. Fixing artifacts are newer algorithms that are currently utilizing artifact manipulation to solve these issues. These algorithms try to adjust any limitations such as patient movement to predict better results. Another problem that arises is the ground truth, which is the reality that a machine learning algorithm models. Experts in charge of reading certain neuroimaging tools such as MRI have a chance of predicting a wrong outcome for a patient. An example of this situation is with nonlesional epilepsy, where an expert may not be able to see a seizure and predict the patient as nonepileptic when in reality, they do have epilepsy. These false predictions can lead to bad training data, ultimately causing machine learning models to predict outcomes that are false.

Solutions to improve the ground truth include using larger data sets for the model so it can identify clear patterns as well as using multiple experts to diagnose a certain condition in a patient. Another aspect to consider when using machine learning models is that there is a lack of transparency of black box. The algorithms these models use only output predictions so scientists do not have a clear idea of what factors are being used in the predictions behind the scenes to produce outcomes. Without knowing what a machine learning model is specifically focusing on when predicting patterns, it can be challenging to use the model to our advantage and for the future of more patients. To address this issue, model interpretability is an active area of research that tries to build methods to understand where a certain model is focusing. For example, to predict cancer outcomes in a patient, heatmaps are used on an MRI scan to see where the ML model placed emphasis.

Applications of ML Models on Epilepsy

Artificial Intelligence has revolutionized machine learning models in today's society through the extraction of large data and the optimization and automation of many processes. There has been recent interest towards precision medicine that can provide accurate diagnosis for seizure disorders such as epilepsy. An inclination towards computational studies, which include artificial intelligence-based studies and biophysical models is one of the approaches that is widely being applied to precision medicine and epilepsy. *[2]* Artificial Intelligence enables healthcare professionals to detect seizures more accurately, identify epileptic patterns in a patient, and analyze responses to medications, which leads to a better prognosis.

ML Models on Animals

Artificial Intelligence has been used to identify patterns in epileptic data which can be useful to distinguish between an epileptic patient and a nonepileptic patient. A team led by Stanford researchers conducted a study with mice that had acquired genetic epilepsies. Utilizing an unsupervised machine learning model, they successfully distinguished between epileptic and nonepileptic mice much better than human observers by examining for repeated behavioral patterns. Additionally, behavioral phenotypes for the development of epilepsy were also identified, improving our abilities to potentially recognize earlier stages of epilepsy. This study provides evidence that AI programs can be used in the future for anti-epileptic drug testing. *[1]* However, this model has only been tested in mice and still needs further validation in human and other large animal subjects.

ML Models for Automatic Seizure Prediction

Machine learning has consistently been used to improve the diagnosis of epilepsy in patients all over the world. The use of AI algorithms has been very useful for automatic seizure detection and prediction. For example, students Hisham Daoud and Magdy Bayoumi from the University of Louisiana developed a model based on CNN, RNN, and deep convolutional autoencoder to learn about spatial and temporal features from raw EEG data. *[14]* The artificial intelligence system they developed in 2022 consisted of different AI algorithms used to provide high-accuracy decisions and automate epilepsy diagnosis. Their model is different from older ones because they combined the feature extraction and classification processes into one single automated system. This was tested on 22 patients at the Boston Children's Hospital and proved to be 99.6% accurate, with the ability to detect epileptic seizures an hour before they actually started. More specifically, the system had a low tendency for false positives with only 0.004 false alarms per hour. However, one of the limitations is that this machine learning model requires large amounts of training data which is difficult to acquire from patient-specific models as a lot of seizures need to be identified from the individual patient because each patient's seizure has a unique pattern. Additionally, even though this model effectively analyzes the data, it doesn't address the inherent limitations of the EEG device itself. The EEG is not convenient for patients to use in terms of scalability because they would be required to wear it for a substantial amount of time in order to notify patients and healthcare providers of future seizures. More research should be done in the future to develop a device that can be more convenient and wearable for the patient during testing.

AI Algorithm for Brain Abnormalities Identification

In 2022, researchers at the University of London created an artificial intelligence algorithm that could be used to identify brain abnormalities relating to epilepsy. The specific brain abnormalities that are identified are called focal cortical dysplasias (FCDs). The identification of these abnormalities is particularly useful for physicians to understand the root cause of certain patients with epilepsy and help with treatment management and planning. The algorithm was developed by quantifying the features of the brain cortex from about 1000 MRI patient scans found in epilepsy centers all over the world. Research assistant Mathilde Ripart at University College London's Great Ormond Street Institute of Child Health states that their algorithm was "interpretable and could help doctors make decisions", as it was able to detect FCDs in 67% of the cases in the cohort. *[19]* Such algorithms will allow physicians to better detect epileptic lesions allowing for better surgical planning in drug-refractory cases. Additionally, in such models, the burden of a false positive is much lower as this technology would assist in screening patients with FCD, however, a patient would only undergo surgical resection of the AI-identified potential epileptic lesion if the clinical presentation necessitates surgery.

New AI Program for Early Epilepsy Diagnosis

Artificial Intelligence has the potential to significantly improve epilepsy prognosis in patients. Machine learning algorithms can analyze large amounts of data and have pattern recognition which enables them to predict seizure frequency and severity. Prediction models based on machine learning algorithms and statistics can integrate multiple clinical or non-clinical parameters to calculate the probability of disease prognosis to help the patient in the future. *[24]* A study presented by researchers at a conference in Breckenridge indicates that a certain AI program that was developed could diagnose genetic forms of epilepsy in children 3.6 years earlier than clinicians were able to diagnose the same patients. *[12]* By having the ability to predict epilepsy ahead of time, these AI algorithms can provide promising hope for the future, especially when certain machine learning models can also predict patients who will be seizure-free after ablative surgery with 85 to 90% accuracy. Prognosis of a patient is essential for doctors to understand the long-term impact of epilepsy so that they can come up with better responses to treatment to improve the quality of life for patients. Machine learning algorithms are revolutionizing this aspect of the healthcare field giving both patients and their doctors a better understanding of their disease.

Segmentation
Segmentation is a process that is used to divide an image into multiple segments and regions during image process applications. Segmentation tasks create a mask of a target region on a brain image that is outputted by a supervised deep-learning model. Specifically, the deep learning approach of segmentation is being applied to epilepsy-specific regions. Hippocampus segmentation plays a key role in identifying abnormalities in the hippocampus region because it can act as biomarkers for epileptic regions. This is necessary to locate epileptogenic foci. An example is that there was a segmentation mask of the hippocampus obtained by a CNN model for a dataset of 132 patients with epilepsy. The dice coefficient was 77%, meaning that there is high similarity between the prediction segment and the ground truth. *[25]* This indicates that hippocampus segmentation techniques are important to indicate epileptogenic foci. However, other reports have shown that hippocampus segmentation is not currently accurate enough to assist with epilepsy treatment and further understanding of the hippocampal anatomy and functional networks is needed before utilization of AI algorithms for hippocampal segmentation.

There are many applications of artificial intelligence on epilepsy that are currently revolutionizing the world. Machine learning algorithms are able to analyze patterns in data and detect features such as abnormalities that correspond with epilepsy. Many algorithms have been developed by scientists to improve the prognosis of this disease. However, there are still drawbacks in AI that we are actively trying to tackle. Certain machine learning models require further validation on human subjects in addition to requiring large training data sets to effectively come up with predictions. Moreover, interpretability is another issue as we need to find better ways to understand how machine learning is processing information.

Conclusion
Currently targeting 50 million people globally, epilepsy is one of the most prevalent neurological disorders today and people living with it face many challenges due to recurrent seizures. About ⅓ of patients experience drug-resistant epilepsy, leading to difficulties when anti-seizure medications are unable to effectively control abnormal brain activity, often necessitating surgical treatment. Neuroimaging tools have been increasingly beneficial to surgical treatment in the healthcare field and over the last decade, the emergence of machine learning in artificial intelligence has improved patient care in various diseases, not just epilepsy specific. Machine learning models have the capability to interpret various amounts of data and identify patterns that can help doctors predict prognosis of diseases and come up with effective treatment plans for patients in the future. Specifically, artificial intelligence plays a major role in treating patients with epilepsy because ML models are able to conduct seizure prediction, identify FCD abnormalities, FCD prediction, and more. In addition, these models are able to generate masks that indicate certain aberrant regions for lesion localization- the process of locating abnormalities and lesions in the human body. Despite the limitations, artificial intelligence poses

a bright hope for the future by revolutionizing healthcare and potentially improving the lives of millions living with epilepsy today.

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