Machine Learning Applications on Neuroimaging for Diagnosis and Prognosis of Epilepsy: A Review

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Abstract

Machine learning is playing an increasingly important role in medical image analysis, spawning new advances in the clinical application of neuroimaging. There have been some reviews on machine learning and epilepsy before, and they mainly focused on electrophysiological signals such as electroencephalography (EEG) and stereo electroencephalography (SEEG), while neglecting the potential of neuroimaging in epilepsy research. Neuroimaging has its important advantages in confirming the range of the epileptic region, which is essential in presurgical evaluation and assessment after surgery. However, it is difficult for EEG to locate the accurate epilepsy lesion region in the brain. In this review, we emphasize the interaction between neuroimaging and machine learning in the context of epilepsy diagnosis and prognosis. We start with an overview of epilepsy and typical neuroimaging modalities used in epilepsy clinics, MRI, DWI, fMRI, and PET. Then, we elaborate two approaches in applying machine learning methods to neuroimaging data: i) the conventional machine learning approach combining manual feature engineering and classifiers, ii) the deep learning approach, such as the convolutional neural networks and autoencoders. Subsequently, the application of machine learning on epilepsy neuroimaging, such as segmentation, localization, and lateralization tasks, as well as tasks directly related to diagnosis and prognosis are looked into in detail. Finally, we discuss the current achievements, challenges, and potential future directions in this field, hoping to pave the way for computer-aided diagnosis and prognosis of epilepsy.

Highlights

• Machine learning plays an increasingly important role in epilepsy neuroimaging.
• We introduce conventional machine learning methods and deep learning methods.
• Segmentation, localization, lateralization, diagnosis and prognosis tasks are listed.
• We discuss achievements and directions in machine learning for epilepsy neuroimaging.
1 Introduction

Epilepsy is a neurological disease characterized by abnormal neurophysiological activity leading to epileptic seizures or abnormal behavior, accompanied by varying degrees of loss of sensation or consciousness. Unlike a single-source disease, epilepsy is usually associated with a set of chronic recurrent transient brain dysfunction syndromes [1]. People with intractable epilepsy usually suffer from severe health problems and may lose the ability to take care of themselves. In 2017, The global lifetime epilepsy incidence rate was 7.60‰, which caused a huge global disease burden [2]. Therefore, the diagnosis and prognosis of epilepsy are important research topics. At present, advances in machine learning and neuroimaging have brought fresh air to this long-lasting research field.

The pathophysiological cause of epileptic seizures is the abnormal discharge of neurons, manifested as high-amplitude bursts on the Electroencephalogram (EEG). To clarify the concept, here we regard seizure as a transient brain dysfunction caused by excessive synchronous firing of neurons, and the epileptogenic foci are the sites of the epileptic attacks. The detection and quantification of epileptogenic foci are essential for the diagnosis of epilepsy. Although about 70% of patients with epilepsy can obtain effective seizure control through anti-epileptic drugs [3], the remaining 30% of patients have failed seizure control, leading to drug-resistant epilepsy or intractable epilepsy. Intractable epilepsy has a high mortality rate and a poor prognosis, requiring surgical treatment [4]. Surgical treatment of epilepsy can be divided into two categories, palliative surgery, and radical surgery, according to whether the surgery is targeted the epileptic foci [4]. Palliative surgery (i.e. corpus callosotomy or neuromodulation) aims at the seizure-related neural circuits, rather than directly at the epileptogenic foci [5], while radical surgery (i.e. radiofrequency thermocoagulation, resection, and dissection) directly deals with epileptogenic foci [6]. All operations require precisely locating the epileptogenic foci, and neuroimaging modalities are the doctor’s main diagnostic tool. Neuroimaging has its important advantages in confirming the range and size of epileptogenic foci compared to the EEG, which means a lot in presurgical evaluation and assessment after surgery. Therefore, there is a great need for automated analysis of neuroimaging to help clinicians.

The clinical workflow of epilepsy diagnosis and presurgical evaluation is illustrated in Figure 1(a). Patients with suspected epilepsy are first screened by non-invasive techniques for diagnosis, and then those who are diagnosed with epilepsy are usually recommended to take anti-epileptic drugs. For patients with intractable epilepsy, clinicians have to conduct the further comprehensive evaluation, including locating the epileptogenic foci and judging whether they contain the eloquent cortex, which – if removed – will result in loss of sensory processing or linguistic ability, or paralysis. This routine evaluation procedure before surgical treatment is called presurgical evaluation [7][8]. Palliative
Figure 1: Epilepsy diagnosis workflow for clinicians and neuroimaging technicians. (a) Clinicians initially treat the semeiology-diagnosed epilepsy patients with medication. If the patient is drug-resistance, the clinician will make a presurgical evaluation and multimodal images will be collected. Then, the clinician decides the type of surgery, either radical surgery or palliative surgery, based on whether the epilepsy is focal or general. (b) Neuroimaging technicians analyze medical data to support clinicians. They extract features from raw data via feature engineering or directly train end-to-end models for segmentation or positioning. Their ultimate tasks are computer-aided diagnosis and prognosis.

surgery would be suggested for intractable epilepsy patients whose epileptogenic foci involve the eloquent cortex, while radical surgery is considered for those whose epileptogenic foci are not in the eloquent cortex. In the latter case, clinicians need to locate the epileptic source accurately in order to preserve the largest functional eloquent cortex [9]. Therefore, more advanced and even invasive screening techniques might be involved. On the one hand, epileptic seizures can be directly located by electrophysiological techniques, such as non-invasive electroencephalograph (EEG) and invasive electrocorticography (ECoG) [10]. On the other hand, brain lesions, presumably indirectly or directly leading to clinical seizures, can be detected by neuroimaging techniques, such as magnetic resonance image (MRI) [11] and positron emission tomography (PET) [12]. In general, when the epileptogenic foci are identifiable in neuroimaging, the chance of no seizures after radical surgery increases by about 2-3 times [13].

However, the clinical workflow is laborious. The outcome it finally achieved with all those medical data is sometimes full of uncertainty because of the eye fatigue of clinicians [14]. Due to the importance and difficulty of presurgical evaluation, technicians are often expected to help clinicians analyze various neuroimaging data in the epilepsy department. The workflow for neuroimaging technicians is shown in Figure 1(b). Their ultimate tasks are complementary diagnosis and computer-aided prognosis. Voxel-based morphometry (VBM) methods are the traditional computer-aided ways for technicians.
to analyze neuroimaging [15]. Voxel-wise statistical comparisons between normalized normal and 
abnormal brain images are always needed. However, VBM methods only capitalize on superficial 
information of brain images such as volume and thickness and sometimes cause misclassification 
between images due to improper registration. Advances in machine learning methods have made it 
possible to analyze images in depth.

Previous reviews mainly focused on the machine learning applied to electrophysiological data 
(such as EEG) for epilepsy [16] [17] [18], very few reviews have paid attention to epilepsy neuroimaging 
so far [19] [20]. In this review, other than electrophysiology, we emphasize the role of neuroimaging 
in epilepsy and the application of machine learning to epilepsy neuroimaging. We will introduce 
the neuroimaging techniques and machine learning models used in epilepsy study, to highlight the 
potentials of the machine learning applications in computer-aided diagnosis and prognosis.

We searched Pubmed, Scopus, and Google scholar for papers with the keywords ‘machine learning’, 
‘deep learning’, ‘epilepsy’, ‘CT’, ‘MRI’, ‘SPECT’ and ‘PET’ in the title or abstract. We surveyed 
more than 120 papers and checked the citations of them. We then excluded articles that used epilepsy 
datasets for super-resolution or other non-clinical related tasks, or those that were ancient. The latest 
update to the included papers is on February 11, 2021.

The rest of this review is structured as follows. We first present the neuroimaging modalities 
commonly used in epilepsy (Section 2). Then we briefly introduce the methodological background, 
including the conventional machine learning approaches and deep learning approaches (Section 3). 
We then present various machine learning tasks for epilepsy and review previous studies on each 
task (Section 4). Finally, we discuss the achievements and challenges in the field to call for more 
attention on the machine learning on neuroimaging for epilepsy (Section 5).
2 Neuroimaging tools for epilepsy

The development of medical imaging technology, especially neuroimaging, opens a window for studying the brain through imaging the structure and examining the functional dynamics. The widely-used image modalities are listed in Figure 2. Various non-invasive neuroimaging techniques can be used to monitor brain structure and function, including T1-weighted MRI (T1w MRI), T2-weighted MRI (T2w MRI), diffusion tensor imaging (DTI), functional MRI (fMRI), and PET.

A typical MRI system consists of the following hardware and software components: a magnet, a gradient coil, a radiofrequency transmitting coil, a radiofrequency receiving coil, and signal processing and image reconstruction algorithms. The nuclear spin of a hydrogen atom in human body can be equivalent to a small magnetic dipole. In a strong magnetic field, the radiofrequency transmitting coil flips the hydrogen nuclei from the direction of the main field to the transverse plane, and their differences form a net magnetization vector. The hydrogen nuclei precess around the main magnetic field. The gradient coil generates magnetic fields whose strength varies with spatial position, and these magnetic fields are used for spatial coding of the signals. The induced current signal is received by the radiofrequency receiving coil and recorded, and eventually the image can be reconstructed by signal processing and image reconstruction algorithms. Fine-tuning the parameters (e.g. the flip angle or the pulse interval) lead to a variety of MRI sequences, such as T1w, T2w, and T2w-FLAIR MRI.
and each sequence highlights different tissues of the brain, such as gray matter or white matter [21]. Specifically, T1w MRI maps the anatomical structure of the brain; T2w MRI captures the aberrant zone in the white matter; T2w-FLAIR MRI provides high contrasts between the gray matter and cerebrospinal fluid (CSF). These neuroimages can aid the detection of patients with focal cortical dysplasia (FCD) [22]. For example, it has been reported that the combination of conventional visual examination and morphometric MRI analysis has significantly high diagnostic sensitivity in both subgroups of FCD (94% for FCD IIa; 99% for FCD IIb) [23].

Unlike the traditional structural MRI, diffusion imaging leverages the extent, directionality, and organization of the motion of free water to provide image contrast [24]. Diffusion-weighted imaging (DWI) detects water molecules diffusion through the transverse magnetization direction, resulting in a phase shift caused by signal attenuation. As an improvement of DWI, DTI reflects the direction of white matter fiber bundles. Diffusion kurtosis imaging (DKI) depicts the molecular weight of water that diffuses out of the Gaussian distribution in the tissue. The Kurtosis information reflects the non-Gaussian characteristics caused by the complex structure of multiple microcellular compartments [25]. Fractional anisotropy (FA) and mean diffusion (MD) maps are commonly used parameter maps derived from DTI and DKI, while the mean kurtosis (MK) map is merely obtained from DKI. In particular, FA measures the degree of directionality, while MD measures the average diffusion along all diffusion directions. MK describes a more complex spatial distribution, that is, the average of the diffusion kurtosis along all diffusion directions. They are important imaging biomarkers for the detection of heterogeneous samples [26].

The brain imaging technique has been extended from structure to function, and some imaging systems based on brain function have been designed, including functional MRI (fMRI) [27] and PET [28]. Magnetic resonance imaging is used to detect the changes in cerebral blood flow and metabolism caused by the neural activity because of the paramagnetism of blood. Thus fMRI can reflect the activities of the brain tissues. PET utilizes radiotracers to observe the local uptake-related variation, which could reflect the abnormal metabolism in brain. For instance, as a complement, PET can locate the regional interictal hypometabolism, guide neuroradiologists to look for lesions [29].

Although EEG directly reflects the abnormal neural activities in epilepsy and thus more appealing for epilepsy detection, the potential of neuroimaging is largely underestimated in epilepsy applications. In this review, we will mainly focus on neuroimaging in epilepsy-related machine learning tasks.

3 Machine learning methods applied in epilepsy

Machine learning, as a data-geared method, builds a myriad of mathematical models that can learn from the structured training data to make predictions or decisions in novel contexts and the newly-
presented data, without being explicitly programmed to perform that task [30]. A wide range of machine learning models have been applied to neuroimaging to aid the diagnosis and prognosis of epilepsy [31, 32, 33, 34, 35, 36]. As the use of machine learning in epilepsy grows, it is necessary to review and summarize methods, tasks, scientific findings, and their interpretations. Here, we categorize the machine learning methods into two classes in the context of neuroimaging applications: i) the conventional machine learning approach and ii) the deep learning approach. The conventional machine learning approach mostly performs hand-craft feature engineering, following a classification or a regression task. The deep learning approach applies deep neural networks to a specific task or to extract features automatically.

There are various open-source tools for machine learning and especially for processing neuroimaging of epilepsy. Firstly, Matlab, Scikit-learn, Keras, TensorFlow, PyTorch, Caffe, and Theano are some well-known toolkits to implement machine learning models. Secondly, the codes for neuroimaging processing related to epilepsy are available on the Github.

![Feature Engineering and Machine Learning Diagram]

Figure 3: The conventional machine learning approach. It consists of a feature engineering step to extract and select features from single/multiple neuroimaging modalities, and a machine learning step to perform a classification or regression task.

1. Epileptic lesion detection: [https://github.com/MELDProject/MELDProject.github.io](https://github.com/MELDProject/MELDProject.github.io)
2. Focal cortical dysplasia detection: [https://github.com/kwagstyl/FCDdetection/](https://github.com/kwagstyl/FCDdetection/)
3. Rs-fMRI alignment to cortical stimulation: [https://github.com/jarodroland/Peds_rfMRI_vs_ECS](https://github.com/jarodroland/Peds_rfMRI_vs_ECS)
4. Hippocampus segmentation on epilepsy: [https://github.com/MICLab-Unicamp/e2dhipseg](https://github.com/MICLab-Unicamp/e2dhipseg)
Table 1: Representative hand-crafted features used in epilepsy

| Modality     | Features                                                                 | Ref  |
|--------------|--------------------------------------------------------------------------|------|
| T1w MRI      | Mean, standard deviation, variance, energy, and entropy of segmented hippocampus | [38] |
|              | Cortical thickness, intensity at the grey-white matter contrast, curvature, sulcal depth, intrinsic curvature | [39] |
| T2w-MRI      | Volume and intensity sampled on the medial sheet of hippocampus           | [40] |
|              | First-order statistical and volumetric gray-level co-occurrence matrix texture features | [41] |
| FLAIR-MRI    | Intensity sampled at 25%, 50% and 75% of the cortical thickness and at the grey-white matter boundary | [39] |
|              | Image intensity features and wavelet-based texture features               | [42] |
| DTI          | Mean diffusion and Fractional Anisotropy                                 | [43] |
| DKI          | Mean Kurtosis                                                            | [44] |
|              | MD, FA, MK and the fusion of FA and MK                                    |      |
| fMRI         | Fractional amplitude of low-frequency fluctuation (fALFF)                | [31] |
| PET          | Hemisphere symmetry tensor                                               | [46] |

Abbrev: MD, Mean diffusion; FA, Fractional Anisotropy; MK, Mean Kurtosis; BOLD, blood oxygenation level-dependent.

3.1 Conventional machine learning approach

The conventional machine learning approach consists of two steps, a manually feature engineering step and a machine learning step (Figure 3). The feature engineering step extracts the hand-crafted features from brain images. The machine learning step then inputs those features to a machine learning model for a certain task, such as classification (to detect the impaired or normal brain) or regression (to predict the severity of epilepsy). The machine learning model applied in this approach is usually a simple classifier, rather than the deep neural network.

3.1.1 Feature engineering

Feature engineering is a necessary step in the conventional machine learning models. Extracting the distinctive features from the medical images can effectively reduce the data dimension and prevent a model from overfitting. In Table 1 we list some representative features extracted from each neuroimaging modality relevant to epilepsy.

The extracted features are usually with large redundancy as we would like to maintain as much information as possible in the original medical images. Thus, feature selection for removing the invalid features and distilling the relevant features is our next step. The dimension reduction techniques, such as Principal components analysis (PCA), have been widely used to transfer data from the original high-dimensional space into a low-dimensional space with minimal information loss by selecting the most distinguishable features or create new features. PCA aims at mapping the high-dimensional features to a low-dimensional space through linear projections via maximizing the variance of the matrix data on the projected dimension. It works best when the variance distribution in different
dimensions of the data set is uneven. The principal components of the feature matrix are obtained by sorting the eigenvectors of its covariance matrix according to the value of the corresponding eigenvalues. In this way, a lower-dimensional representation (i.e. the principal components) of features contains the intrinsic characteristics of the original dataset.

After feature engineering, the selected features will be input into the machine learning models for real-world tasks. To be noted, the performance of conventional machine learning models, such as linear discrimination analysis and support vector machine, relies heavily on the extracted features.

3.1.2 Linear discrimination analysis

Linear discrimination analysis (LDA, also called Fisher linear discrimination analysis) is a classic supervised method in machine learning problems such as data dimensionality reduction, feature extraction, and pattern recognition. LDA was first described in a two-class problem by Ronald A. Fisher [48], and later generalized as multi-class linear discriminant analysis. Different from the variance maximization theory of PCA, the main idea of LDA is to project the data from a high-dimensional space onto a lower-dimensional space so that the same classes are clustered together while the different classes are far apart. Firstly, the mean of class \(i\) is given by:

\[
u_i = \frac{1}{n_i} \sum_{x \in \text{class } i} x
\]

The overall sample mean is given by:

\[
u = \frac{1}{m} \sum_{i=1}^{m} x_i
\]

According to the definition of the between-class scatter matrix \(S_b\) and the within-class scatter matrix \(S_w\), the following formula can be obtained:

\[
S_b = \sum_{i=1}^{c} n_i (u_i - u)(u_i - u)^T
\]

\[
S_w = \sum_{i=1}^{c} \sum_{x_k \in \text{class } i} (u_i - x_k)(u_i - x_k)^T
\]

By maximizing the following objective functions, the within-class distance is minimized and the between-class distance is maximized:

\[
J_{\text{fisher}}(w) = \frac{w^T S_b w}{w^T S_w w} = \frac{\sum_{i=1}^{c} n_i w^T (u_i - u)(u_i - u)^T w}{\sum_{i=1}^{c} \sum_{x_k \in \text{class } i} w^T (u_i - x_k)(u_i - x_k)^T w}
\]

where the optimal transformation \(w\) would maximize the objective function.
LDA is a pre-processing step in Machine Learning and pattern classification applications. The variants of LDA include quadratic discriminant analysis (QDA) \[49\], flexible discriminant analysis (FDA) \[50\], and regularized discriminant analysis (RDA) \[51\].

3.1.3 Random forest

Random Forest (RF) is a combination of decision trees. Each tree depends on the value of an independently sampled random vector and has the same distribution for all trees in the forest \[52\]. RF creates Bagging ensemble \[53\] based on decision tree learner, and further introduces random features selection in the training process of decision tree. Specifically, the traditional decision tree selects an optimal one from the feature set of the current nodes when selecting features. However, for RF, a subset containing \(k\) features is randomly selected from the feature set of the nodes in the decision tree, and then an optimal feature is selected from this subset for division.

3.1.4 Support vector machines

Initial SVM aims to find a hyperplane in \(N\)-dimensional space to separate the samples from two classes, where \(N\) is the number of features \[54\]. It was originally designed for two-class classification but was later extended to multi-class classification. Besides, support vector regression (SVR) \[55\] is known for solving regression problems.

The SVM problem for the training data set of \(m\) points \(\{x_i, y_i\}_{i=1}^m\) is given by:

\[
\begin{align*}
\min & \frac{1}{2} \|w\|^2 + C \sum_{i=1}^m (\xi_i + \xi_i^*) \\
\text{s.t.} & \quad y_i - (w^T x_i + b) \leq \varepsilon + \xi_i \\
& \quad (w^T x_i + b) - y_i \leq \varepsilon + \xi_i^* \\
& \quad \xi_i, \xi_i^* \geq 0
\end{align*}
\]

where \(w\) and \(b\) are the learning parameters corresponding to the weight vector and the bias. They determine a hyperplane, \(f(x_i) = w^T x_i + b\), which can separate two classes. \(C\) as the regularization parameter and \(\varepsilon\) is a margin of tolerance. These hyperparameters have to be pre-defined in order to solving the optimization problem. \(\xi_i\) and \(\xi_i^*\) are the slack variables \[55\].

The kernel function of SVM is to take data as input and transform it into the required form and define it as follows:

\[
K(\overline{x}) = \begin{cases} 
1, & \text{if } \|\overline{x}\| \leq 1 \\
0, & \text{otherwise}
\end{cases}
\]

where the value of this function is 1 inside the closed ball of radius 1 centered at the origin, and 0 otherwise.

A variety of kernel functions have been proposed for SVMs. Gaussian kernel is a general-purpose kernel. It is usually used when no prior knowledge about the data is known. The equation of Gaussian
The Gaussian radial basis function (RBF) is defined as:

\[ k(x_i, x_j) = \exp\left(-\gamma \|x_i - x_j\|^2\right) \]  

(9)

where \( \gamma > 0 \). The polynomial kernel is defined as follow:

\[ k(x_i, x_j) = (x_i \cdot x_j + 1)^d \]  

(10)

where \( d \) is the degree of the polynomial kernel. The polynomial kernel is popular in image processing.

Many extensions and variants of SVMs have been proposed for the versatility of SVMs, such as, one-class SVM (OC-SVM) \[56\], least square SVM (LS-SVM) \[57, 58, 59\], fuzzy SVM \[60, 61, 62\], weighted SVM \[63\], transductive SVM \[64\], and twin SVM \[65\]. They significantly facilitate the classification of neuroimaging.

3.1.5 Shallow neural networks

Neural network refers to the machine learning model with a layered network architecture which is composed of many artificial neurons in each layer. The artificial neurons are connected between layers, and the connection strength is the learning parameter (i.e. weight). A large number of studies have reported that neural networks can achieve superior performance in complex medical tasks \[66\]. The shallow neural network has formed the groundwork for the deep neural network (DNN) \[67\], which can be trained rapidly and flexibly with error backpropagation on large data sets \[68\].

Shallow neural networks usually use a fully-connected architecture, which consists of neurons, weights, and bias. Neurons have three types: input unit, hidden unit, and output unit. When the input vector is fed into the network as an input unit, it will propagate through the network to the output unit, and it represents the probability of a particular category. Additionally, the expression of each neuron in hidden units is as follows:

\[ y = \sigma \left( \sum_{i=1}^{n} w_i x_i - b \right) . \]  

(11)

where \( w_1, ..., w_n \) are the weights and \( b \) is the bias. Also, \( \sigma(\cdot) \) is the activation function that provides a non-linear element, enabling the shallow neural network suffices to approximate any well-behaved functions like bounded continuous functions \[69\].

The choice of loss function depends on the specific task, for example, the cross-entropy loss for classification tasks, and the root mean squared error (RMSE) loss for regression tasks. Sometimes
regularization terms are added into the loss function to represent our prior knowledge. For instance, the L1 norm ensures sparsity and L2 norm for smoothness. The design of loss function is still an ongoing research topic in machine learning field.

After the network structure and the loss function are designed, parameters of neural networks, such as weights and bias, can be learned by error backpropagation [68].

### 3.2 Deep learning approach

The deep learning approach trains a learning system with multiple functional layers [70] like the deep neural network with complex nonlinear mapping. Comparing to the conventional machine learning approach, the merit of the deep learning model is that the raw data can be directly input into the model without the need for complicated preprocessing operations on the neuroimaging. Notwithstanding the convenience of the end-to-end models, they have some limitations such as the demand for giant data size and the weak interpretability [71].

Deep learning models for diagnosis and prognosis of epilepsy include the supervised learning models and the unsupervised learning models (Figure 4). Supervised learning models require labels (such as disease or health, the degree of severity, the types of epilepsy). They can be trained to reveal a relationship between the features of data and the label, hoping to be generalized to the newly generated data without its label [72]. Unsupervised learning models do not require labels and can capture the patterns of probability densities or neuronal predilections by the intrinsic characteristics of features [73].

![Figure 4: The deep learning approach. Examples of a supervised learning model (a) and an unsupervised learning model (b) used for neuroimaging analysis.](image-url)
3.2.1 Convolutional neural networks

Convolutional neural network (CNN) \cite{lecun1995convolutional,krizhevsky2012imagenet} is the most popular machine learning method nowadays and has been widely used in image processing. The powerful ability of CNN to extract complex hidden features from high-dimensional data with deep convolutional structure enables it to be used as a feature extractor in medical image classification \cite{huang20173d} and segmentation \cite{ronneberger2015u,ronneberger2015u+}. CNN usually consists of a series of layers with each layer following a differentiable activation function. A variety of activation functions have been proposed, such as sigmoid, tanh, softmax, Rectified Linear Unit (ReLU) \cite{glorot2010understanding,krizhevsky2012imagenet}, leaky ReLU \cite{maas2013rectifier}, etc. Figure 4(a) illustrates a typical CNN architecture with three types of neural layers: convolutional layer, pooling layer, and fully-connected layer. The convolutional layers are interspersed with pooling layers and ended with the fully connected layers. The convolutional layer takes a small patch of the input images (i.e. $3 \times 3 \times 3$ for three-dimension image), called the local receptive field, and then utilizes various learnable kernels to convolve the receptive field to generate multiple feature maps. A pooling layer performs the non-linear downsampling to reduce the input volume’s spatial dimensions for the next convolutional layer and to adapt the larger size features. The fully-connected layer pools the 2D feature maps into a 1D feature vector. The local response normalization is a non-trainable layer and performs “lateral inhibition” by normalizing over the local input regions.

In practice, one of the main problems in training deep models is the over-fitting, which is caused by the gap between a limited number of training samples and a large number of learnable parameters. Overfitting during training would reduce the performance on the test dataset. Therefore, many approaches focused on avoiding overfitting such as dropout and batch normalization. Dropout is a typical deep learning technique, referring to randomly dropping a fraction of the units or connections during each training iteration. It has been proven that dropout can considerably avoid over-fitting \cite{hinton2012improving}. Batch normalization is performed as an additional regularization through the running average of the mean variance statistics in each mini-batch. Batch normalization can drastically accelerate the convergence speed of training and improve the generalization performance \cite{ioffe2015batch}.

Epilepsy diagnosis and prognosis based on the CNN framework is currently an emerging and active research field \cite{benedetti2017deep}. More details will be presented in the Section 4.

3.2.2 Autoencoders

Auto-encoder (AE) is a typical unsupervised learning method, consisting of an encoder and a decoder (see Figure 4(b)). AEs learn the latent representation of input data and then reconstruct the input data into output. AE involves multiple hidden layers which are stacked to form a deep network, which called deep auto-encoder (DAE). Compared with the shallow networks, DAEs are capable of
discovering more complex patterns inherent in the input data due to the deep layers. So far, a number of AE variations have been proposed, such as denoising auto-encoder (denoising AE) [84], sparse auto-encoder (sparse AE) [85], variational auto-encoder (VAE) [86, 87], adversarial auto-encoder (AAE) [88], and stacked sparse auto-encoder (SSAE) [89]. These extensions of AE have the potential to learn useful latent representations from neuroimaging data and improve the robustness of medical image reconstruction, which could serve better applications for epilepsy diagnosis. For example, stacked convolutional autoencoder could be used to learn the representation of brain images [33].

3.2.3 Hybrid models

More recently, the hybrid approach combining conventional machine learning and deep learning has been brought into the epilepsy study [33, 46]. This architecture has high flexibility to improve the performance.

The hybrid approach starts with extracting the hidden features as latent representations through unsupervised model instead of the hand-crafted features, and then employs machine learning algorithms for classification. For instance, convolutional autoencoders were stacked to form the siamese network to learn the representations of each patch at the same space in healthy brain MRIs. In the testing stage, the representations can further distinguish the normal patches and the abnormal patches with FCD lesions [33]. Besides the unsupervised end-to-end model, supervised deep neural networks are also capable of hidden feature extraction. As an example, Jiang et al. integrated four sets of features that were extracted from four classic deep neural networks (ResNet - 50, VGGNet - 16, Inception - V3, SVGG - C3D) and classified the epileptic and the normal through these fused features by a fully-connected layer [46].

4 Machine learning tasks

Machine learning model learns the internal representation of multiple dimensions of numerical features through classification or regression. Then the new-come instance will be identified by its representation. Researchers have exploited multiple machine learning applications based on different objectives. Specifically, some focused on segmentation, localization, and lateralization which belong to the neuroimaging processing tasks (See section 4.1). Some focused on the computer-aided diagnosis tasks (See section 4.2). Finally, others emphasized the computer-aided prognosis tasks (See section 4.3).

Different tasks have different evaluation criteria for the quality of the model used. Generally, the most basic evaluation criterion in machine learning tasks is accuracy (ACC), that is, the proportion of correctly classified samples to the total number of samples. In medical application, sensitivity
and specificity are other common criterion. Sensitivity refers to the proportion of patients whose lesions are accurately detected in all patients. Specificity is the proportion of control instances that are not classified into the patients among the controls. High sensitivity is equivalent to low missed diagnosis rate while specificity is equivalent to low misdiagnosis rate. Ideally, we want both sensitivity and specificity to be high, but in fact we find a balance between sensitivity and specificity. This process can be represented by the receiver operating characteristic (ROC) curve. The abscissa value of the curve is 1-specificity, and the ordinate value is sensitivity. After the curve is drawn, the area under ROC curve (AUC) can be calculated, which refers to the probability that the model ranks a random positive instance more highly than a random negative instance. The larger the value of AUC, the better the performance of the model. Besides, Dice coefficient (i.e. Dice similarity coefficient), as a measure of the similarity between two sets of data, is the most broadly used assessment to evaluate the performance of segmentation algorithms. The higher the dice coefficient is, the better the performance is.

Figure 5: An example of U-net for brain tissues segmentation. This framework is adapted from an open-source project [90].

4.1 Brain image processing

Neuroimaging processing tasks are for certain brain areas including tissues that are in the fixed areas of all brains and abnormalities that are different from the ones in normal brains. They sometimes output the masks. Among the methods, U-net [91], named for its network shape, is a commonly used tool for neuroimaging processing. It specifically generates masks in segmentation and localization tasks for epilepsy applications [78] [92]. Additionally, the structure of U-net is shown in (Figure 5) [90]. U-net consists of an encoder to learn the representation of the image and a decoder to reconstruct
the mask corresponding to original image. The encoder and decoder can be any deep neural network backbones, which enables U-net to adjust the structure according to the application.

4.1.1 Segmentation

The segmentation task generates a mask of the target region (i.e. the region of interests) on a given brain image. This mask is usually output by a supervised deep learning model. So the model requires a prior label mask. In the training stage, the annotation of the mask requires cumbersome label work by clinical experts.

The deep learning approach has been applied to epilepsy-specific regions. Onofrey et al. applied a registration method based on dictionary learning to segment the post-surgical brain surface from the fusion of CT and MRI data. Specifically, preoperative MRI was used to guide the surgical resection of epileptic tissue, and SEEG records use postoperative CT images as the standard for epileptic areas. The dice coefficient between the segmented result and the standard was 94% [93].

Also, segmentation of certain functional regions, especially the hippocampus, is of special interests in epilepsy. The abnormalities in volume and shape of hippocampus have been reported as biomarkers for diagnosis of epilepsy [94]. There was an end-to-end model trained on the epilepsy dataset to segment the hippocampus. Carmo et al. designed a CNN model based on the U-net architecture to obtain the segmentation mask of hippocampus, with the dice coefficient being 77%. A native database HCUnicamp was used in their study, which was collected by personnel from the Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), containing 132 patients with epilepsy [78].

4.1.2 Lesion Localization

Applying to the localization tasks, machine learning models generate a mask to indicate the aberrant region. Some of the representative work are listed in Table 2. Among various localization tasks, the localization of cortical lesions is one of the most important tasks. Precise localization of the pathological lesion will greatly inform neurosurgeons; in particular, intractable epilepsy is usually associated with brain lesion. Benefiting from advances in the field of computer vision, various deep learning methods have been proposed and effectively applied to the task of localizing epileptogenic lesions.

The field of FCD localization has aroused special interest of researchers due to its high incidence and misdiagnosis rate. The subtle lesions could be manifested on MRI as thickened cortex, blurred gray matter-white matter interface, etc [95]. However, some FCD lesions may be seen as normal by clinicians on structural MRI when the histology is confirmed to be positive. Studies on this task usually use sensitivity and specificity as evaluation indicators and they would define the overlap.
standard between the localization outcome and ground truth.

Conventional machine learning methods have been widely used in this field. The earliest compositional method selected six feature maps to locate the clusters of candidate lesion voxels based on the one-class SVM via ranking T1w MRI voxels by size and suspicion degree [96]. This method unbiasedly detects FCD lesions in two patients [96]. A follow-up study by the same team captured more distinguishing features and reached general results to locate the FCD lesions. In three MRI-positive cases, the detection rate was 100%, while in 10 MRI-negative cases, the detection rate was 70% [97]. Further, the tree-structured hierarchical conditional random field was utilized to identify the abnormally segmented cortical surface regions patch-wise by thresholding the posterior probabilities, and it located the FCD region of MRI-positive instances with 90% accuracy and MRI-negative instances with 80% accuracy [98]. The accuracy of MRI-negative cases was the highest in the FCD localization field [98].

Three studies chose the shallow neural network as the classifier in conventional machine learning method [22, 99, 39]. With regard to feature extraction, FreeSurfer (a brain image processing software) is a commonly adopted feature extracted tool [5] for the conventional models. Adler et al. added a novel feature (local cortical deformation) to the FreeSurfer’s features, which was designed for the developing cortex of children. Sensitivity improved from 53% to 73% with the novel features [22]. Jin et al. combined the surface-based morphometry feature sets extracted by FreeSurfer from T1w, T2w, and FLAIR MRI, effectively localizing the FCD with 73.7% sensitivity and 90% specificity [99]. Additionally, the morphological and intensity features could be extracted to locate the FCD regions with up to 73.5% sensitivity and 100% specificity by wagsty et al. [39].

More recently, deep learning models were performed in the field of FCD localization. Gill et al. leveraged MRI vertex and voxel respectively to locate the FCD region by decision tree (DT) and CNN [100, 101], among which CNN outperformed compositional method with 91% sensitivity and 95% specificity. Furthermore, the customized U-Net was used to locate the FCD lesions using only FLAIR MRI in 2019 with 82.5% accuracy [92].

Besides the structural MRI, diffusion images can identify the white matter tracks involved in epileptic abnormality. Xu et al. designed a CNN with a combined focal and central loss and a soft attention scheme, and applied it to DWI streamline data, achieving a clinically acceptable accuracy of 73%-100% to detect the white matter pathway connected to eloquent areas [102]. A following-up study from the same group applied the CNN method to the DWI to locate the pediatric eloquent cortex [103]. In addition, MD map and the fusion of FA and MK maps extracted from DKI were segmented into hippocampus masks to perform abnormal identification of certain brain regions. This work

[http://surfer.nmr.mgh.harvard.edu/](http://surfer.nmr.mgh.harvard.edu/)
can indirectly locate anomalies in the hippocampus. They classified the patients with hippocampus epilepsy and the healthy subjects through a deep CNN to locate the abnormal hippocampus with the accuracy of 90.8% [44].

FMRI during a task or at resting state can pinpoint the abnormal regions involved in a functional network, such as the language network. Torlay applied the Extreme Gradient Boosting algorithm (XGBoost) on fMRI data to identify the atypical patterns of language networks on a phonological and semantic language task in patients with focal epilepsy [45]. Besides, using MLP to assign the resting state network to every voxel on the resting-state fMRI (rs-fMRI) has been reported to locate the eloquent function like sensorimotor cortex [104], which is essential in the presurgical evaluation.

4.1.3 Lateralization

Lateralization is an important task that involves two different purposes: 1) to identify the hemisphere where the epileptogenicity is located, 2) is to identify the dominant hemisphere of the eloquent cortex, such as language regions. The former is helpful for lesion localization and epilepsy diagnosis. For example, the hippocampal atrophy usually lateralizes toward the focus in drug-resistant temporal lobe epilepsy (TLE). The latter is essential for the surgical evaluation because the eloquent cortex must be maintained during the treatment. Some results are listed in Table 3.

The structural images have been widely used in lateralization tasks. For instance, Kim et al. manipulated LDA to classify the left- or right-sided seizure focus with manually extracted features after the segmentation of hippocampus in MRI [40]. Similarly, the LDA classifier can be replaced by SVM or DNN classifier for higher accuracy [106, 34]. SVM based on the graph theory network characteristics of the DTI structural connectomes has been used to classify the right TLE, the left TLE, and the control group [107]. Another study showed that even in visual MRI-negative TLE, it is possible to predict the laterality of epileptic seizures by training a RF classifier, which contains an ensemble of 5000 decision trees, using a set of 117 features from their structural brain images [108].

Besides the structural images, the functional images can also be utilized to lateralize the dominant hemisphere. Yang et al. extracted features from rs-fMRI within local brain regions, between brain regions, and across the whole network. Then the RF was used to reduce the dimension of data and SVM was employed to classify the laterality of TLE patients with 83% accuracy [109]. Gazit et al. suggested using the selected features in the verb-generation fMRI task, and then choosing the probabilistic logistic regression method to help lateralize the language regions of patients with epilepsy [110].
Table 2: Localization of abnormal brain regions or pathways

| Task                              | Inputs                                      | Model                                      | Performance                  | Data Size | Ref |
|-----------------------------------|---------------------------------------------|--------------------------------------------|------------------------------|-----------|-----|
| Locate FCD region                 | MRI vertex                                  | Intensity & RUSBoosted/AdaBoosted DTs     | Sensitivity: 83.0%          | 41\38    | 100 |
| Locate FCD region                 | MRI voxel                                   | CNN                                        | Sensitivity: 91.0%          | 107\38   | 101 |
| Locate FCD region                 | Two texture parameters on T1-weighted brain MRI | oc-svm                                    | MRI-positive ACC: 100.0%    | 11\77    | 97  |
| Locate FCD region                 | Cortical thickness, Gray/white-matter contrast, Sulcal depth, Curvature and Jacobian distortion | Restricted boltzmann machines + a bayesian non-parametric mixture model | MRI-positive ACC: 99.0%    | 24\50    | 105 |
| Locate FCD region                 | Morphological and intensity features        | ANN                                        | Sensitivity: 73.7%          | 15\35    | 99  |
| Locate FCD region                 | Morphological and intensity features        | ANN                                        | Sensitivity: 73.5%          | 34\38    | 39  |
| Locate the atypical patterns of language networks | Atypical language patterns from fMRI | XGBoost                                    | AUC: 91.5%                  | 16\39    | 45  |
| Locate the sensorimotor network    | rs-fMRI voxel                                | Multilayer perceptron                      | Mean dice coefficient: nearly 50.0% | 16        | 104 |
| Locate the functionally white matter pathway including eloquent areas | DWI streamline                              | CNN                                        | ACC: 73.0%-100.0%          | 70\70    | 102 |
| Locate the functionally white matter pathway including eloquent areas | DWI tract segmentation                      | CNN                                        | ACC: 98.0%                 | 89        | 103 |
| Locate hippocampus lesions        | DKI hippocampus segmentation                | CNN                                        | ACC: 90.8%                 | 59\70    | 104 |

* In \( N_p, N_c \), \( N_p \) is the number of the patients while \( N_c \) is the number of the controls.
Table 3: Tasks of the lateralization

| Tasks                        | Inputs                                                                 | Model            | Performance     | Data Size | Ref |
|------------------------------|------------------------------------------------------------------------|------------------|-----------------|-----------|-----|
| Lateralize epileptic foci    | Intensity-based vector MR features of hippocampal subfields            | LDA              | ACC: 93.0%      | 15        | [40] |
| Lateralize epileptic foci    | Shape features from the hippocampi of TLE                              | Ensemble of SVM, KNN, DT | ACC: 94.0%      | 40\15    | [34] |
| Lateralize epileptic foci    | Volume and intensity-based manual features                             | RF               | AUC of MRI-positive: 98.1% AUC of MRI-negative: 84.2%  | 104       | [108]|
| Lateralize language regions  | language lateralization index                                          | logistic regression | ACC: 89%        | 76        | [110]|

4.2 Epilepsy Diagnosis

Researchers characterize the potential epileptic subjects and reveal the essentiality of the features by machine learning models, which can guide the clinicians and improve the diagnostic evaluation workflow. On the one hand, these tasks were designed to save unnecessary time for well-trained doctors. On the other hand, algorithms with high sensitivity increase the chance of detecting potential 'invisible' regions that may be ignored by human experts. We listed some work relevant to epilepsy diagnosis in Table 4.

The good old-fashioned machine learning methods had been widely applied to classify the patients and the healthy controls [32, 31, 111, 43, 112, 113]. It may also identify the most contributory features corresponding to a specific disease in the process. Some studies relied on several manual features through their prior knowledge. For example, SVM was utilized to distinguish patients with tonic-clonic seizures from the normal cohort by using two hand-crafted MRI features (Gray matter volume from T1 and fALFF from fMRI). The fALFF feature got better performance with an accuracy of 83.72% [31]. Moreover, taking the DTI features (i.e., MD and FA) and the DKI feature (i.e., MK) into consideration, MK achieved the best accuracy (82%) among three features based on SVM classifier [43]. Similar conventional methods have also been applied on PET images. Features from the hemisphere symmetry tensor were extracted by multi-linear PCA, and then SVM were applied to classify the abnormal images and the normal ones [111]. Other studies used a large number of features of neuroimaging data that can be easily extracted by existing toolbox (FreeSurfer) in feature engineering. Usually, PCA was used to reduce the dimension of features, and then SVM can gain more discernible results with 88.90% accuracy [32].

Deep learning models have been brought into epilepsy diagnosis since 2018 [76]. The first
application of CNN for the recognition of epilepsy by Pominova [76] used the structural MRI and fMRI separately to classify the subjects with epilepsy. This work confirmed the feasibility of CNN in an end-to-end fashion which directly inputs the high dimensional neuroimaging data without feature engineering. Later, Yan et al. presented a 3D CNN on the raw MRI image data to predict the benign epilepsy with centrotemporal spikes and achieved 89.80% accuracy [114]. Jiang et al. fused the features extracted from 2D and 3D PET ROIs respectively by three natural images pretrained networks (ResNet - 50, VGGNet - 16, Inception - V3), and a pulmonary nodules CT pretrained network (SVGG - C3D). Then, a fully connected layer was applied as a binary classification [46]. Recently, deep learning method was applied to PET for the first time. Zhang et al. developed a Siamese CNN which is able to track the metabolic symmetricity of PET because the epileptic focus is strongly correlated to the high-dimensional inter-hemispheric symmetricity changes. Their proposed model had a high detection accuracy of 90% [115].

Besides the end-to-end supervised models, the unsupervised machine learning approaches have been used to automatically extract the latent representation of brain images, which can be further input to a classifier. Alaverdyan applied the unsupervised Siamese network to improve the latent feature extraction [116, 33]. Then the latent representation of the T1w MRI voxels inputs to a one-class SVM classifier for the outlier detection, which can determine whether it is the abnormal data. They further compared the variants of siamese networks, the stacked convolutional autoencoder, and the Wasserstein autoencoder, and the results suggested that the regularized siamese network has great potential to extract the hidden features and eventually achieved the best classification performance. Surprisingly, this method has even been shown to outperform human experts for MRI-negative cases.

### 4.3 Epilepsy Prognosis

Computer-aided prognosis tasks are important to guide clinicians in appropriate treatment. The prognosis of epilepsy is usually quantified with some clinical indexes, such as epidemiology-based mortality score in status epilepticus and Engel classification. Machine learning models can be trained to predict the treatment outcome based on the brain images from patients, offering useful information for treatment decisions in advance. Prognosis prediction usually refers to the classification task of classifying the postoperative state (i.e, no seizures or persistent seizures)We list some work relevant to epilepsy prognosis in Table [5].

Many studies applied conventional models (that is, first extract features and then conduct classification) to predict the outcome of surgery [35][119]. For instance, Memarian et al. extracted 88 features (including demographic, clinical, electrophysiological, and structural MRI features) from mesial TLE patients, and then input them into a SVM classifier, resulting 95% accuracy of prognostic
Table 4: Classification of epileptic patients and healthy controls

| Task | Features | Model | Performance | Data Size | Ref |
|------|----------|-------|-------------|-----------|-----|
| Classify generalized tonic-clonic seizures and the normal | Gray matter volume and fractional amplitude of low-frequency fluctuation differences on MRI | SVM | ACC of GM: 74.4% ACC of fALFF: 83.7% | 14\30 | 31 |
| Classify TLE and the normal | Extracting white matter fibers from DTI, generating weighted structural connectivity graphs | Logistic regression | ACC: 91.0% | 17\17 | 117 |
| Classify TLE and the normal | FreeSurfer extracted 936 features per subject from T1, T2 and DTI (624 mean intensity features and 312 intensity difference features) | PCA+SVM | ACC: 88.9% | 17\19 | 32 |
| Classify epilepsy and the normal | Curve (Perimeter of a VOI); VOI extracted from two lateral ventricles | K-Nearest Neighbour | ACC: 78.5% | 105\105 | 118 |
| Classify TLE and MCI | Spherical harmonics features from hippocampus | SVM | ACC: 84.2% | 17\20 | 112 |
| Prediction of cognitive decline in TLE | Volumetry, local binary patterns, and wavelets | SVM | ACC: 86.0% | 9\18 | 113 |

| Task | Inputs | Model | Performance | Data Size | Ref |
|------|--------|-------|-------------|-----------|-----|
| Classify epilepsy and the normal | MRI voxel | 3D-CNN | AUC: 61.0% -76.0% | 21\23 | 76 |
| Classify epilepsy and the normal | MRI pixel | AE extract features + oc-SVM | Sensitivity: 60.0% | 21\75 | 110 |
Table 5: Prediction of prognosis in patients with epilepsy

| Task                | Inputs                                                                 | Model          | Performance                  | Data Size | Ref |
|---------------------|------------------------------------------------------------------------|----------------|-----------------------------|-----------|-----|
| Predict surgical outcome | Structural MRI, sEEG, clinical as well as demographic features | SVM            | ACC : 95.0%                 | 20        | 35  |
| Predict surgical outcome | Whole-brain connectome from DTI                                        | DNN            | Surgical success prediction ratio: 88.0% Surgical failure prediction ratio: 79.0% | 50        | 36  |
| Predict surgical outcome | Strength of each connection between all possible brain regions | DNN            | ACC: 95.0%                  | 50        | 120 |
| Predict surgical outcome | Surface morphology of hippocampus, amygdala, and entorhinal cortex      | K-means clustering | ACC: 92.0%                | 114       | 119 |

Apart from the conventional machine learning methods, end-to-end DNNs have also been applied to predict the most likely outcome of the treatment [36, 120, 121]. For example, Gleichgerrcht et al. trained a neural network with the whole-brain connectome matrix obtained from DTI and the corresponding binary label (i.e. surgical success or failure), achieving 88.0% prediction accuracy for the surgical success cases and 79.0% for the surgery failure cases [36].

5 Discussion

In short, among the various machine learning models, the feature engineering based conventional machine learning models account for a large proportion of applications, and the data-driven deep learning models for neuroimaging analysis have just emerged. Although the first study using deep learning models for epilepsy neuroimaging data did not appear until 2018 [76], deep learning approach has been a success in computer vision, recommendation systems, and natural language processing [122, 123]. We can imagine that deep learning approach would play a more important role in epilepsy neuroimaging in the future. Along this line, neuroimaging will contribute to the computer-aided diagnosis and prognosis of epilepsy.

However, there are obstacles when applying deep learning methods to the epilepsy neuroimaging field. The challenges of deep learning in epilepsy neuroimaging have multiple manifolds. First, labeling
data is challenging. The ambiguity in diagnosing particular epilepsy can make it difficult to label the disease type. It is particularly difficult to mark epileptic lesions unless the neurologist conducts longitudinal observations and confirms seizure-free after surgery. Moreover, patients with epilepsy may suffer from multiple complications, making it difficult to use one-hot vector labels to train machine learning models. Since the loss function defined by the discrepancy between network output and label is the key to the supervised learning algorithm based on gradient descent, noisy labels will inevitably bring serious negative effects. The consequences of mislabeling data can be fatal. Second, the imbalance between classes is another challenge in epilepsy medical images. The fact that different types of epilepsy have different frequencies of occurrence leads to an imbalance between the types of epilepsy. For example, temporal lobe epilepsy is common, while focal epilepsy on the motor cortex is relatively rare [124]. Therefore, the samples in the diagnosis task are tilted towards TLE, which might largely bias classification results. Third, neuroimaging requires high spatial resolution to detect subtle abnormalities, and neuroimaging also needs a large field of view for locating abnormal brain areas of all spans. These two are difficult to meet in a single brain imaging modality. As a result, there are more and more modalities of epilepsy images, which increases the difficulty of modeling. Finally, due to the diversity of neuroimaging equipment and patient conditions, medical images are usually heterogeneous; therefore, it is very challenging to improve the generalization ability of machine learning models. In fact, comprehensive validations of the universality and reliability of machine learning algorithms come at a cost. When encountering MRI negative images, clinicians rarely have fully validated methods, so the algorithm is almost unreliable in clinical applications. This distrust is further amplified by the shortcomings of machine learning in the absence of a clear physical explanation. When algorithm developers boast their high accuracy rate, it is still difficult for clinicians to understand why it succeeded, and those few failed samples did not explain why or when they failed.

The cutting-edge machine learning models provide potential tools for addressing the above challenges. For example, generative adversarial networks (GAN) [125, 126, 127] might be beneficial for data augmentation to address the problem of unbalanced neuroimaging samples [128]. Likelihood-based generative models (e.g., VAEs [86, 87], Pixel CNN [129] and Glow [130]) have been reported to be highly robust to the anomaly data and out-of-distribution (OOD) inputs and therefore can be used to detect the anomaly samples. Anomaly detection has wide medical applications. For instance, when an untypical disease is not seen in the training samples, likelihood-based generative models equipped with medical OOD detection might deal with noisy labels and largely improve the robustness [131, 132, 133, 134]. The recent advancements in graph convolutional networks (GCN) can work with the non-regular data structures. In contrast to the node classification tasks of medical
image analysis [135][136], GCN can handle unstructured data [137]. As a generalization of CNN, GCN is compatible with neuroimaging data in the non-Euclidean domain such as the BOLD signal and the DWI streamline between different brain areas. Segmentation [138], localization [139], and prediction [140] tasks have been tested applicable to GCN, although the performance of GCN in epilepsy data has yet to be proven.

On the other hand, the challenges and special needs in epilepsy applications can greatly motivate the development of machine learning methods. For example, Zhao et al. [105] came up with a new approach to solve the problems of patients’ heterogeneity by combining a restricted Boltzmann machine with a Bayesian non-parametric hybrid model. The heterogeneity of patients with epilepsy requires personalized medical care, which calls for accurate diagnosis of the stratification of each patient, such as the cause of epilepsy, the location, and symptoms of epilepsy [141][142]. Since the prognosis of epilepsy is vital for the patient’s quality of life, the longitudinal medical records of each patient should be recorded and analyzed. These are strong drives of machine learning theory and method.

6 Conclusion

Just as machine learning, especially deep learning, brings benefits to machine vision and natural language processing, machine learning on neuroimaging promises to extend those same benefits to epilepsy diagnosis and prognosis prediction. However, clinic-oriented machine learning applications have their unique context, such as the small data size, the low certainty in labeling, and the large heterogeneity across patients. It requires more efforts from multi-disciplinary experts on learning theory, neuroimaging, and epilepsy clinical applications.

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Figure legends

Figure 1. Epilepsy diagnosis workflow for clinicians and neuroimaging technicians. (a) Clinicians initially treat the semiology-diagnosed epilepsy patients with medication. If the patient is drug-resistant, the clinician will make a presurgical evaluation and multimodal images will be collected. Then, the clinician decides the type of surgery, either radical surgery or palliative surgery, based on whether the epilepsy is focal or general. (b) Neuroimaging technicians analyze medical data to support clinicians. They extract features from raw data via feature engineering or directly train end-to-end models for segmentation or positioning. Their ultimate tasks are computer-aided diagnosis and prognosis.

Figure 2. The non-invasive multi-modal images and electrophysiology for diagnosis and prognosis of epilepsy, including (a) T1, T2, DTI, PET images, (b) fMRI, (c) semiology video, (d) EEG.

Figure 3. The conventional machine learning approach. It consists of a feature engineering step to extract and select features from single/multiple neuroimaging modalities, and a machine learning step to perform a classification or regression task.

Figure 4. The deep learning approach. An example of a supervised learning model (a) and an unsupervised learning model (b) used for neuroimaging analysis.

Figure 5. An example of U-NET for segmentation of brain tissues. This framework is adapted from an open-source project.
Tables

Table 1: Representative hand-crafted features used in epilepsy
Table 2: Localization of abnormal brain regions or pathways
Table 3: Tasks of the lateralization
Table 4: Classification of epileptic patients and healthy controls
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