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Multivariate analysis and machine learning in pediatric epilepsy research: A literature review

Abstract

Due to brain immaturity, pediatric epilepsy has some unique challenges and opportunities in seizure management. Multivariate analysis and machine learning methods have been increasingly used in childhood epilepsy, mainly in seizure detection and prediction, epileptogenic lesion identification, and clinical outcome prediction. In order to provide an overview of this field, this paper reviewed such studies and found that these methods have made it possible to detect seizures on electroencephalogram (EEG) and detect lesions on imaging automatically. In addition, although seizure occurrence has been regarded as random or unpredictable for long, it has been found that seizures may occur non-randomly in complex patient-specific patterns. Preictal changes on EEG can be detected and distinguished from interictal activities by machine learning approaches, which makes it possible to predict seizure occurrence, but there are significant obstacles in seizure prediction, for example, sufficient clinical data and good machine learning algorithms are needed to identify complex seizure occurrence patterns. Further, outcome studies using multivariate analysis and machine learning methods have identified outcome predictors for seizure outcome prediction. To make these relatively new methods accurate and reliable, confirmatory studies are warranted and further research is needed to improve these methods. It is anticipated that multivariate analysis and machine learning will contribute more to identifying complex seizure patterns, epileptogenic lesions, and outcome predictors to improve seizure detection/prediction, lesion detection, and seizure outcome prediction, which will lead to better seizure control to prevent seizure-related accidents/injury in children with epilepsy, reduce mortality rate, improve quality of life and eventually set them free from seizures.

Keywords: multivariate analysis, machine learning, pediatric epilepsy, seizure detection, seizure prediction, outcome prediction

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Introduction

Epilepsy is a common neurological disorder and approximately 50 million people in the world are affected by it.[1] The estimated annual cost of epilepsy-related expenses is over $12 billion in the U.S.[2,3] The life risk of epilepsy is around 1%, and the incidence of seizures is high in children (3-4%).[4] Most seizures in children are similar to those in adults, but certain seizure types such as febrile seizures and infantile spasms only occur in children. Due to brain immaturity, children are more vulnerable than adults to brain malformation and brain insults (brain injury, lack of oxygen, infection, stroke, genetic or temporary metabolism disorder, etc.). In addition, it may be difficult to recognize some seizures such as absence seizure in children. On the other hand, vigorous brain growth and maturation allow children to have more treatment options (such as multi-lobe resection and hemispherectomy) than adults. Idiopathic epilepsy (which has unknown causes) predominates childhood epilepsy, and loss of consciousness during a seizure can be life-threatening. The risk of death in children and adolescence with epilepsy is much higher than in those that are seizure-free.[5,6] Due to sudden and seemingly unpredictable seizures, childhood epilepsy is often disabling and devastating to children, which deserves further research to reduce mortality rate, improve patient care and enhance their quality of life.

The occurrences of epileptic seizures have been regarded as random or unpredictable for long, but recent studies have revealed that seizures may occur non-randomly in a complex and unique-to-patient manner,[7,8] which facilitates seizure detection and makes seizure prediction possible. Seizure detection systems such as video-electroencephalogram (EEG), intracranial EEG, electrocardiography and accelerometry provide detailed seizure data for an objective assessment of seizures, which allows seizure management tailored to individual patient, but no single detection system or device can detect every type of seizure (tonic, clonic, hypermotor, atonic, absence, etc.).[9,10] Thus, selection of seizure detection device is based on a patient's seizure type and characteristics. Seizure prediction might greatly enhance seizure management and patients' quality of life, but the challenge is to identify complex seizure occurrence patterns.

Lesion detection is another challenging area of active research. Epileptogenic lesions such as focal cortical dysplasia (FCD), gliosis, periventricular nodular heterotopia and hippocampal sclerosis are often subtle on CT or MRI imaging. A study has shown that 58% of pediatric patients with intractable epilepsy and cortical dysplasia (n=43) did not have positive MRI findings that could guide surgical treatment, which highlighted the need for improved imaging techniques and a multimodal approach for lesion detection.[11] Therefore, computer-aided quantitative imaging analysis and a multimodal approach (that includes MRI, Positron Emission Tomography (PET), and magnetoencephalography (MEG), etc.) are often used to identify epileptogenic lesions.[12,13]

In addition, there are challenges in clinical outcome (or prognosis) evaluation and prediction. Knowing in advance the prognosis of a treatment such as an anti-epileptic drug (AED) or an epilepsy surgical procedure may aid clinical decision making. Predicting prognosis for individual patients and identifying clinical data variables that are associated with seizure outcome may guide seizure management.

For instance, early prediction of AED outcomes and identification of outcome predictors may save time for alternative therapies, which may set patients free from seizures earlier than conventional seizure management.[14]

What in common across these challenging problems (i.e., seizure detection or prediction, lesion identification, and outcome evaluation/prediction) is that the numbers of clinical data variables are often larger than the number of patients who participated in research (i.e., sample size). Such problems are high-dimensional problems, which can be handled by multivariate analysis. Multivariate analysis is a statistical analytic approach that analyzes multiple outcome variables simultaneously (such as multiple EEG signals across time in multi-channel EEG data, and the intensities of all voxels in the brain across time in fMRI data). Data-driven multivariate analysis is more powerful than univariate analysis in identifying data patterns and relationships between data variables (e.g., those associated with seizure outcome), classifying data into groups (e.g., according to epilepsy histopathology such as focal cortical dysplasia and periventricular nodular heterotopia), and developing new diagnostic tests (e.g., to differentiate epilepsy subtypes). Some examples of multivariate analytic methods are multivariate analysis of variance (MANOVA),[15] multivariate linear regression,[16] and independent component analysis (ICA).[17]

Machine learning (ML) is a number of multivariate analytic methods that involve data feature selection/reduction, and classification.[18] In machine learning, variables used as input data are called features, and the process of selecting the most significant features for classification (i.e., to classify data features into different groups/classes) is called feature selection. Patterns in data (in terms of center, spread, shape, rhythm or other spatial or temporal features) are referred to as data patterns. Further, a cross-validation method is often used to evaluate a machine learning method or model which partitions the original data into a training set to train the machine learning model, and a test set to test and evaluate it. Machine learning is classified as supervised or unsupervised learning. Supervised learning uses a training dataset labelled by humans (e.g., clinicians) for data group/class membership (e.g., patients or healthy controls), while unsupervised learning does not use a training dataset or human-defined data labels, but identifies data patterns that are often invisible to humans. Machine learning has been increasingly applied to research of neurological disorders such as epilepsy.[19,20] Supervised learning includes methods such as linear discriminate analysis (LDA),[21] support vector machine (SVM),[22] artificial neural networks (ANN)[23] and random forest,[24] and unsupervised learning includes methods such as cluster analysis.[25]

Although multivariate analysis has been applied to epilepsy research for decades, its application in pediatric epilepsy is relatively young. With growing clinical demands and interests, multivariate analysis and machine learning approach have been increasingly used in childhood epilepsy in recent years. This mini-review identified such studies in order to provide an overview (or big picture) of this field.

Methods

A Pubmed search was performed with keywords "multivariate analysis MRI pediatric epilepsy", "machine learning imaging pediatric epilepsy", "machine learning pediatric epilepsy", "multivariate pediatric epilepsy outcome" and "multivariate pediatric epilepsy". The search yielded 177 papers. The abstracts of the papers were screened to make sure the subjects in the paper were pediatric, the statistical methods used were multivariate, and the paper was published after year 2000. In addition, few papers in areas such as cognitive impairment identification and treatment (or patient) selection were excluded in order to keep focus on studies in major areas (that include the majority of the studies) in this research.

Results

40 papers were included in this review. 12 of the papers reported research that applied multivariate analysis and machine learning methods to seizure detection and prediction. Table 1 summarizes these studies. Another 14 of the papers reported research studies applied multivariate analysis and machine learning approaches to epileptogenic lesion identification, and the classification/diagnosis of childhood epilepsy, which are listed in Table 2. The rest of the papers reported studies of multivariate analyses applied to outcome assessment and prediction in childhood epilepsy, which are summarized in Table 3.

Table 1 Summary of studies that applied multivariate analysis to seizure detection and prediction

Study	Subject sample	Data features	Methods	Main findings	Other findings
Siniatchkin et al.[26]	7 pts with focal epilepsy	IED spikes identified from EEG with 2 artifact correction methods (MSC compared with conventional AAS) from EEG-fMRI data	PCA used in MSC correction method; False positive and false negative IEDs computed	MSC method effectively removed EEG artifacts in EEG-fMRI data while keeping the IED signals which improved IED detection (generated less false negative IEDs than AAS)	MSC-based IED seizure detection increased the sensitivity of EEG-fMRI studies in focal epilepsy
Galka et al.[27]	2 pts with epilepsy	Components of power spectrum extracted from the EEG (one was pure EEG data, the other EEG was from EEG-fMRI)	ICA and State space modelling decompositions	State space modelling decomposition identified spikes (epileptic foci), alpha components, sleep spindles and noise	ICA decomposition identified spikes (epileptic foci), but not alpha components, sleep spindles and some artifacts
Johnson et al.[28]	22 pts with epilepsy	Spectral features (Cepstral coefficients) extracted from filtered EEG data	3 methods for seizure detection, (1) SVM; (2) standard GMM; (3) GMM + MCE; Validation, 10-fold cross validation	Sensitivity, (1) SVM 81.0%; (2) standard GMM 64.2%; (3) GMM + MCE 91.4%; Specificity, (1) SVM 90.0%; (2) standard GMM 92.2%; (3) GMM + MCE 84.9%	Speech processing techniques (e.g. MCE) are good in EEG seizure detection

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Table Continued...

Study	Subject sample	Data features	Methods	Main findings	Other findings
Cabrerizo et al.[29]	9 pts vs. 8 controls	Frequency and temporal features (global parametric features) extracted from EEG data	ANNs and SVM used to classify patients from controls; Random 50/25/25 for validation	Classification Accuracy, 96.03±2.49% (ANN); 96.79±1.48% (SVM)	EEG classification useful to infer high-risk (epileptic) and low-risk pts for follow up treatments
Mandal et al.[30]	1 pt with epilepsy	Spatio-temporal features extracted from video monitoring data	SVM used to classify seizure-like movements	Accuracy, 50% (Sensitivity, 100%)	
Williamson et al.[31]	19 pt with epilepsy (from the Freiburg database)	Principal components of eigen-spectra of space-delay correlation and covariance matrices computed from EEG data	SVM used to classify preictal or interictal state	Prediction accuracy, 83.7% (sensitivity, 85.5%)	
Lin et al.[32]	23 pts with idiopathic epilepsy (12 good-seizure control; 11 refractory)	16 EEG segments from good-seizure-control pts; 12 EEG segments from refractory pts; 10 EEG feature descriptors (related to decorrelation time or relative power of delta/gamma) selected for classification	Multivariate analysis used to classify refractory and non-refractory pts; Higher values in the seven feature descriptors in the well-controlled group as compared to the refractory group	Weighted precision rate of 94.2%; recall rate, 93.3%	
Wang and Lyu.[33]	19 pt with epilepsy (from Freiburg dataset)	Dominant amplitude and frequency components from EEG and icEEG data	Patient-specific binary classifiers used to classify preictal and interictal stages	Classification performance, Sensitivity, 98.8%; a false prediction rate of 1.2%	
Juhász et al.[34]	10 pts with unilateral SWS and epilepsy	GLU/Cr and NAA/Cr ratios from MRSI, and regional hyperglucose metabolism from FDG-PET	Multivariate regression analysis used to assess the correlations between variables	High GLU/Cr ratios were found in the affected hemisphere in most pts	Mean ipsilateral/ contralateral GLU/ Cr ratios associated with seizure frequency scores
Li et al.[35]	10 pts with absence epilepsy	Multiscale permutation entropy extracted from EEG data	Feature reduction, LDA; Classification, Relevance feedback method (direct biased discriminant analysis) to classify between seizure-free, pre-seizure, and seizure phases	Averaged classification accuracy, 97.5%	
Song and Zhang.[36]	21 pts with epilepsy	Sample entropy-based features extracted from icEEG	Extreme learning machine classifier to discriminate interictal and preictal brain activities	Classification performance, a sensitivity of 86.75% and a specificity of 83.80%	
Lin et al.[37]	5 pts with epilepsy	216 global EEG feature descriptors used to extract EEG feature vector from video-EEG data; Identified a best subset with 5 valid descriptors to select features	SVM used to classify preictal and interictal EEG segments	Overall accuracy, 97.50% (96.92% Sensitivity; 97.78% Specificity)	Most of the 5 descriptors were different between the preictal and interictal stages for each patient, useful in seizure occurrence prediction

Pts, patients; CE, cryptogenic epilepsy; CPS, complex partial seizures; IED, interictal epileptiform discharges; AAS, averaged artifact subtraction; MSC, multiple source correction; PCA, principal component analysis; FCD, focal cortical dysplasia; LDA, linear discriminant analysis; SVM, support vector machine; MCD, malformations of cortical development; NDF, Nonlinear Decision Functions; AEDs, antiepileptic drugs; v-EEG, video-EEG; icEEG, intracranial-EEG; TLE, temporal lobe epilepsy; SWS, Sturge–Weber syndrome; NNC, Nearest-neighbor classifier; DFC, distance-based fuzzy classifier; MANCOVA, multivariate analysis of covariance; AST, aspartate transaminase; ALT, alanine transaminase; AESD, Acute encephalopathy with biphasic seizures and late reduced diffusion; ANNs, artificial neural networks; GMM, Gaussian Mixture Models; MCE, Minimum Classification Error

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Table 2 Summary of studies that applied multivariate analyses to epileptogenic lesion identification and epilepsy classification

Study	Subject sample	Data features	Methods	Main findings	Other findings
Daley et al.[38]	19 pts with CE and CPS vs. 21 children without epilepsy	Hippocampal volumes (total, anterior, posterior, left, right) from MRI; hippocampal asymmetries (left–right volumes)	Repeated measures analyses of covariance	Patients had smaller anterior hippocampal volumes than controls	Difference in hippocampal asymmetry was insignificant
Loyek et al.[39]	5 pts with FCD caused partial epilepsy	Texture features (including statistical, GLCM and RLM features) from MRI	FCD region on MRI manually segmented; SVM used for classification	Sensitivity, 92.8% (85~98%); Specificity, 85.9% (73~92%)	Combined feature sets performed better than single features
Kawakami et al.[40]	3 pts with FCD	Intensity profiles (of cortical layer) from MRI	SVM; Leave-one-out sampling for validation	Sensitivity, 90.5%; Specificity, 54.7%	
Kobashi et al.[41]	3 pts with FCD	Texture features (GLCM-based) and fractal dimension from MRI	SVM; Leave-one-out sampling	Sensitivity, 88.5%; Specificity, 85.8%	
Fellah et al.[42]	17 pts with epilepsy associated brain tumor (DNET and gangliomas)	Quantitative MRI parameters extracted from MRI (T1, T2, FLAIR) images; ADC from DWI images; NAA, Cr and Cho ratios from MRS	Univariate and multivariate analyses (LDA) used to classify brain lesions (FCD, DNET and gangliomas)	Combining the measures from MRI, DWI and MRS separated the 3 patient groups (FCD, DNET or gangliomas) completely	LDA with MRI parameters alone failed classifying two pts. LDA with MRI and DWI parameters misclassified one patient
Amarreh et al.[43]	20 pts with epilepsy vs. 29 healthy children	FA, MD, RD, AD from DTI images; 5 data reduction (250, 500, 1000, 2000, and 3000 voxels) of FA, MD, RD, AD	SVM; 10-fold cross validation	2-way (epilepsy vs. healthy) classification with MD, Sensitivity 90–100%; Specificity 96.6-100%	3-way (active vs. remitted epilepsy vs. healthy) classification with FA (at 500 voxels), 100% sensitivity and specificity
Connolly et al.[44]	405 pts in 4 hospitals (135 pts in each hospital)	Data selected from electronic health records	SVM used to classify different types of epilepsy; 20-fold cross-validation	2-class (partial vs. generalized epilepsy) classification accuracy, 0.83±0.05	3-class (partial vs. generalized vs. unclassified epilepsy) classification accuracy, 0.49±0.15
Ahmed et al.[45]	31 pts with FCD (7 MRI-positive, 24 MRI-negative) vs. 62 healthy controls	Five cortical features (cortical thickness, gray/white matter contrast, sulcal depth, mean curvature, Jacobian distortion) computed from MRI images	Constructed a set of "base-level" classifiers (trained with logistic regression) to classify lesional and non-lesional vertices; Leave-one-out resampling	Classification accuracy, 86% for MRI-positive pts; 58% for MRI-negative pts	MRI-negative images can aid in the detection of FCD lesions
Garcia-Ramos et al.[46]	24 pts with BECTS vs. 41 healthy controls	Data from cognitive assessment; cortical thickness and putamen volumes from T1 MRI at baseline and 2 years later	MANCOVA performed examining group differences with age, gender, and ICV as covariates	Baseline cognitive and structural brain (abnormal cortical thickness, larger bilateral putamen volumes) abnormalities in pts persisted over 2 years	
Paldino et al.[47]	45 pts with epilepsy	Metrics (modularity, clustering coefficient, transitivity, path length and global efficiency) computed from rs-fMRI	Random forest method used to predict epilepsy duration	Epilepsy duration predicted by random forest (based on the five global network metrics) was highly correlated with actual epilepsy duration	rs-fMRI functional network metrics might be patient-level markers of cognitive deterioration

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Table Continued...

Study	Subject sample	Data features	Methods	Main findings	Other findings
Vecchi et al.[48]	259 pts with focal epilepsy	Variables from clinical data, EEG, MRI, and neuropsychological examinations	Multivariate analysis used to examine specific association across variables	Abnormal findings were in 29.2% neurologic examination reports, 59.9% brain MRI, 30% cognitive tests, 21% behavioral profiles	Younger pts and those with TLE were more likely to have frequent seizures (after epilepsy onset)
Juhász et al.[34]	10 pts with unilateral SWS and epilepsy	GLU/Cr and NAA/Cr ratios from MRSI, and regional hyperglucose metabolism from FDG-PET	Multivariate regression analysis used to assess the correlations between variables	High GLU/Cr ratios were found in the affected hemisphere in most pts	Mean ipsilateral/ contralateral GLU/ Cr ratios associated with seizure frequency scores
Paldino et al.[49]	30 pts with focal epilepsy	Metrics (modularity, clustering coefficient, transitivity, path length and global efficiency) computed from rs-fMRI	Random forest used to measure the independent contribution to the intelligence quotient	Clustering coefficient and path length were associated with full-scale intelligence quotient; A longer history of epilepsy was associated with shorter path lengths	Imaging-based metrics of functional network was associated with intelligence in pediatric epileptic brain
Jin et al.[50]	61 pts with epilepsy and 120 healthy controls in the training set from 3 centers; 15 pts with epilepsy and 35 healthy controls in the test set	Surface-based morphometry features extracted from MRI	A neural network classifier used to detect FCD; ROC analysis; k-fold cross-validation	Classification performance, sensitivity, 73.7%; specificity, 90.0%; AUC=0.75	Robust classification performance across pts from different centers and scanners
Wang et al.[69]	14 pts with generalize seizures and 30 healthy controls	Gray matter volume and fALFF of the right thalamus	SVM used to classify patients and controls; Leave-one-out for cross validation	Classification performance, Accuracy, 83.72%	Epileptic history was correlated with gray matter volume reduction and fALFF increase in the right thalamus

Pts, patients; CE, cryptogenic epilepsy; CPS, complex partial seizures; AAS, averaged artifact subtraction; MSC, multiple source correction; PCA, principal component analysis; FCD, focal cortical dysplasia; GLCM, grey-level co-occurrence matrices; RLM, grey-level run length matrices; LDA, linear discriminant analysis; SVM, support vector machine; MCD, malformations of cortical development; NDF, Nonlinear Decision Functions; MD, mean diffusivity; FA, fractional anisotropy; RD, radial diffusivity; AD, axial diffusivity; ADC, apparent diffusion coefficient; AEDs, antiepileptic drugs; TLE, temporal lobe epilepsy; SWS, Sturge–Weber syndrome; DNET, dysembryoplastic neuroepithelial tumor; GLU, glutamate; Cr, creatine; NAA, N-acetyl-aspartate; Cho, choline; MRS, magnetic resonance spectroscopy; MRSI, magnetic resonance spectroscopic imaging; BECTS, Benign epilepsy with centrotemporal spikes; NNC, Nearest-neighbor classifier; DFC, distance-based fuzzy classifier; MANCOVA, multivariate analysis of covariance; ICV, intracranial volume; CT, computed tomography; AST, aspartate transaminase; ALT, alanine transaminase; LD, lactate dehydrogenase; AESD, Acute encephalopathy with biphasic seizures and late reduced diffusion; rs-fMRI, resting-state fMRI; ANNs, artificial neural networks; ROC, receiver operating characteristic; AUC, area under the curve of the ROC; fALFF, fractional amplitude of low-frequency fluctuation

Table 3 Summary of studies that applied multivariate analysis to outcome evaluation and prediction

Study	Subject sample	Data features	Methods	Main findings	Other findings
Hemb et al.[51]	571 pts (192 pre-1997; 379 post-1997) who underwent surgery	Clinical variables, surgical procedures, and postsurgical outcomes	Univariate statistical tests used to compare surgical outcomes; Multivariate analyses (logistic regression and log-linear analysis) used to identify outcome predictors	Better outcome (seizure-free rate 5 years after surgery 74%), fewer complications and reoperations in the post-1997 group than the pre-1997 group (seizure-free rate 5 years after surgery 45%)	Seizure-free predictors, post-1997 series and less aggressive medication withdrawal; Improved technology and surgical procedures, clearer lesion identification and complete resection may lead to better outcome
Dragoumi et al.[52]	303 pts with idiopathic epilepsy	Variables defined at intake and after the initial year of treatment	Multivariate analysis used to identify prognostic variables	70.3% seizure –free and 53.1% had excellent clinical course; 2% had poor outcome; Prognostic variables for poor outcome, Early seizure onset, multiple seizure types and history of status epilepticus	Early response to treatment has positive predictive value; multiple seizure types and history of migraine have negative predictive value

Table Continued...

Study	Subject sample	Data features	Methods	Main findings	Other findings
Krsek et al.[53]	33 pts with TSC who underwent surgery	29 clinical, neuropsychological, EEG, MRI, and surgical variables	Univariate Barnard's exact test, Wilcoxon's rank-sum test, multivariate statistical Cox's model	55% pts seizure-free (2 years after surgery); 15% had post-surgery complications; Predictors of seizure-free outcome, complete removal of epileptogenic tissue, regional scalp interictal EEG patterns, and consistency of interictal and ictal EEG localization	Other predictors of seizure-free outcome, Occurrence of regional scalp ictal EEG patterns, fewer brain regions affected by tubers, presence of preoperative hemiparesis, and one-stage surgery
Moosa et al.[54]	186 pts with epilepsy who underwent hemi-spherectomy	Preoperative clinical, electroencephalography (EEG), imaging, and surgical data	Multivariate regression analysis used to examine predictors	56% pts seizure-free (6.05 years after surgery); 83% walked independently; 24% pts had new visual symptoms after surgery; 65.2% were in school	Major predictors of poor outcomes in ambulation, spoken language, and reading function, Seizure recurrence; contralateral hemisphere abnormalities on MRI
Seker et al.[55]	200 pts with intractable epilepsy	Age of onset, seizure frequency, seizure type, specific epileptic syndrome, Motor deficiency, Mental deficiency, Symptomatic etiology, MRI abnormality, etc.	Univariate analysis and multivariate logistic regression model used to identify predictors of intractable epilepsy	Predictors of intractable epilepsy, a previous history of epilepticus status, abnormal electroencephalogram results, and multiple seizures in 1 day	
Incecik et al.[56]	308 pts with epilepsy	Clinical data (mental development, history of febrile seizure, etiological of epilepsy, EEG and neuroimaging findings, total number of AED, etc.)	Univariate and multivariate survival analysis used to assess the outcome of AED withdrawal	Recurrence rate after AED withdrawal was 23.7% in pts and most occurred during the 1st year	Risk factors of seizure recurrence, abnormal first EEG and number of AED before remission (polytherapy)
Yang et al.[57]	137 pts with epilepsy who underwent surgery	Age, gender, MRI lesion, prior epilepsy surgery, type of invasive evaluation, hemisphere implanted, main lobe of coverage, surgery type	Univariate and multivariate logistic regression analyses used to identify predictors for intracranial hematoma	Seizure-free rate (at least 2 years after surgery), 48.9%; 21.7% had complications after surgery; 11.3% had hematoma	Risk factors for intracranial hematoma, number of electrode contacts
Mandell et al.[58]	10 pts with TLE who underwent surgery vs. 6 normal controls	Temporal lobe volumes, whole brain and fluid volumes measured from CT and MRI images	LDA used to classify seizure outcome; Bootstrapping used for validation	Seizure-free rate (1 year after surgery), 40% for Engel IA; 60% for Engel IA or Engel IB; Classification accuracy, 89%~91%; Temporal lobe volumes separated normal subjects vs. pts with Engel IA outcome vs. pts with other outcomes	Outcome predictors, volume of each temporal lobe; age-normalized whole brain volume; Temporal lobe volumes together with whole brain volumes may improve outcome prediction
Sun et al.[59]	122 pts with epilepsy including 72 who underwent surgery, and 50 no surgery	Data from chart review, age at epilepsy onset, age at video-EEG monitoring, duration of epilepsy, MRI findings, current number of AEDs, number of prior AEDs failed for lack of efficacy, prior ketogenic diet, etc.	Two-sample t test, univariate and multivariate linear regression used to evaluate associations between each variable and length of stay	Mean length of stay (in hospital), 4.0 ± 3.7 days; Use of SISCOM correlated with longer length of stay; AEDs-reduced pts had longer length of stay	Predictors of shorter length of stay, younger age at seizure onset, shorter interval from most recent seizure, lack of SISCOM and AED reduction

Table Continued...

Study	Subject sample	Data features	Methods	Main findings	Other findings
Arya et al.[60]	47 pts with MRI-negative drug-resistant epilepsy who underwent surgery	Relevant clinical, neurophysiological, imaging (MRI), and surgical data extracted	Univariate analysis and multivariate logistic regression (with forward stepwise variable selection) used to identify prognostic factors	25.5% pts seizure free (ILAE class I) 2.75 ±1.72 years after surgery; Predictors for non-seizure-free outcome, Children with daily seizures, earlier onset of seizures	Other factors affected non-seizure-free outcome, each additional AED used before surgery; but surgical variables were not predictors of seizure-freedom
Overwater et al.[61]	102 pts with tuberous sclerosis complex	Data from the first 24 months of life including details on epilepsy, motor development and mutation status	Univariate and multivariate analyses used to determine factors predicting cognitive development	Factors predicting cognitive development, age at seizure onset (contributing to 28% of the variation in intellectual equivalent)	Factors predicting cognitive development could aid support and schooling selection
Pelliccia et al.[62]	120 pts with focal epilepsy and epilepsy-associated tumors who had surgery	Data variables (age at the time of epilepsy onset and surgery, illness duration, seizure frequency; histological findings, characteristics of surgical procedures, and sites of surgery)	Kaplan–Meier method used to estimate seizure-free time; logistic regression; multivariate analysis used to select prognostic variables	Pts' age at surgery < 18 had better seizure outcome, 80% Engel Class Ia outcome (2 years after surgery) for all epilepsy types; 71.8% Engel Class Ia for pts with TLE	Determinant factors for seizure-free outcome, complete resection of the lesion, a shorter duration of epilepsy, and temporal lobe localization
Tomlinson et al.[63]	17 pts with epilepsy who underwent surgery	Global network synchrony computed as the average pairwise connectivity strength (global synchrony) and local signal heterogeneity obtain from icEEG data	Classify pts by surgical outcome using SVM, with leave-one-out resampling permutation test	Seizure-free rate (>=3 years after surgery), 52.9%; Accuracy of classification, 94.1%; Global synchrony was higher in the seizure-persistent group than seizure-free group	SOZ electrodes had higher signal heterogeneity than non-SOZ electrodes, mainly in seizure-persistent pts
An et al.[14]	53,618 pts (including adults) with epilepsy (in the test set)	Longitudinal claim data (from 2006 to 2015) (demographics, comorbidities, medications, procedures, epilepsy status, etc.)	Logistic regression, SVM and random forest used to identify drug-resistance; ROC used for model performance; Breier scores and calibration plots used for model validation	Classification accuracy (in AUC), Random forest, 0.753; Logistic regression, 0.732; SVM, 0.720; Benchmark model (age and gender), 0.664	Machine- learning-based models using claim data can identify drug resistance in pts on average 2.25 years earlier than conventional seizure managment

Pts, patients; TSC, tuberous sclerosis complex; icEEG, intracranial EEG; AED, anti-epileptic drug; SISCOM, Subtraction ictal single-photon emission computed tomography coregistered to MRI; TLE, temporal lobe epilepsy; FC, febrile convulsions; HS, hippocampal sclerosis; MTS, mesial temporal sclerosis; IEDs, interictal epileptiform discharges; LDA, Linear discrimination analysis; SVM, support vector machine; SOZ, Seizure-onset zone; AST, aspartate transaminase; CRP, C-reactive protein; AUC, area under the curve of ROC (receiver operating characteristic)

Multivariate analysis in seizure detection and prediction

Key seizure features in pediatric patients' electroencephalogram (EEG) data such as amplitude distribution histograms and spectral power features of the ictal and interictal spikes in the temporal and frequency domains have been identified to distinguish seizure (ictal or interictal) spikes from normal EEG. Multivariate analysis of EEG or video-EEG data based on such features has made it possible to detect seizures automatically. The advantage of multivariate analysis is that it can effectively remove EEG artifacts while keep signals of interictal epileptiform discharges (IEDs). Therefore, it can improve the signal-to-noise ratio of EEG or EEG-fMRI data and enhance detection of IEDs in focal epilepsy.[26,27] Johnson et al. applied speech processing techniques such as Gaussian Mixture Models (GMM) to seizure detection on EEG data (n=22) and found that GMM with Minimum Classification Error improvement had more favorable detection rate (sensitivity: 91.4%, specificity: 84.9%) than frequently-used support vector machine (SVM) (sensitivity: 81%; specificity: 90%).[28] In addition, Cabrerizo et al. examined seizures with EEG to distinguish patients (n=9) from controls by applying 2 classifiers (artificial neural network (ANN) and SVM) to the frequency and temporal features of EEG data, and obtained high classification accuracy (ANN: 96.03±2.49%; SVM: 96.79±1.48%).[29-31] To identify refractory epilepsy in children with idiopathic epilepsy, Lin et al. classified EEG feature descriptors such as decorrelation time and relative power of delta/gamma, which yielded a weighted accuracy rate of 94.2% (n=23).[32]

Although computer-aided EEG data analysis with machine learning approach has made it possible to detect seizures automatically, the samples of most seizure detection/prediction studies are relatively small (range of n: 5~22, average n=12). In addition, a number of studies lack validation of the classification results. Validation methods

in machine learning and statistical resampling such as N-fold cross-validation and leave-one-out are useful to prevent model overfitting (i.e., classification performance in the test set is much lower than that in the training set which may be due to noise in the training data and the machine learning method models noise in the training data). Confirmatory studies with validation methods and large samples are warranted, and further research is needed to improve seizure detection.

In addition to seizure detection, a number of studies have explored prediction of seizure occurrence by classifying a patient's preictal or interictal state on EEG. Seizure occurrence has been regarded as random, spontaneous or unpredictable for long, but recent studies have discovered that factors such as circadian oscillators, quality of sleep, seizure location, and hormonal factors are associated with the patterns of seizure occurrence, and seizures have a tendency to occur in non-random, complex and patient-specific patterns.[7,8] Preictal changes on EEG can be detected, characterized and used to predict seizures, which is important to minimize patients' risk of injury and improve patient care.[64,65] Williamson et al. computed the principal components of the eigen-spectra of space-delay correlation and covariance matrices, classified the features with SVM and achieved a seizure prediction accuracy of 85.5% (n=19).[31] In addition, Li et al. applied a relevance feedback method (direct biased discriminant analysis) to distinguishing between seizure-free, pre-seizure, and seizure phases on EEG and yielded an accuracy of 97.5% (n=10) .[35]. To identify seizure preictal and interictal stages, Lin et al. selected an optimal subset of discriminative EEG feature descriptors, classified artifact-free preictal and interictal EEG segments with SVM, and achieved a high weighted accuracy rate (97.5%) (n=5).[37] Further, intracranial-EEG data was used in seizure prediction to improve detection rate. Wang et al. built patient-specific binary machine learning classifiers to classify EEG features into preictal or interictal state on, and reported 98.8% sensitivity and a false detection rate of 1.2% (n=19).[33] Song and Zhang used sample entropy and extreme learning machine to discriminate preictal and interictal states on intracranial-EEG data and obtained a sensitivity of 86.75% and a specificity of 83.80% (n=21).[36] Although the data samples of these studies are relatively small, these studies demonstrated that seizure prediction is possible through detecting seizure preictal changes and identifying seizure preictal and interictal stages on scalp or intracranial EEG. Nevertheless, a recent study with a large sample (including adult patients) from multi-centers (n=216; 185 intracranial EEG, 31 scalp EEG) showed that the overall seizure prediction performance (using multi-class SVM) was limited (an overall sensitivity: 38.47%; an overall accuracy: 11%), which revealed significant challenges in seizure prediction in reality.[66] For comprehensive reviews on seizure detection in patients with epilepsy (including adults).[9,10]

Seizure prediction is challenging and the overall accuracy of seizure prediction is low. A bottleneck problem is to identify complex patient-specific seizure occurrence patterns. Information collected from short-term intracranial EEG (e.g., the number of recorded seizures) is often insufficient (e.g., to establish probability distribution), while long-term intracranial EEG (weeks or months) might not be applicable to pediatric patients at young age (due to the risk of neurosurgery or implantable intracranial device). Nevertheless, sufficient clinical data (e.g., large number of seizures on EEG or intracranial EEG) and good machine learning algorithms (that can model complex data) are useful to identify complex seizure patterns.[67,68] Once validated, such machine learning algorithms may be integrated into clinically applicable devices for seizure detection and prediction. In addition, factors such as AED withdrawal, lack of sleep and flickering visual stimuli may trigger occurrence or recurrence of seizures. Therefore, seizure prediction models that incorporate long-term intracranial EEG (or equivalent), clinical biomarkers (such as medication use) and powerful machine-learning algorithms may lead to breakthroughs in seizure prediction, which will prevent seizure-caused injury or accident, enhance seizure treatment and improve patients' quality of life. For in-depth reviews on seizure prediction.[64,65,68]

Taken together, multivariate analysis and machine learning methods have made it possible to automatically detect seizures, but there are significant challenges and obstacles in seizure prediction. Sufficient clinical data and good machine-learning methods are needed to identify complex seizure patterns for seizure prediction. Further studies are warranted to verify and improve these new methods in seizure detection and prediction.

Multivariate analysis in epileptogenic lesion detection and epilepsy classification

Imaging features of epileptogenic lesions such as hyper-(or hypo-) intensity in the gray matter, increased cortical thickness and gray-white matter junction blurring have been identified by imaging analytic methods such as voxel-based morphometry, cortical thickness calculation, gradient map construction, and texture analysis.[12] Commonly used data variables or features in lesion detection include voxel intensity profiles, texture features, and morphometry features. Based on these imaging features, multivariate analysis has made it possible to detect focal cortical dysplasia (FCD) lesions on structural imaging automatically. When applying support vector machine (SVM) to FCD detection, different MRI imaging features could make a difference in detection rates.[39-41] For example, using imaging voxel intensity profile, the detection rate was not specific enough (sensitivity: 90.5%; specificity: 54.7%) (n=3),[40] but using grey-level co-occurrence matrices (GLCM)-based texture and fractal dimension features, FCD detection improved (sensitivity: 88.5%; specificity: 85.8%) (n=3);[41] while using texture features such as statistical, GLCM and run length matrices (RLM) features, FCD detection rate was further improved (average sensitivity: 92.8%; specificity: 85.9%) (n=5).[39] However, the samples of these studies were small, and confirmatory studies with large samples are needed. A recent multi-center study using a large sample (n=61 in the training set; n=15 in the test set) showed that classification of MRI surface-based morphometry features by a neural network classifier for FCD detection yielded a sensitivity of 73.7% and specificity of 90.0%. Although the FCD detection performances were robust across 3 different centers and scanners,[50] this study revealed the challenges of automated machine-learning based FCD detection in a large sample.

When structural MRI findings were negative, multivariate analysis and machine learning approach could identify FCD lesions on MRI using key cortical features with a limited accuracy of 58% (n=24).[45] For epileptogenic lesions such as FCD that elude from MRI, multivariate analysis based on features from multimodal imaging can detect them and distinguish different lesion types. For example, to detect and differentiate lesions between FCD and epilepsy associated tumors, Fellah et al. examined children with epilepsy associated brain tumors such as dysembryoplastic neuroepithelial tumor (DNET) and gangliomas (n=17) using MRI, Diffusion weighted imaging (DWI) and Magnetic resonate spectroscopy (MRS), and Linear Discriminate Analysis (LDA) demonstrated that combined imaging measures from MRI, DWI and MRS could separate the 3 patient groups (FCD, DNET and gangliomas) completely, while measures of MRI alone or measures of MRI and DWI could not.[42] A recent imaging study

used SVM and combined imaging features of gray matter volumes (from MRI) and fractional amplitude of low-frequency fluctuation (fALFF from resting-state functional MRI) to distinguish children with generalized tonic-clonic seizures (n=14) from healthy controls and obtained an accuracy of 83.72%.[69] Further, imaging features of epileptogenic lesions on Diffusion Tensor Imaging (DTI) such as increased diffusivity and reduced anisotropy in the white matter near the lesion have been identified. Amarreh et al. examined children with epilepsy (n=20) using DTI imaging, applied SVM to DTI features such as fractional anisotropy (FA), and achieved high classification accuracy (classification between patients and controls using mean diffusivity: sensitivity: 90-100%; specificity: 96.6-100%; classification for active epilepsy vs. remitted epilepsy vs. controls using FA: sensitivity and specificity: 100%).[43]

In addition to imaging data, multivariate classification has been applied to other clinical data such as patients' demographics, seizure characteristics, and laboratory data for children with epilepsy. For example, Connolly et al. used SVM to classify epilepsy progress notes on data from electronic health records across 4 hospitals (n=405) and obtained a 2-class (partial vs. generalized epilepsy) classification accuracy of 83±5%, which suggested that the similarity of epilepsy progress notes across different hospitals enabled inter-hospital epilepsy classification.[44]

Computer-aided imaging analysis with machine learning approach is useful to identify epileptogenic lesions on imaging, but classification performances of lesion detection varies across studies. Since variations in the processing steps (data selection, feature extraction and selection, feature classification, and validation) along data processing chains of machine learning-based lesion detection may contribute to large variations in the classification results across studies,[70] lesion detection may be improved by optimizing the machine-learning-based data processing (e.g., select an optimal set of data features, or a best performed classifier) to reduce such variations across studies. In addition, it is challenging to identify subtle lesions on structural MRI (i.e., when MRI has negative findings), further research is needed to improve machine-learning-based lesion detection that incorporates multi-modal imaging features. For a comprehensive review on epileptogenic lesion detection on neuroimaging in patients with epilepsy (including adults).[12] In addition, for a recent comprehensive review on imaging applications of machine learning in epilepsy.[71]

Taken together, multivariate analysis and machine learning methods have made it possible to identify epileptogenic lesions automatically. Further studies with large samples are warranted to validate and improve such lesion detection approaches and make these methods clinically useful and reliable.

Multivariate analysis in clinical outcome assessment and prediction

Multivariate outcome analysis in pediatric epilepsy is useful in revealing treatment effects (anti-epileptic drugs (AEDs), epilepsy surgery, etc.) and identifying factors associated with clinical outcomes for prognosis prediction, which may aid clinical decision making and guide seizure management.

Clinical outcomes of AEDs or AED withdrawal: The effect of AED medications on pediatric patients has been confirmed by a large sample study of AED outcomes on children with idiopathic epilepsy (n=303) that seizure-free rate (at 1 year) was 70.3%, and multivariate analysis has identified prognostic factors for initial poor (non-seizure-free) outcome of AEDs (such as early seizure onset, history of status epilepticus, and multiple seizure types), and predictors for long-term poor outcome (such as initial non-response to treatment, and multiple seizure types).[52] In this study, multiple seizure types were found to be the predictor for both initial and long-term poor outcomes of AEDs in pediatric patients.[52] In addition, it has been shown that early AED withdrawal may lead to seizure recurrence. An outcome study of AED withdrawal in epileptic children (n=308) has reported that seizure recurrence rate was high (23.7%) and multivariate analysis identified the risk factors for seizure recurrence were abnormal initial EEG and the number of AEDs used in polytherapy.[56] Further, a recent study using claims data of a super large sample (n>50,000 patients including adults) indicated that machine learning methods could help identify drug-resistant epilepsy in patients as early as when they prescribed their first AEDs, which may save time for alternative therapies and set patients free from seizures earlier than conventional seizure management.[14]

Clinical outcomes of surgical treatment: Surgical treatment can set patients free from seizures, but outcome studies have indicated that seizure-free rate of surgical treatment varied across the studies in pediatric patients. For example, for the most common epilepsy surgical procedure anterior temporal lobe resection in children with drug-resistant temporal lobe epilepsy (TLE), seizure-free rate was 40% (1 year after surgery) in Uganda (n=10)[58] while 86% (5 years after surgery) at UCLA (n=37) (post-1997);[51] in children who underwent hemispherectomy, seizure-free rate was 56% (6.05 years after surgery) at Cleveland Clinic (n=186),[54] while 83% (5 years after surgery) at UCLA (n=77).[51] A comprehensive study at UCLA reported the seizure outcomes of a large group of pediatric patients who underwent epilepsy surgery (n= 571, including 192 pre-1997, and 379 post-1997): seizure-free rate (5 years after surgery) for all epilepsy types was 74% (post-1997) vs. 45% (pre-1997), and better seizure outcome in the post-1997 group was mainly due to improved technology and surgical procedures.[51]

Seizure-free (or positive) predictors identified by multivariate outcome assessments also varied across the studies in pediatric patients. The UCLA group found that seizure-free predictors were post-1997 series and less aggressive medication withdrawal, and better seizure outcome might be due to clearer lesion identification and complete resection[51] Using linear discriminate analysis (LDA) on brain volume data (extracted from MRI of children with drug-resistant epilepsy) (n=10), Mandell et al. identified volume of each temporal lobe and age-normalized whole brain volume as seizure outcome predictors, and found that temporal lobe volumes and whole brain volumes could improve surgical outcome prediction.[58] Further, Tomlinson et al. studied the surgical outcomes of epileptic children, classified global synchrony and local heterogeneity features (from intracranial EEG) with support vector machine (SVM) and reported that the seizure-persistent group had higher global synchrony than the seizure-free group, and outcome prediction reached an accuracy of 94.1% (n=17).[63] In addition, in children with epilepsy associated tumors (n=120), the determinant factors for seizure-free outcome identified by Pelliccia et al. were temporal lobe localization, a shorter duration of epilepsy and complete resection of the lesion.[62] On the other hand, predictors for non-seizure-free (or negative) predictors included frequent seizures, earlier onset of seizures and number of failed AEDs (n=47),[60] and for hemispherectomy, seizure recurrence and abnormalities in the contralateral hemisphere on MRI were the major predictors of poor outcomes in motor, language, and reading functions (n=186).

Further, based on multivariate meta-regression, two meta-analyses revealed the positive and negative predictors of two major epilepsy surgeries in pediatric patients with drug-resistant epilepsy.[72,73] First, for common temporal lobe epilepsy: Englot et al. pooled 1,318 pediatric patients together (from 36 studies) in a meta-analysis and found that the pooled seizure-free rate was 76%; positive predictors were abnormal MRI, partial seizures, lesional epilepsy etiology, and gross-total lesionectomy; and negative predictors were normal MRI, nonlesional epilepsy, generalized seizures and subtotal resection.[72] Second, for less common extra-temporal lobe epilepsy: Englot et al. included 1,259 pediatric patients (from 36 studies) in a meta-analysis and found that the pooled seizure-free rate was 56%; positive predictors were lesional epilepsy, shorter epilepsy duration (≤7 years), focal seizures and localizing ictal EEG findings; negative predictors were nonlesional epilepsy, nonlocalizing EEG, generalized seizures and over 7-year epilepsy history.[73]

Methods of clinical outcome evaluation and prediction: Identification of reliable outcome predictors is critical to improve clinical outcome evaluation/prediction and guide seizure management. Conventional method for outcome evaluation employed by most outcome assessment studies is a 2-step approach: First, use univariate analysis to identify which variables are associated with outcomes (e.g., seizure-free rate); Second, use multivariate analysis to assess the variables (identified by univariate analysis) to further determine outcome predictors.

In recent years, machine learning methods such as linear discriminate analysis (LDA) and support vector machine (SVM) have been found useful in outcome prediction.[58,63] Compared with conventional approach, machine-learning-based outcome evaluation and prediction is a relatively new approach. Although the two recent outcome studies of surgical treatments have demonstrated the value of machine learning methods in seizure outcome prediction,[58,63] the odds ratios of the outcome predictors are relatively low which limits their predictive power.[74] A recent large-sample study predicting mortality in EEG-monitored pediatric patients (including children with epilepsy) in the intensive care unit has reported limited prediction accuracy in terms of area under the receiver operating characteristic curve (AUC) of 0.45~0.82 (SVM: AUC=0.79; random forest: AUC=0.71) (n=414).[75] Consequently, the overall prediction accuracy for seizure outcome needs to be improved.

Prediction of seizure outcome with high accuracy is possible through selecting optimal feature sets (that include the most characteristic or significant data features) and optimizing classifiers. An outcome study in adult patients (who suffered left mesial temporal lobe epilepsy and underwent amygdalo-hippocampectomy) classified the patients into gender-specific groups (due to morphological gender differences) (19 male; 30 female), applied SVM to over 20 (small or large) volumes of white matter segments extracted from the MRI, and predicted individual patients' seizure outcomes with high precision (94% balanced accuracy for male; 96% balanced accuracy for female). However, pooling male and female patients together, the outcome prediction was poor (58% balanced accuracy).[76] It is unclear whether such gender-specific grouping makes a difference in outcome prediction for pediatric patients, but what is clear is that using optimal feature sets and/or an optimized classifier can improve seizure outcome prediction.

In addition, large sample size implies strong statistical power and high confidence level in statistical analysis. Therefore, to obtain reliable outcome predictors for epilepsy surgical treatments, meta-analysis (based on multivariate meta-regression) is advantageous, which creates large samples by pooling the subject samples in individual outcome studies together and thus gains strong statistical power.[77] The results of those two meta-analyses on surgical outcomes provide a big picture of seizure outcomes and relatively reliable outcome predictors due to the pooled large samples (n>1000).[72,73]

Taken together, although multivariate analysis and machine learning approaches are relatively new in clinical outcome evaluation and prediction, they have been proved to be useful. However, the overall prediction accuracy for seizure outcome needs to be improved, and large-sample studies are needed to identify reliable outcome predictors.

Discussion

Multivariate analysis and machine learning approach has been applied to three major areas of seizure management in pediatric epilepsy: seizure detection and prediction, epileptogenic lesion identification, and clinical outcome assessment and prediction. Much progress has been made in these applications over the years, but there are still a lot of challenges and obstacles in this field.

The value and role of multivariate analysis and machine learning in seizure management

The 2-step approach in the multivariate analysis of clinical outcome evaluation and prediction has more validity than univariate analysis alone. In addition, the value and potential of machine learning methods have been revealed by comparative studies that compared machine learning methods with conventional techniques (e.g., univariate analysis) in lesion detection and outcome prediction.[14,42] For example, Fellah et al. used both multivariate (machine learning method) linear discriminate analysis (LDA) and univariate analysis to differentiate 3 types of lesions on MRI and showed the advantage of LDA over univariate analysis in that when adding apparent diffusion coefficient (ADC) features (of DWI imaging) to MRI features, LDA was more powerful (than the univariate analysis) and yielded a classification accuracy of 94.1%, and when adding MRS features to MRI and DTI features, LDA yielded a classification accuracy of 100% over the 3 different types of lesions.[42] However, the field of applying machine learning methods to childhood epilepsy is still in infancy, and currently, there are only few studies that compared the performance of computer-aided system based on machine learning methods with that of conventional (manual, or semi-quantitative) methods. More comparative studies are needed to further reveal the value and potential of machine learning methods in pediatric epilepsy management.

Machine learning methods can automatically process, manage and classify clinical data including multimodal imaging data in pediatric epilepsy. However, the role of multivariate analysis and machine learning is not to substitute clinicians, but to assist clinicians in clinical decision support, to relieve clinicians from complex data inspection (or analysis), to save clinicians from simple repetitive clinical data processing (or management), to help them better focus on important clinical decision-making issues to reduce medical errors, and assist them in improving seizure management.

Current limitations and challenges

Machine learning "black-box" and result interpretation: The mechanisms and logic of some machine learning approaches such as artificial neural network and deep learning network may be hard to interpret, especially when machine learning techniques identify data patterns invisible to humans. For example, AutoLearn system is an

individualized machine learning system that uses an artificial neural network classifier with spectral features to detect focal seizures at a detection rate of 97%.[78] Clinicians and patients do not have to learn and understand the details of the inner workings of such ML methods, but basic knowledge of the overall mechanism of a machine learning method and its potential statistical pitfalls will help clinicians to make sound judgements (e.g., whether a seizure alert given by a machine-learning based system is true or false) and avoid errors.

On the other hand, although there is an abstraction in the mechanism of machine learning methods, machine learning applications shall follow the principle of evidence-based medicine and provide as much information or interpretation as possible. For example, when a machine learning system gives a seizure alert, it needs to provide sample sizes (in the training and test sets), and the detection/prediction accuracy or classification error rate (i.e., the possibility of such seizure occurrence) to support clinical decision-making.

Supervised vs. unsupervised learning: In supervised machine learning, clinician (or expert)-labeled (such as an ictal spike/preictal change, or a lesion) training data is needed for feature classification in seizure detection/prediction, and lesion detection. However, clinician or expert labeling might not be 100% correct, especially for preictal changes. Therefore, unsupervised learning may be needed to let a machine learning method identify hidden or invisible data patterns (e.g., preictal changes) by itself, which might improve seizure detection/prediction, and lesion detection. Further study is needed to explore unsupervised learning in these areas.

Future directions

Improve machine learning methods: Despite the progress made in machine learning applications in pediatric epilepsy, there is still much to explore to improve classification accuracy. First, optimization of data features to seek an optimal feature set will facilitate data feature classification. Second, optimization and standardization of ML classification methods or classifiers will improve classification accuracy. Third, validation methods (such as N-fold cross-validation and leave-one-out) may be standardized to validate machine learning methods and make the results comparable across studies.

In addition, recently developed deep learning techniques have been applied to seizure prediction.[79] Deep learning techniques are promising in complex data feature classification which may help overcome the challenges in seizure detection and prediction, lesion detection and clinical outcome prediction. Confirmatory studies are needed to validate these new machine learning approaches and make them accurate and reliable.

Integrate machine learning-based applications into seizure management system: In order to identify non-random, complex and patient-specific seizure patterns, machine learning algorisms may be integrated into seizure management system in a seizure detection and treatment loop where a patient's data (electroencephalogram (EEG), electrocardiogram (EKG), accelerometer, surface electromyogram, etc.) are continuously measured and analyzed to track seizures. Once a preictal change is identified by the machine learning algorism, a clinician is informed who needs to determine whether it is a false alarm or not, and if not, proper care and treatment shall be provided timely.[9,10]

To this end, a framework that facilitates the development, deployment, validation and regulation of such machine learning-based clinical applications is needed. For instance, benchmark data and measurements as well as criteria of classification/prediction accuracy for multivariate analysis and machine learning-based applications need to be established to aid optimization and standardization of machine learning applications. Further, before machine learning-based clinical applications can be deployed in the clinical settings, it is necessary to run clinical trials to assess the clinical benefits of such applications over conventional systems. Consequently, relevant rules and regulations are needed to guide such clinical trials, and make such machine learning-based systems available to clinicians and patients. Some clinical trials have shown promising results. For instance, a multicenter randomized controlled trial revealed the safety and efficacy of a responsive neurostimulator which detected abnormal eletrocorticographic activity in patients' brain, significantly reduced seizure frequency, and improved quality of life in patients with drug-resistant epilepsy (n=191).[80]

Conclusions

In summary, the studies that this paper reviewed have demonstrated that multivariate analysis and machine learning methods are useful in automated seizure detection on EEG and identification of epileptogenic lesions on imaging. In addition, machine learning approaches can detect preictal changes on EEG and distinguish preictal changes from interictal activities, which makes it possible to predict seizure occurrence. Seizure prediction is promising in improving seizure treatment and enhancing patients' quality of life, but it is challenging to detect complex patient-specific seizure occurrence patterns. Sufficient clinical data and good machine learning algorithms are needed to identify complex seizure occurrence patterns for seizure prediction. Furthermore, outcome studies using multivariate and machine learning methods have identified treatment outcome predictors for outcome evaluation and prediction to enhance epilepsy treatments. To make these multivariate and machine learning methods reliable in clinical settings, confirmatory studies with large samples are warranted to validate and optimize these methods. It is foreseeable that multivariate analysis and machine learning will contribute more to identifying complex patient-specific seizure patterns, epileptogenic lesions, and seizure outcome predictors to improve seizure detection/prediction, lesion detection, and outcome prediction, which will lead to better seizure control to prevent seizure-related accidents in children with epilepsy, reduce mortality rate, minimize the risk of seizure injury, improve quality of life and eventually set them free from seizures.

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Declarations of interest

None.

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