INPLASY

AI-Based EEG Analysis in Rodent Models of Epilepsy: A Systematic Review

INPLASY202470108

doi: 10.37766/inplasy2024.7.0108

Received: 27 July 2024

Published: 27 July 2024

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ADMINISTRATIVE INFORMATION

Support - This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the NeuroInsight Marie Skłodowska-Curie grant agreement No. 101034252. This publication has emanated from research supported in part by a research grant from Science Foundation Ireland (SFI) under Grant Number 16/RC/3948 and co-funded under the European Regional Development Fund and by FutureNeuro industry partners. We acknowledge the Research IT HPC Service at University College Dublin for providing computational facilities and support that contributed to the research results reported in this paper.

Review Stage at time of this submission - Completed and submitted for publication.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202470108

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 July 2024 and was last updated on 27 July 2024.

INTRODUCTION

Review question / Objective RQ1: What rodent models of epilepsy and seizure/epilepsy types have been automatically analysed with machine learning (ML) or deep learning (DL) algorithms?
RQ2: What features and feature engineering techniques have been considered in the classical machine learning detection and prediction of seizures in the rodent model of epilepsy?
RQ3: What ML or DL methods have been exploited in detecting and predicting seizures from EEG of rodent models of epilepsy?
RQ4: What training methodologies and evaluation metrics have been used in the rodent models of epilepsy, and which of the developed DL/ML models have been implemented?

Rationale Epilepsy is a neurological disorder characterised by recurrent seizures. Seizures are transient, vigorous, and synchronised electrical activity in a group of neurons, leading to behavioural alterations in persons or animals. Epilepsy is a global health issue that adversely impacts the social, economic, and psychological well-being of those with the condition.} About 70 million people globally have been diagnosed with epilepsy. sout{EEG} textcolor{red}{Electroencephalogram} devices are the primary method for identifying and monitoring seizures. sout{Ethical issues make it impossible to completely examine the nuances of epilepsy and drug-resistant seizures in clinical settings.} sout{Thus, using} textcolor{red}{The use of} EEG expands the preclinical research involving the long-term recording of neuro-activities in rodent models of epilepsy targeted towards efficient testing of prospective anti-epileptic medications. Typically, trained epileptologists visually analyse the long-term EEG recordings, which is time-consuming and subject to expert variability. Automated epileptiform discharge detection using machine learning or deep learning methods is an effective approach to tackling these challenges.This review aims to evaluate the literature on the application of machine learning and deep learning in analysing EEG epileptiform discharges on rodent models of epilepsy.

Condition being studied Epilepsy is a heterogeneous neurological disease characterised by recurrent seizures (1, 2). The physiologic feature of seizures is the transient excessive and synchronous discharges by a group of neurons in the brain, leading to the behavioural alteration of a person or animal (3). An estimated 70 million people globally have been diagnosed with epilepsy (4), which is a global health burden with adverse social, economic, and psychological impacts on people with epilepsy (5, 6).

The epilepsy research community has devoted decades of time and resources to studying epilepsy and researching anti-seizure drugs (ASDs) to mitigate the symptoms of epilepsy. Despite the number of anti-epileptic drugs available, one-third of people with epilepsy experience resistance to pharmacotherapy, (7) where ASDs fail to control seizures. This group of people bear the major burden of epilepsy in the general population. Thus, a great unmet clinical need exists for identifying and developing new ASDs that efficiently manage pharmaco-resistant spontaneous recurrent seizures (SRSs).

The complexity of epilepsy and pharmaco-resistant seizures can not be thoroughly researched in the clinical setting with humans for ethical reasons (8). Electroencephalography (EEG), introduced by Hans Berger, is a clinical procedure for reading spontaneous neural activities (9). The ability to read the electrical signals in the brain can provide insight into the abnormalities that may occur in the brain. It may be useful in assisting with the diagnosis or assessing the presence of comorbidities in various neurological disorders. With the use of EEG, neurologists can understand the alterations in the human brain that accompany epileptic seizures. Its usage extends to rodent models of epilepsy. The analysis of the rodent brain fluctuations in rodent models of epilepsy uncovers the disease development, leading to understanding disease mechanisms and evaluating the effects of ASDs and experimental treatments. The waveforms in EEG activity that characterise seizures are known as epileptiform discharges (10). Epileptiform discharge is a transient burst of spikes, polyspikes, polyspike-wave and spike-wave complexes with varying shapes and amplitude indicative of cortical hyperexcitability and disruption (10, 11). Generally, epileptiform discharge is categorised into four states: interictal, preictal, ictal, and postictal.

Epileptiform discharge identification includes seizure detection (the identification of ictal discharges), seizure prediction (the identification of preictal discharges), and seizure type classification (the categorisation of the different types of seizures). Increasingly, epilepsy research is moving towards determining the disease-modifying effects of drugs, which requires persistent assessment of brain activities, including epileptiform discharges, through long-term recording of EEG in animal models of epilepsy (13). Traditionally, detecting epileptiform discharges can be achieved through visual analysis of the long-term EEG signal by a team of epileptologists. However, there are certain drawbacks to the visual identification of epileptiform discharges in long-term EEG recordings. In addition to the time spent reviewing the EEG recording, the subjective seizure identification between epileptologists on the same EEG recording due to various seizure morphologies and the similarity of seizure patterns with noise and artefacts is another major challenge.

In contrast to the manual detection of seizures, algorithmic approaches have been explored to analyse EEG signals automatically. Researchers are moving towards improving clinical practice by applying machine learning (ML) to analyse long EEG recordings. Therefore, this study aims to present a systematic literature review to identify the processes and state-of-the-art ML and deep learning (DL) detection of epileptiform discharges in rodent models of epilepsy.

METHODS

Search strategy Selecting precise search terms to retrieve broad and relevant articles was challenging. We combined different search terms and their synonyms into logical search strings (S1-S4). After preliminary searches yielded few articles, we focused on articles published in the last three

decades, between 1st January 1994 and 1st January 2024. Articles not retrieved by the S1 and S2 search strings were retrieved by quoting the search phrases in the S3 and S4 logical search strings. These logical search strings were used to search Google Scholar and PubMed databases. For ease of download, the Google Scholar database was queried through Publis or Perish.
S1: ((EEG OR Electroencephalogram) AND (Seizure detection OR Machine learning seizure detection OR Deep learning seizure detection OR Interictal spike detection OR Ictal spike detection) AND (Rodent model of epilepsy OR Mouse model of epilepsy OR Rat model of epilepsy))

S2: ((EEG OR Electroencephalogram) AND (Seizure prediction OR Machine learning seizure prediction OR Deep learning seizure prediction OR Spike detection OR Preictal spike detection) AND (Rodent model of epilepsy OR Mouse model of epilepsy OR Rat model of epilepsy))

S3: (("EEG" OR "Electroencephalogram" OR "iEEG") AND ("Seizure detection" OR "Machine learning seizure detection" OR "Deep learning seizure detection" OR "Interictal spike detection" OR "Ictal spike detection") AND ("Rodent model of epilepsy" OR "Mouse model of epilepsy" OR "Rat model of epilepsy"))

S4: (("EEG" OR "Electroencephalogram" OR "iEEG") AND ("Seizure prediction" OR "Machine learning seizure prediction" OR "Deep learning seizure prediction" OR "Spike detection" OR "Preictal spike detection") AND ("Rodent model of epilepsy" OR "Mouse model of epilepsy" OR "Rat model of epilepsy"))

A total of 3021 articles were retrieved through the four search strings. Precisely, Google Scholar returned 2443 articles, while PubMed returned 578.

Participant or population Although cellular models are frequently employed initially to clarify molecular pathways in disease processes, animal models are increasingly useful for pre-clinical research in studying human diseases and clinical aspects, (13) and discover new drugs and drug targets (14). In the study of epilepsy and its resistance to ASDs, no singular animal can model the different types of epilepsy (15). Most animals with central nervous systems are likely to experience epilepsy, and dogs, cats, primates, rats, mice and zebrafish have all been used to model different types of epilepsy (16). The selection of a particular animal may be based on practical needs (16). Although humans and rodents such as mice have different neurobiologies, mice are frequently used to model human neurological disorders (17, 18), and recently, rodents (rats and mice) have been prioritised for epilepsy research (16).

Intervention This study is not clinical but AI-based. The review is focused on analysing EEG signals obtained from rodent models of epilepsy.

Comparator Not applicable.

Study designs to be included Defining the research questions, Execution of article searches within specified databases, Filtering articles through the evaluation of their relevance , Data extraction, Synthesizing of results.

Eligibility criteria A total of 3021 articles were retrieved according to the search procedure. After removing 1012 duplicate articles, 2009 articles were left for the eligibility screening. Following the screening of articles for eligibility using the inclusion and exclusion criteria and evaluation of abstracts, 1965 articles were excluded (articles not written in English: 3, other exclusion criteria: 1962), leaving behind 44 articles for further assessment. The abstract evaluation specifically targeted the identification of articles that utilised computational analysis of EEG data collected from rodent models of epilepsy. After reading the full text, 23 studies were discovered to have used non-machine learning and deep learning techniques. These studies were excluded, and 21 articles based on ML/DL techniques met the eligibility criteria. One article from the reference list was also found to be relevant. The articles were independently filtered by two researchers. A total of 22 papers have been considered eligible and included in this review study.

Inclusion Criteria
Conference papers published by ACM, IEEE or Springer
Published between 1st January 1994 and 1st January 2024
Focused on automatic seizure detection and prediction with machine learning and deep-learning techniques
The study is conducted using EEG on rodent models of epilepsy
Full text available
The study reported in the article is empirical

Exclusion Criteria
The study uses EEG from humans or other animals, not rodents.
Full-text inaccessible

Literature review studies, books, short papers/abstract
The study is focused on other neurological disorders (Alzheimer's, Dementia, sleep disorder, etc)
The study uses other clinical methods of determining epilepsy (e.g. genomics)
Studies not written in English
Studies focusing on clinical studies only
Studies performed using other non-machine or deep learning techniques
Journals not listed in Journal Citation Report (JCR).

Information sources These logical search strings were used to search Google Scholar and PubMed databases. For ease of download, the Google Scholar database was queried through Publis or Perish.

Main outcome(s) The study focused on seizure type, features and feature engineering, ML/DL methods, training methodologies, evaluation metrics, and model deployment. We discovered that seizure detection receives more attention than seizure prediction. Also, the number of mice included in the studies was limited, invariably leading to insufficient training data. Amidst the prevalence of drug resistance in focal epilepsy, absence seizures and generalised tonic-clonic seizures have received more attention. Although time-frequency and linear features are proven effective tools for studying dynamic signals, this crucial feature domain has not been utilised. Probabilistic classification has not been appropriately explored to model cross-over EEG signal samples. With the high performance of the models, delay latency, which is a crucial metric in evaluating epileptiform discharge detection, has been greatly ignored. Except for one model, all other models are experimental and lack real-world validation. As important as interpretability is in the biomedical domain, there is a scarcity of intrinsically interpretable epileptiform discharge detectors. Given these limitations in the current studies, further studies are required to develop, deploy, and validate ML/DL models for rodent epileptiform discharge in real-world settings.

Quality assessment / Risk of bias analysis Not applicable.

Strategy of data synthesis Relevant data were gathered and analysed to synthesise and answer the research questions from the included studies. In the process, the following data fields were extracted:
D1: The aim of the
D2: The rodent models of epilepsy
D3: The epileptiform discharge recognition task: detection or prediction of
D4: The feature engineering techniques
D5: Employed ML or DL technique, either classical or a combination of techniques and evaluation
D6: The implementation of the machine learning or deep learning models.

Subgroup analysis Not applicable.

Sensitivity analysis Not applicable.

Language restriction Only studies published in English was considered and included this survey.

Country(ies) involved Republic of Ireland.

Keywords Epilepsy; Electroencephalogram; Epileptiform discharge; Seizure detection; Seizure prediction; Rodent models of epilepsy; Machine learning; Deep learning.

Dissemination plans Objective: This review is intended for researchers in the field of EEG epilepsy detection in rodent models of epilepsy who seek to address the existing gaps in the literature about the approaches proposed in recent years.

Target audience: Data science researchers researching and developing models for detecting epileptiform discharges in the EEG of rodent models of epilepsy. This will enhance pre-clinical research for developing and testing new anti-seizure drugs, thus leading to translation into healthcare.

Key message: This study identifies the gaps in the current literature on detecting epileptiform discharges in the EEG of rodent models of epilepsy.

Dissemination: The article is submitted to the Applied Science Journal.

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