BMJ Open

Computer-assisted analysis of routine EEG to identify hidden biomarkers of epilepsy: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066932
Article Type:	Protocol
Date Submitted by the Author:	26-Jul-2022
Complete List of Authors:	Lemoine, Émile; University of Montreal, Department of Neurosciences; Ecole Polytechnique de Montreal, Institute of Biomedical Engineering Neves Briard, Joel; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Rioux, Bastien; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Podbielski, Renata; University of Montreal Hospital Centre Research Centre Nauche, Bénédicte; University of Montreal Hospital Centre Research Centre Toffa, Denahin; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Keezer, Mark; University of Montreal, Department of Neurosciences; Stichting Epilepsie Instellingen Nederland Lesage, Frederic; Ecole Polytechnique de Montreal, Institute of Biomedical Engineering Nguyen, Dang ; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Bou Assi, Elie; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre
Keywords:	Epilepsy < NEUROLOGY, Neurophysiology < NEUROLOGY, NEUROLOGY

Title: Computer-assisted analysis of routine EEG to identify hidden biomarkers of epilepsy: protocol for a systematic review

Authors

Émile Lemoine[1, 2, 3]
Joel Neves Briard[1, 3]
Bastien Rioux[1, 3]
Renata Podbielski[3]
Bénédicte Nauche[3]
Denahin Toffa[1,3]
Mark Keezer[1,3-5]
Frédéric Lesage[2]
Dang K. Nguyen[1,3]
Elie Bou Assi[1,3]

[1]Department of Neurosciences, University of Montreal, Canada
[2]Institute of biomedical engineering, Polytechnique Montreal, Canada
[3]University of Montreal Hospital Center's Research Center, Canada
[4]School of Public Health, University of Montreal, Canada
[5]Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

Corresponding author

Émile Lemoine, emile.lemoine@umontreal.ca
1051 rue Sanguinet, Montréal, Québec. H2X 3E4

Abstract

Introduction: The diagnosis of epilepsy frequently relies on the visual interpretation of the electroencephalogram (EEG) by a neurologist. The hallmark of epilepsy on EEG is the interictal epileptiform discharge (IED). This marker lacks sensitivity: it is only captured in a small percentage of 30-minute routine EEGs in patients with epilepsy. In the past three decades, there has been growing interest in the use of computational methods to analyze the EEG without relying on the detection of IEDs, but none have made it to the clinical practice. We aim to review the diagnostic accuracy of quantitative methods applied to ambulatory EEG analysis to guide the diagnosis and management of epilepsy.

Methods and analysis: The protocol complies with the recommendations for systematic reviews of diagnostic test accuracy by Cochrane. We will search MEDLINE, EMBASE, EBM reviews, IEEE Explore along with grey literature for articles, conference papers and conference abstracts published after 1961. We will include observational studies that present a computational method to analyze the EEG for the diagnosis of epilepsy in adults or children without relying on the identification of IEDs or seizures. The reference standard is the diagnosis of epilepsy by a physician. We will report the estimated pooled sensitivity and specificity, and receiver operating characteristic area-under-the-curve (ROC AUC) for each marker. If possible, we will perform a meta-analysis of the sensitivity and specificity and ROC AUC for each individual marker. We will assess the risk of bias using an adapted QUADAS-2 tool. We will also describe the algorithms used for signal processing, feature extraction and predictive modeling, and comment on the reproducibility of the different studies.

Ethics and dissemination: Ethical approval was not required. Findings will be disseminated through peer-reviewed publication and presented at conferences related to this field.

PROSPERO registration number: CRD42022292261

Strengths and limitations of this study:

- This systematic review will be the first to critically evaluate the diagnostic accuracy of computational markers of epilepsy on routine EEG, with an emphasis on identifying the barriers towards clinical translation of this technology;
- The publication of this protocol ensures transparency, and evaluation of all studies during screening, selection, and data extraction by independent reviewers reduces the risk of bias in the selection and analysis of included studies;

- High heterogeneity in reporting standards and inclusion criteria is anticipated, possibly preventing the reliable estimation of diagnostic performance metrics;
- Our review will constitute a comprehensive reference of current practices in the automated processing and analysis of routine EEG for epilepsy.

Keywords: Epilepsy – Electroencephalogram – Machine Learning – Diagnosis – Computer-assisted – Biomarker

Word count (abstract): 290

Background

Epilepsy is characterized by an enduring propensity towards epileptic seizures—transient neurological manifestations provoked by a state of abnormal and excessive neuronal activity in the brain[1]. Epilepsy affects over 65 millions of people worldwide, and 10% of the population will experience at least one seizure in their lifetime[2,3]. Epileptic seizures can lead to fractures, road accidents, isolation, anxiety, cognitive decline, and death[4]. In specialized-care settings, the first anti-seizure medication (ASM) achieves seizure freedom in approximately 47% of patients[5]. A prompt diagnosis is key in the prevention of epilepsy-related morbidity and mortality[4].

A history of epileptic seizures or a high recurrence risk after a single seizure are the basis for the definition of epilepsy by the International League Against Epilepsy (ILAE)[1]. Ancillary tests are often needed to estimate seizure recurrence risk after a single seizure. These include the neurological examination, neuroimaging, and the electroencephalogram (EEG).

An EEG records the electrical activity of the brain. It is recommended that all patients who present with a first unprovoked seizure or with new diagnosis of epilepsy undergo an EEG[6,7]. The initial EEG is generally performed with electrodes applied to the patient's scalp (scalp EEG or *routine EEG*) for a duration of 20–40 minutes[8]. The EEG tracing is then interpreted visually by a neurologist, who attempts to identify interictal epileptiform discharges (IEDs; *aka* spikes). IEDs are brief (20–200ms) sharp discharges, clearly emerging from background oscillations, often negative in polarity and sometimes followed by a typical slow wave[8]. The presence of interictal spikes on the EEG is considered a hallmark of epilepsy, as it represents a strong predictor of seizure recurrence[9,10]. Furthermore, the identification of interictal spikes can help localize an epileptic focus that may be amenable to surgical resection, and can guide the withdrawal of ASMs in patients after a prolonged period of seizure freedom[11,12].

The interictal spike has several limitations. It occurs very sporadically: in patients with epilepsy, only 29 – 55% of routine EEGs will capture these transient abnormalities[8]. After a first unprovoked seizure in

adults, the sensitivity of a single routine EEG for detecting epileptiform abnormalities is only 17%[9]. Furthermore, their identification is somewhat subjective: the percent agreement between EEG experts is around 76%[13]. Many physiological transient discharges can be misinterpreted as epileptiform spikes. This can lead to the erroneous diagnosis of epilepsy, with sometimes important consequences[14,15]. In patients labelled with drug-resistant epilepsy, over 25% may have had an erroneous diagnosis as a result of both inadequate history taking and misinterpretation of the EEG[16]. Despite the abundant information on brain activity recorded by the EEG, no other interictal anomalies have been validated for use in clinical settings[1,17,18].

Compared to other neuroimaging modalities, a scalp EEG is inexpensive, easy to acquire, and confers functional information with high temporal resolution[19,20]. Moreover, great effort was put in the last decade by the ILAE in standardizing the equipment, recording and storage of EEG data[10,21]. Decades of research have demonstrated that the automated analysis of EEG can identify hidden differences between with epilepsy and non-epileptic subjects in terms of connectivity[22–24], signal predictability and complexity[25,26], spectral power[27,28], and chaoticity[29]. Computational analysis of EEG holds the promise of extracting information that is invisible to the naked eye of the human interpreter, in an objective and reproducible manner. Discovering new, non-visible markers of epilepsy could increase the diagnostic yield of the EEG, improve its accessibility, and reduce costs, especially in settings where the expertise of a fellowship-trained neurophysiologist is unavailable[18,30]. In spite of this, none of the proposed non-visible markers of epilepsy have made it into clinical practice[10,31].

We will perform a systematic review of diagnostic test accuracy for automated methods of EEG analysis to distinguish between patients with and without epilepsy without relying on the detection of spikes and seizures. The questions that this review addresses are the following: What is the current evidence on the performances of automatically extracted hidden markers of epilepsy for the diagnosis of epilepsy? And what are the different algorithms that have been tested and how does their diagnostic accuracy compare?

Methods

Study design

This will be a systematic review and meta-analysis following guidance from the Cochrane Diagnostic Test Accuracy group. We will report the results according to the PRISMA statement for diagnostic test accuracy (PRISMA-DTA)[32].

Study selection criteria

Type of studies

We will include all studies that describe a computed marker of epilepsy on routine (scalp) EEG which does not explicitly rely on the identification of interictal spikes or ictal activity (seizures). Studies must compare the EEG signal of individuals with and without epilepsy. We will include retrospective or prospective comparative studies enabling the assessment of diagnostic accuracy (cohort or case-control studies). We will exclude studies reporting data on non-human animals only, studies that include only intracranial or critical care EEG recordings, studies that do not include both individuals with and without epilepsy, and studies that are focused solely on seizure/spike detection or on short-term (<24h) seizure prediction. For studies that include multiple EEG types, we will only extract data that meet the inclusion criteria. We restricted the search to studies published after 1961 (the first use of digital EEG)[33]. There are no restrictions for language.

Population

Our population of interest is individuals undergoing routine EEG in a clinical or research setting. A routine EEG is defined as a 20- to 60-minute scalp recording using the international 10–20 electrodes system, with or without prior sleep deprivation. There is no restriction for age groups or diagnoses.

Reference standard

We defined the reference standard as the diagnosis of epilepsy by a physician based on criteria specified by the authors (clinical or para-clinical). These criteria must accord with the definition of epilepsy by the ILAE: having had at least one seizure and long-term enduring predisposition to other unprovoked seizures[1,34].

Index test

The index test is a characteristic or feature which is computationally extracted from the EEG signal to identify patients with epilepsy, without relying on detecting IEDs or seizures. These include measures of connectivity, entropy, chaoticity, and power spectrum density[35]. Also included are statistical models that combine several features or models that take as input the raw or processed EEG.

Search strategy

The search strategy (**Appendix 1**) was developed by two medical librarians specialized in systematic reviews (BN and RP), and peer-reviewed by a senior colleague. We will search MEDLINE (Ovid), EMBASE (Ovid), EBM reviews (Ovid), IEEE Explore along with grey literature for articles, conference papers and conference abstracts. We will use the Covidence platform (Melbourne, Australia) to manage our data for eligibility assessment, selection, and data collection. Two independent reviewers (EL, and either JNB or BR) will screen the records for eligibility using their title and abstract. Any item selected by either reviewer will proceed to the next phase. This process will be repeated on the screened items, this time by consulting the items' full text. A third, senior reviewer (EBA) will settle conflicts as necessary during the final selection.

Data items

Data collection will be performed using Covidence by two independent reviewers (EL and JNB/BR), and conflicts will be resolved by a third author (EBA). Authors of the primary study will be contacted if the

required data are not available in the original publication. Data collection will include the following information:

1. Title and authors of the study, country of sampling, year of publication;
2. Study type: retrospective vs. prospective, design (cohort, case control);
3. Study sample: exclusion and inclusion criteria, number of screened and included patients;
4. Data collection:
    a. Number of patients, number of EEGs, duration of EEG recordings, use of activation procedures (hyperventilation, photic stimulation, sleep deprivation), setting of recording (hospitalized or ambulatory), whether the same protocol was used for all patients;
    b. Number of electrodes, sampling frequency;
    c. If public dataset: reference to the original dataset, dataset name, exclusion/inclusion criteria used on the EEG segments from the dataset;
    d. Participant characteristics: age, sex, comorbidities, number of ASM, age of first seizure;
5. Reference standard: whether a predefined reference standard was used, definition of reference standard, whether all patients underwent the same reference standard, time lapse between reference standard and EEG;
6. Index test:
    a. Pre-processing: artifact detection and removal (automated or manual), filtering method, filtering frequencies, segmentation protocol (whole EEG vs. EEG segments, window size, overlapping vs. non-overlapping segments, manual vs. automated selection of segments), channel selection;
    b. Feature extraction and selection: multi-channel vs. single channel, number of channels selected, whether feature selection was performed, feature extraction algorithm, feature selection method, whether feature selection was applied to data before vs. after excluding testing data;

c. Classification: algorithm(s) used for classification, testing methodology (cross-validation vs. held out testing set);

d. Metric used to report diagnostic performances: ROC AUC, accuracy/sensibility/specificity, F_1-score, reporting of confidence intervals (CI);

7. Diagnostic performances: number of true positives, number of true negatives, number of false positives, number of false negatives, reported accuracy, reported sensitivity, reported specificity, reported F_1-score, reported ROC AUC (if more than one index test is performed on the same patient, we will only consider the first test);
8. Reproducibility: whether every data processing step is detailed, whether methods can be reproduced easily, data availability, code availability, open-source computer libraries referenced.

Risk of bias

The risk of bias of all included studies will be assessed through an adapted version of the QUADAS-2 tool[36]. Risk of bias for each of the following four elements will be evaluated by two independent reviewers (EL and JNB/BR) as low, high, or unclear. Conflicts will be resolved by a third author (EBA). In addition, all publicly available datasets used by at least one of the included studies will be evaluated with the same tool. The following items will be assessed:

1. Patient selection
    a. Is the population representative of clinical practice?
    b. Are inclusion and exclusion criteria identical for cases (patients with epilepsy) and controls?
    c. Are withdrawals explained and appropriate? If individual EEG segments were excluded, were the same criteria used for all segments?
2. Index test
    a. Were the protocols used for recording the EEG identical in all patients, irrespective of the epilepsy diagnosis?

b. Was the index test validated on an independent sample of patients (patients which were not used to identify the index test's threshold or train the learning algorithm)?

3. Reference standard
    a. Are the criteria used for the diagnosis of epilepsy specified and acceptable (likely to correctly classify the target condition)?
    b. Was the reference standard assessment independent and blinded to the index test?
4. Flow and timing
    a. Did the whole sample undergo the reference standard?
    b. Did the whole sample undergo the same reference standard?
    c. Was the time lapse between reference standard and EEG acceptable?
    d. Was the same data used in the index method available at the time of the reference standard?
    e. Were all EEGs included in the analysis?

Data synthesis

We will provide a table summarizing every published study included in the review, comparing the studies' design, population, reference standard, dataset size, data processing methods, and diagnostic accuracy. We will also provide a table summarizing the risk of bias for all items in the adapted QUADAS-2 tool, comparing 1) every individual article included in the review, and 2) every public dataset that is used in ≥ 2 studies.

We will describe the number of patients, number of EEGs, duration of EEGs, and the EEG-duration-per-patient ratio across all included studies. We will report the pooled proportion of patients with focal vs. generalized epilepsy, adult vs. children, structural vs. non-structural epilepsy, and with specific epilepsy syndromes. For every publicly available dataset identified during the review, we will report the number of studies that used that dataset in their work.

We will summarize the methods used by the different articles during the pipeline's algorithm (pre-processing, feature extraction, feature selection, and classification algorithm), along with the proportion of studies that used each method.

Analyses

We will estimate the specificity and sensitivity for each study, using the Wilson score to compute 95% CI. For studies with varying thresholds, we will estimate the ROC AUC and 95% CI.

If there are sufficient (≥ 5) studies that report the number of true/false positives and true/false negatives, we will estimate the pooled sensitivity and specificity of each individual marker using a hierarchical, bivariate generalized linear mixed model[37]. This allows us to account for the correlation between specificity and sensitivity in a single study. If ≥ 5 studies report these numbers for varying thresholds, we will estimate the pooled ROC curve using the Rutter and Gatsonis HSROC model[38]. All analyses will be implemented with the R statistical language. A p-value <0.05 will be considered statistically significant. Given insufficient data for the pooled estimates, we will only describe the diagnostic performances (sensitivity, specificity, ROC AUC) narratively. We will present the results of the analyses with forest plots.

We will quantify heterogeneity using the variances of the logit specificity and sensitivity, as well as the median odds ratio (median OR)[39]. The median OR is a measure of inter-study variance translated on the OR scale. It corresponds to the increase in the odds of being true positive/negative in a patient/control going from a study with lower sensitivity/specificity to a study with higher sensitivity/specificity. For heterogeneity in the ROC plane, we will compute the area of the 95% prediction ellipse[39]. The median OR and the area of the 95% prediction ellipse are easily obtained and interpreted, and take into account the correlation between a single study's specificity and sensitivity in contrast to univariate methods like Cochrane's Q and I^2[37,40]. We will perform subgroup analysis for the following variables: epilepsy type (focal, generalized), epilepsy etiology (structural vs. non-structural), age groups (children (< 18 y.o.), adults (≥ 18 y.o.)), epilepsy syndromes, extracted marker, and dataset used. We will assess heterogeneity

for all subgroup analyses. We will consider a study as belonging to a particular subgroup if ≥80% of the studied population belongs to that subgroup. Sensitivity analysis will be conducted for the main analyses by excluding studies with overall high/unclear risk of bias.

Some studies use m ultiple markers to classify patients with epilepsy from controls (*e.g.,* as input features for a machine learning algorithm). For each marker that is used in ≥ 2 of such studies, we will evaluate the number of studies for which these markers were identified as "important" (selected for the classification task or statistically significant in separating the two classes) and the ratio between the number of studies in which this marker was extracted vs. identified as important.

Reporting bias for sensitivity and specificity will be evaluated by visual inspection of funnel plots.

Discussion

The interictal EEG is key in the diagnosis of epilepsy, solely based on the visual identification of interictal spikes.[41] Despite years of research on computational biomarkers of epilepsy, only these spikes are currently used in clinical settings.[1,17,18] This review aims to systematically evaluate the diagnostic performances of hidden interictal markers of epilepsy on EEG, describe the data processing pipelines favored by the researchers to classify the EEG for epilepsy diagnosis, and identify the pitfalls that prevent clinical translation of these algorithms.

Algorithms have gained growing interest in medicine for their potential to assist diagnosis and guide clinical decision-making.[42] EEG analysis is well-suited for this application due to the complex nature of the EEG signal. Automated extraction of new epilepsy markers on routine EEG could lead to reduced rate of misdiagnosis, increased availability in areas without access to an expert neurophysiologist, and more efficient clinical trials. Research on automatic analysis of EEG data is thriving, in part assisted by the recent increase in computational capacities.[43–50] However, automatic analysis of EEG is not mentioned in any of the high-quality clinical practice guidelines systematically reviewed by the ILAE.[17]

In recent years, increased computational capacities have allowed the development of powerful algorithms that can learn complex representations such as medical images and EEG signals.[43,51,52] A growing number of algorithms have now been approved by the United States Food and Drug Administration for assisting in the diagnosis of several diseases.[53] Recent systematic reviews have found that most of the studies on automated diagnosis using artificial intelligence have high risk of bias, mostly due to patient selection methodology and absence of validation on external data.[54–56] Systematic reviews on computer-based clinical-decision support systems also highlight the need for more robust patient selection.[57–62]

Translation of technology to clinical practice requires strong evidence based on high quality research. This review is important because it will establish the potential of automatic analysis of EEG as a diagnostic tool for epilepsy, and if evidence to support its use is lacking, it will identify the pitfalls that need to be overcome in future research. Also, by systematically describing current practices that are used by research groups, it will serve as a reference for new researchers in the field.

We anticipate that diagnostic accuracy of automatic analysis of EEG for epilepsy will be hard to estimate because of the high heterogeneity between the different dataset used and between the data processing methodology. We also anticipate high risk of bias in many studies, because of the high volume of "proof-of-concept" studies that emphasize computation performances and algorithm development over rigorous diagnostic study methodology. In these cases, we hope to produce recommendations that will assist in bridging the gap between the development of new automated markers and validation in appropriate populations, for ultimate implementation into clinical practice.

List of abbreviations

ASM: anti-seizure medication; CI: confidence interval; EEG: electroencephalogram; IED: interictal epileptiform discharge; ILAE: International League Against Epilepsy; ROC AUC: receiver operating-characteristic area-under-the-curve.

Funding

MRK and DKN report unrestricted educational grants from UCB and Eisai, and research grants for investigator-initiated studies from UCB and Eisai. Émile Lemoine is supported by a scholarship from the Canadian Institute of Health Research. Dang Nguyen is supported by the Canada Research Chairs Program, the Canadian Institutes of Health Research, and Natural Sciences and Engineering Research Council of Canada.

Authors' contributions

EL planned the study, drafted the protocol, reviewed the search strategy, and is the guarantor of the review. DT, FL, DKN, and EBA participated in the design of the study. JNB, BR, DT, MRK, FL, DKN, and EBA provided content expertise and critically reviewed the manuscript and the search strategy. BN and RP designed the search strategy. All authors read and approved the final manuscript.

Competing interests

None of the authors have any competing interest to declare.

Patient and public involvement

No patient involved.

Data sharing statement

Data collected for this study will be available upon reasonable request.

References

1. Fisher, R. S. *et al.* ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* **55**, 475–482 (2014).
2. Ngugi, A. K., Bottomley, C., Kleinschmidt, I., Sander, J. W. & Newton, C. R. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia* **51**, 883–890 (2010).

3. Hauser, W. A. & Beghi, E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* **49 Suppl 1**, 8–12 (2008).

4. Devinsky, O., Spruill, T., Thurman, D. & Friedman, D. Recognizing and preventing epilepsy-related mortality: A call for action. *Neurology* **86**, 779–786 (2016).

5. Kwan, P. & Brodie, M. J. Early identification of refractory epilepsy. *N Engl J Med* **342**, 314–319 (2000).

6. Krumholz, A. *et al.* Practice Parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* **69**, 1996–2007 (2007).

7. Hirtz, D. *et al.* Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. *Neurology* **55**, 616–623 (2000).

8. Pillai, J. & Sperling, M. R. Interictal EEG and the Diagnosis of Epilepsy. *Epilepsia* **47**, 14–22 (2006).

9. Bouma, H. K., Labos, C., Gore, G. C., Wolfson, C. & Keezer, M. R. The diagnostic accuracy of routine electroencephalography after a first unprovoked seizure. *European Journal of Neurology* **23**, 455–463 (2016).

10. Tatum, W. O. *et al.* Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. *Clinical Neurophysiology* **129**, 1056–1082 (2018).

11. Lamberink, H. J. *et al.* Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol* **16**, 523–531 (2017).

12. West, S. *et al.* Surgery for epilepsy. *Cochrane Database of Systematic Reviews* (2019) doi:10.1002/14651858.CD010541.pub3.

13. Jing, J. *et al.* Interrater Reliability of Experts in Identifying Interictal Epileptiform Discharges in Electroencephalograms. *JAMA Neurology* **77**, 49–57 (2020).

14. Amin, U. & Benbadis, S. R. The Role of EEG in the Erroneous Diagnosis of Epilepsy. *J Clin Neurophysiol* **36**, (2019).

15. Kang, J. Y. & Krauss, G. L. Normal Variants Are Commonly Overread as Interictal Epileptiform Abnormalities. *J Clin Neurophysiol* **36**, 257–263 (2019).

16. Smith, D., Defalla, B. A. & Chadwick, D. W. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM* **92**, 15–23 (1999).

17. Sauro, K. M. *et al.* The current state of epilepsy guidelines: A systematic review. *Epilepsia* **57**, 13–23 (2016).

18. Engel Jr, J., Bragin, A. & Staba, R. Nonictal EEG biomarkers for diagnosis and treatment. *Epilepsia Open* **3**, 120–126 (2018).

19. DellaBadia Jr, J., Bell, W. L., Keyes Jr, J. W., Mathews, V. P. & Glazier, S. S. Assessment and cost comparison of sleep-deprived EEG, MRI and PET in the prediction of surgical treatment for epilepsy. *Seizure* **11**, 303–309 (2002).

20. Abdelhady, S., Shokri, H., Fathy, M. & wahid el din, mona M. Evaluation of the direct costs of epilepsy in a sample of Egyptian patients following up in Ain Shams University Hospital. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery* **56**, 112 (2020).

21. Velis, D., Plouin, P., Gotman, J., Da Silva, F. L., & members of the ILAE DMC Subcommittee on Neurophysiology. Recommendations Regarding the Requirements and Applications for Long-term Recordings in Epilepsy. *Epilepsia* **48**, 379–384 (2007).

22. Schmidt, H. *et al.* A computational biomarker of idiopathic generalized epilepsy from resting state EEG. *Epilepsia* **57**, e200–e204 (2016).

23. Lopes, M. A. *et al.* Revealing epilepsy type using a computational analysis of interictal EEG. *Scientific Reports* **9**, 10169 (2019).

24. Verhoeven, T. *et al.* Automated diagnosis of temporal lobe epilepsy in the absence of interictal spikes. *NeuroImage: Clinical* **17**, 10–15 (2018).

25. Ouyang, C.-S., Yang, R.-C., Wu, R.-C., Chiang, C.-T. & Lin, L.-C. Determination of Antiepileptic Drugs Withdrawal Through EEG Hjorth Parameter Analysis. *Int. J. Neur. Syst.* **30**, 2050036 (2020).
26. Zhang, J.-H. *et al.* Personalized prediction model for seizure-free epilepsy with levetiracetam therapy: a retrospective data analysis using support vector machine. *Br J Clin Pharmacol* **84**, 2615–2624 (2018).
27. Oliva, J. T. & Rosa, J. L. G. Differentiation between Normal and Interictal EEG Using Multitaper Spectral Classifiers. in *2018 International Joint Conference on Neural Networks (IJCNN)* 1–8 (2018). doi:10.1109/IJCNN.2018.8489503.
28. Pegg, E. J., Taylor, J. R. & Mohanraj, R. Spectral power of interictal EEG in the diagnosis and prognosis of idiopathic generalized epilepsies. *Epilepsy & Behavior* **112**, 107427 (2020).
29. Jacob, J. E., Sreelatha, V. V., Iype, T., Nair, G. K. & Yohannan, D. G. Diagnosis of epilepsy from interictal EEGs based on chaotic and wavelet transformation. *Analog Integrated Circuits and Signal Processing* **89**, 131–138 (2016).
30. Wahl, B., Cossy-Gantner, A., Germann, S. & Schwalbe, N. R. Artificial intelligence (AI) and global health: how can AI contribute to health in resource-poor settings? *BMJ Global Health* **3**, e000798 (2018).
31. Pitkänen, A. *et al.* Advances in the development of biomarkers for epilepsy. *The Lancet Neurology* **15**, 843–856 (2016).
32. McInnes, M. D. F. *et al.* Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* **319**, 388–396 (2018).
33. November, J. Biomedical computing: Digitizing life in the United States. *Biomedical Computing: Digitizing Life in the United States* 1–344 (2012).
34. Fisher, R. S. *et al.* Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* **46**, 470–472 (2005).

35. Supriya, S., Siuly, S., Wang, H. & Zhang, Y. Automated epilepsy detection techniques from electroencephalogram signals: a review study. *Health Information Science and Systems* **8**, 33 (2020).

36. Whiting, P. F. *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* **155**, 529–536 (2011).

37. Reitsma, J. B. *et al.* Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology* **58**, 982–990 (2005).

38. Rutter, C. M. & Gatsonis, C. A. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* **20**, 2865–2884 (2001).

39. Plana, M. N., Pérez, T. & Zamora, J. New measures improved the reporting of heterogeneity in diagnostic test accuracy reviews: a metaepidemiological study. *Journal of Clinical Epidemiology* **131**, 101–112 (2021).

40. Rücker, G., Schwarzer, G., Carpenter, J. R. & Schumacher, M. Undue reliance on I2 in assessing heterogeneity may mislead. *BMC Medical Research Methodology* **8**, 79 (2008).

41. Smith, S. J. M. EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry* **76**, ii2–ii7 (2005).

42. Obermeyer, Z. & Emanuel, E. J. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. *N Engl J Med* **375**, 1216–1219 (2016).

43. Roy, Y. *et al.* Deep learning-based electroencephalography analysis: a systematic review. *Journal of Neural Engineering* **16**, 051001 (2019).

44. Craik, A., He, Y. & Contreras-Vidal, J. L. Deep learning for electroencephalogram (EEG) classification tasks: a review. *J. Neural Eng.* **16**, 031001 (2019).

45. Rasheed, K. *et al.* Machine Learning for Predicting Epileptic Seizures Using EEG Signals: A Review. *IEEE Rev. Biomed. Eng.* **14**, 139–155 (2020).

46. Gemein, L. A. W. *et al.* Machine-learning-based diagnostics of EEG pathology. *NeuroImage* **220**, 117021 (2020).

47. Mesraoua, B. *et al.* Electroencephalography in epilepsy: look for what could be beyond the visual inspection. *Neurological Sciences* **40**, 2287–2291 (2019).
48. van Diessen, E. *et al.* Brain Network Organization in Focal Epilepsy: A Systematic Review and Meta-Analysis. *PLOS ONE* **9**, e114606 (2014).
49. Faiman, I., Smith, S., Hodsoll, J., Young, A. H. & Shotbolt, P. Resting-state EEG for the diagnosis of idiopathic epilepsy and psychogenic nonepileptic seizures: A systematic review. *Epilepsy & Behavior* **121**, 108047 (2021).
50. Pegg, E. J., Taylor, J. R., Keller, S. S. & Mohanraj, R. Interictal structural and functional connectivity in idiopathic generalized epilepsy: A systematic review of graph theoretical studies. *Epilepsy & Behavior* **106**, (2020).
51. Esteva, A. *et al.* A guide to deep learning in healthcare. *Nature Medicine* **25**, 24–29 (2019).
52. Litjens, G. *et al.* A survey on deep learning in medical image analysis. *Medical Image Analysis* **42**, 60–88 (2017).
53. FDA Cleared AI Algorithms. *American College of Radiology Data Science Institute* https://models.acrdsi.org.
54. Aggarwal, R. *et al.* Diagnostic accuracy of deep learning in medical imaging: a systematic review and meta-analysis. *npj Digital Medicine* **4**, 65 (2021).
55. Liu, X. *et al.* A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. *The Lancet Digital Health* **1**, e271–e297 (2019).
56. Nagendran, M. *et al.* Artificial intelligence versus clinicians: systematic review of design, reporting standards, and claims of deep learning studies. *BMJ* vol. 368 m689 (2020).
57. Riches, N. *et al.* The Effectiveness of Electronic Differential Diagnoses (DDX) Generators: A Systematic Review and Meta-Analysis. *PLoS One* **11**, e0148991 (2016).
58. Bright, T. J. *et al.* Effect of clinical decision-support systems: a systematic review. *Ann Intern Med* **157**, 29–43 (2012).

59. Jaspers, M. W. M., Smeulers, M., Vermeulen, H. & Peute, L. W. Effects of clinical decision-support systems on practitioner performance and patient outcomes: a synthesis of high-quality systematic review findings. *J Am Med Inform Assoc* **18**, 327–334 (2011).

60. Garg, A. X. *et al.* Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* **293**, 1223–1238 (2005).

61. Varghese, J., Kleine, M., Gessner, S. I., Sandmann, S. & Dugas, M. Effects of computerized decision support system implementations on patient outcomes in inpatient care: a systematic review. *J Am Med Inform Assoc* **25**, 593–602 (2018).

62. Vasey, B. *et al.* Association of Clinician Diagnostic Performance With Machine Learning–Based Decision Support Systems: A Systematic Review. *JAMA Network Open* **4**, e211276–e211276 (2021).

Appendix 1: Search strategy

Medline [OVID]

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 13, 2021>

#	Searches	Results
1	exp Electroencephalography/	173584
2	(EEG* or Electroencephalograph* or "electr* encephalograph*" or "brain wave*").tw,kf.	111352
3	1 or 2	201652
4	exp Epilepsy/	118716
5	Epilep*.tw,kf.	152323
6	(seizure* or convulsion* or infantile spasm*).tw,kf.	147989
7	(BCECTS or BECTS).tw,kf.	346
8	(panayiotopoulos adj2 syndrome*).tw,kf.	166
9	((Nodding or dravet or doose or may white or fukhura) adj2 (disease* or syndrome*)).tw,kf.	1407
10	(myoencephalopathy ragged red fiber* disease* or MERRF).tw,kf.	530
11	((Lafora or Unverricht or Landau-Kleffner or Lennox Gastaut) adj2 (disease* or syndrome* or disorder* or seizure*)).tw,kf.	2534
12	or/4-11	244612
13	exp Algorithms/	375058
14	Machine learning.tw,kf.	54804
15	((Deep or hierarchical) adj1 learning).tw,kf.	25347
16	((transfer* or representation* or network*) adj2 learning).tw,kf.	7945
17	((artificial or machine or computer or computational) adj2 intelligence).tw,kf.	19275
18	algorithm*.tw,kf.	299232
19	((data or binary or multiclass or multilabel) adj2 classification).tw,kf.	4758

20	((artificial or computational or computer* or convolutional or connectionist or mathematical) adj2 neur* network*).tw,kf.	28375
21	exp Pattern Recognition, Automated/	26085
22	(Automat* adj2 pattern* adj2 recognition*).tw,kf.	155
23	(Back* propagation* or backpropagation*).tw,kf.	4397
24	exp Bayes Theorem/	40554
25	(Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kf.	21469
26	(feature* adj2 (detecti* or extracti* or learning* or ranking* or selection*)).tw,kf.	21577
27	(Fuzzy or neurofuzzy).tw,kf.	13240
28	exp Markov chains/	15485
29	(Markov adj2 (model* or chain$1 or process*)).tw,kf.	21918
30	K nearest neighbor*.tw,kf.	3529
31	(Kernel$1 adj2 (method* or algorithm* or approach or correlation or estim* or regression or model* or string or tree)).tw,kf.	3950
32	exp Knowledge discovery/	130
33	(Knowledge adj2 discover*).tw,kf.	1589
34	exp Multifactor Dimensionality Reduction/	226
35	Dimensionality reduction*.tw,kf.	3836
36	(predicti* adj2 model*).tw,kf.	79862
37	connectom*.tw,kf.	4980
38	neur* decod*.tw,kf.	361
39	(outlier* adj2 detection*).tw,kf.	893
40	Neural networks, computer/	35265
41	(neural adj2 network*).tw,kf.	70371
42	perceptron*.tw,kf.	3390
43	radial basis function*.tw,kf.	2359
44	random forest*.tw,kf.	13717

45	recursive feature* elimination*.tw,kf.	688
46	recursive partition*.tw,kf.	2380
47	exp Support Vector Machine/	8553
48	(vector* adj2 (machine* or classifi* or network* or regression)).tw,kf.	22248
49	support vector*.tw,kf.	21483
50	rough set*.tw,kf.	397
51	((automat* or electron* or comput* or information or analytic*) adj2 (processing or reasoning)).tw,kf.	38719
52	(quantitative adj2 analys*).tw,kf.	90324
53	(Peak* adj2 (alpha* or frequenc*)).tw,kf.	5453
54	Entrop*.tw,kf.	45494
55	Lyapunov exponent*.tw,kf.	2179
56	Hjorth*.tw,kf.	184
57	Sub-band energ*.tw,kf.	18
58	exp fourier Analysis/	17272
59	(Fourier* or (cyclic adj2 (analys* or series or transform* or approach*)) or FFT).tw,kf.	87439
60	(Hilbert* adj2 transform*).tw,kf.	1008
61	(dimension* adj2 (fractal* or correlation*)).tw,kf.	8106
62	(Hurst adj2 exponent*).tw,kf.	575
63	exp wavelet analysis/	2541
64	(Wavelet* adj2 (analysis or processing or transform*)).tw,kf.	7248
65	phase locking value*.tw,kf.	311
66	Fisher information*.tw,kf.	870
67	Dynamic network*.tw,kf.	1839
68	Principal component* analys*.tw,kf.	47819
69	Independant component* analys*.tw,kf.	2
70	Functional connectivit*.tw,kf.	22171

71	(gradient* boost* or Adaboost*).tw,kf.	3337
72	(QEEG or Quantitative Electroencephalogra*).tw,kf.	1750
73	(chaotic feature* or chaos).tw,kf.	9755
74	comput*.tw,kf.	958508
75	quantitative.tw,kf.	689806
76	or/13-75	2378446
77	(sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp.	11325259
78	di.fs.	2760821
79	or/77-78	11325259
80	3 and 12 and 76 and 79	5990
81	(Animals/ or Models, animal/ or Disease models, animal/) not Humans/	4900078
82	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient* or women or men)).tw,kf.	3315730
83	81 or 82	5542727
84	80 not 83	5627
85	limit 84 to yr="1961 -Current"	5627

EMBASE [OVID]

Embase <1974 to 2021 December 13>

#	Searches	Results
1	exp electroencephalography/	124495
2	(EEG* or Electroencephalograph* or "electr* encephalograph*" or "brain wave*").tw,kf.	146325
3	1 or 2	206929
4	exp epilepsy/	251058
5	Epilep*.tw,kf.	214171
6	(seizure* or convulsion* or infantile spasm*).tw,kf.	216888
7	(BCECTS or BECTS).tw,kf.	509

8	(panayiotopoulos adj2 syndrome*).tw,kf.	249
9	((Nodding or dravet or doose or may white or fukhura) adj2 (disease* or syndrome*)).tw,kf.	2324
10	(myoencephalopathy ragged red fiber* disease* or MERRF).tw,kf.	711
11	((Lafora or Unverricht or Landau-Kleffner or Lennox Gastaut) adj2 (disease* or syndrome* or disorder* or seizure*)).tw,kf.	3984
12	or/4-11	371364
13	Machine learning/	49774
14	Machine learning.tw,kf.	63858
15	((Deep or hierarchical) adj1 learning).tw,kf.	28566
16	exp network learning/	886
17	((transfer* or representation* or network*) adj2 learning).tw,kf.	8790
18	exp artificial intelligence/	55153
19	((artificial or machine or computer or computational) adj2 intelligence).tw,kf.	23056
20	exp algorithm/	465121
21	algorithm*.tw,kf.	381089
22	((data or binary or multiclass or multilabel) adj2 classification).tw,kf.	6087
23	exp artificial neural network/	62826
24	((artificial or computational or computer* or convolutional or connectionist or mathematical) adj2 neur* network*).tw,kf.	33889
25	exp pattern recognition/ or exp automated pattern recognition/	68427
26	(Automat* adj2 pattern* adj2 recognition*).tw,kf.	199
27	exp back propagation/	2553
28	(Back* propagation* or backpropagation*).tw,kf.	5107
29	exp Bayesian learning/	4303
30	(Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kf.	24116
31	exp Feature detection/ or exp feature extraction/ or exp feature learning/ or exp feature ranking/ or exp feature selection/	31030

32	((feature* or representation) adj2 (detecti* or extracti* or learning* or ranking* or selection*)).tw,kf.	28097
33	exp fuzzy system/	4077
34	(fuzzy or neurofuzzy).tw,kf.	16138
35	exp Markov chain/ or exp Markov state model/	12093
36	(Markov adj2 (model* or chain$1 or process*)).tw,kf.	29000
37	exp k nearest neighbor/	4553
38	K nearest neighbor*.tw,kf.	4260
39	kernel method/	6720
40	(Kernel$1 adj2 (method* or algorithm* or approach or correlation or estim* or regression or model* or string or tree)).tw,kf.	4389
41	exp Knowledge discovery/	727
42	(Knowledge adj2 discover*).tw,kf.	1804
43	exp multifactor dimensionality reduction/	864
44	Dimension* reduction*.tw,kf.	7086
45	(predicti* adj2 model*).tw,kf.	105404
46	connectom*.tw,kf.	6225
47	neur* decod*.tw,kf.	433
48	exp Outlier detection/	470
49	(outlier* adj2 detection*).tw,kf.	1010
50	exp artificial neural network/	62826
51	exp Perceptron/	2478
52	perceptron*.tw,kf.	3962
53	(neural adj2 network*).tw,kf.	84786
54	exp radial basis function/	942
55	radial bas* function*.tw,kf.	2927
56	exp random forest/	14358
57	(random adj2 forest*).tw,kf.	17752

58	exp recursive feature elimination/	393
59	recursive feature* elimination*.tw,kf.	860
60	exp recursive partitioning/	462
61	recursive partition*.tw,kf.	3567
62	exp relevance vector machine/ or exp support vector machine/	28522
63	(vector* adj2 (machine* or classifi* or network* or regression)).tw,kf.	27021
64	support vector*.tw,kf.	26266
65	exp rough set/	248
66	rough set*.tw,kf.	531
67	exp online analytical processing/	187
68	((automat* or electron* or comput* or information or analytic*) adj2 (processing or reasoning)).tw,kf.	44254
69	Quantitative analysis/	367570
70	(quantitative adj2 analys*).tw,kf.	113093
71	(Peak* adj2 (alpha* or frequenc*)).tw,kf.	6315
72	Entrop*.tw,kf.	43483
73	Lyapunov exponent*.tw,kf.	1600
74	Hjorth*.tw,kf.	264
75	Sub-band energ*.tw,kf.	23
76	exp Fourier analysis/	10056
77	(Fourier* or (cyclic adj2 (analys* or series or transform* or approach*)) or FFT).tw,kf.	89584
78	Hilbert transform/	183
79	(Hilbert* adj2 transform*).tw,kf.	1253
80	(dimension* adj2 (fractal* or correlation*)).tw,kf.	8947
81	(Hurst adj2 exponent*).tw,kf.	555
82	exp wavelet transform/	2217
83	(Wavelet* adj2 (analysis or processing or transform*)).tw,kf.	9182

84	phase locking value*.tw,kf.	425
85	Fisher information*.tw,kf.	746
86	Dynamic network*.tw,kf.	1972
87	Principal component* analys*.tw,kf.	58526
88	Independent component* analys*.tw,kf.	7493
89	Functional connectivity/	21903
90	Functional connectivit*.tw,kf.	30389
91	(gradient* boost* or Adaboost*).tw,kf.	4097
92	(QEEG or Quantitative Electroencephalogra*).tw,kf.	2861
93	(chaotic feature* or chaos).tw,kf.	8412
94	comput*.tw,kf.	1156500
95	quantitative.tw,kf.	852081
96	or/13-95	2994032
97	(sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp.	14413096
98	di.fs.	3343316
99	or/97-98	14413096
100	3 and 12 and 96 and 99	8362
101	(exp animal/ or animal experiment/ or nonhuman/) not (exp human/ or human experiment/)	6801969
102	(animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey ormonkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.	2062187
103	101 or 102	6872024
104	100 not 103	7906
105	limit 104 to yr="1961 -Current"	7890
106	limit 105 to embase	5134

EBM Reviews [OVID]

All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCA, CCTR, CMR, HTA, and NHSEED <executed on December 14>

#	Searches	Results
1	(EEG* or Electroencephalograph* or "electr* encephalograph*" or "brain wave*").tw,kw,sh.	12245
2	Epilep*.tw,kw,sh.	10099
3	(seizure* or convulsion* or infantile spasm*).tw,kw,sh.	11675
4	(BCECTS or BECTS).tw,kw,sh.	31
5	(panayiotopoulos adj2 syndrome*).tw,kw,sh.	5
6	((Nodding or dravet or doose or may white or fukhura) adj2 (disease* or syndrome*)).tw,kw,sh.	413
7	(myoencephalopathy ragged red fiber* disease* or MERRF).tw,kw,sh.	5
8	((Lafora or Unverricht or Landau-Kleffner or Lennox Gastaut) adj2 (disease* or syndrome* or disorder* or seizure*)).tw,kw,sh.	339
9	or/2-8	16595
10	algorithm*.tw,kw.	16401
11	Machine learning.tw,kw,sh.	1918
12	((Deep or hierarchical) adj1 learning).tw,kw,sh.	708
13	((transfer* or representation* or network*) adj2 learning).tw,kw,sh.	691
14	((artificial or machine or computer or computational) adj2 intelligence).tw,kw,sh.	827
15	algorithm*.tw,kw,sh.	18549
16	((data or binary or multiclass or multilabel) adj2 classification).tw,kw,sh.	335
17	((artificial or computational or computer* or connectionist or convolutional or mathematical) adj2 neur* network*).tw,kw,sh.	782
18	(Automat* adj2 pattern* adj2 recognition*).tw,kw,sh.	15
19	(Back* propagation* or backpropagation*).tw,kw,sh.	66
20	(Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kw,sh.	1841
21	(feature* adj2 (detecti* or extracti* or learning* or ranking* or selection*)).tw,kw,sh.	607

22	(fuzzy or neurofuzzy).tw,kw,sh.	197
23	(Markov adj2 (model* or chain$1 or process*)).tw,kw,sh.	4373
24	K nearest neighbor*.tw,kw,sh.	73
25	(Kernel$1 adj2 (method* or algorithm* or approach or correlation or estim* or regression or model* or string or tree)).tw,kw,sh.	90
26	(Knowledge adj2 discover*).tw,kw,sh.	26
27	Dimensionality reduction*.tw,kw,sh.	73
28	(predicti* adj2 model*).tw,kw,sh.	5378
29	connectom*.tw,kw,sh.	308
30	neur* decod*.tw,kw,sh.	2
31	(outlier* adj2 detection*).tw,kw,sh.	14
32	perceptron*.tw,kw,sh.	76
33	(neural adj2 network*).tw,kw,sh.	1672
34	radial basis function*.tw,kw,sh.	39
35	random forest*.tw,kw,sh.	615
36	recursive feature* elimination*.tw,kw,sh.	30
37	recursive partition*.tw,kw,sh.	282
38	(vector* adj2 (machine* or classifi* or network* or regression)).tw,kw,sh.	555
39	support vector*.tw,kw,sh.	544
40	rough set*.tw,kw,sh.	3
41	((automat* or electron* or comput* or information or analytic*) adj2 (processing or reasoning)).tw,kw,sh.	7510
42	(quantitative adj2 analys*).tw,kw,sh.	8960
43	(Peak* adj2 (alpha* or frequenc*)).tw,kw,sh.	357
44	Entrop*.tw,kw,sh.	951
45	Lyapunov exponent*.tw,kw,sh.	37
46	Hjorth*.tw,kw,sh.	29
47	Sub-band energ*.tw,kw,sh.	0

48	(Fourier* or (cyclic adj2 (analys* or series or transform* or approach*)) or FFT).tw,kw,sh.	1043
49	(Hilbert* adj2 transform*).tw,kw,sh.	19
50	(dimension* adj2 (fractal* or correlation*)).tw,kw,sh.	184
51	(Hurst adj2 exponent*).tw,kw,sh.	14
52	(Wavelet* adj2 (analysis or processing or transform*)).tw,kw,sh.	126
53	phase locking value*.tw,kw,sh.	11
54	Fisher information*.tw,kw,sh.	7
55	Dynamic network*.tw,kw,sh.	12
56	Principal component* analys*.tw,kw,sh.	1207
57	Independant component* analys*.tw,kw,sh.	0
58	Functional connectivit*.tw,kw,sh.	2220
59	(gradient* boost* or Adaboost*).tw,kw,sh.	168
60	(QEEG or Quantitative Electroencephalogra*).tw,kw,sh.	448
61	(chaotic feature* or chaos).tw,kw,sh.	141
62	comput*.tw,kw,sh.	80820
63	quantitative.tw,kw,sh.	33706
64	or/10-63	145496
65	(sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp.	810011
66	di.tw,kw,sh.	17162
67	65 or 66	811399
68	1 and 9 and 64 and 67	350
69	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient* or women or men)).tw,kw,sh.	5147
70	68 not 69	346
71	limit 70 to yr="1961 -Current" [Limit not valid in DARE; records were retained]	321
72	remove duplicates from 71	315

IEEE Xplore

<executed on December 14>

(((((((((All Metadata:predicted OR All Metadata:prediction OR All Metadata:predictions OR All Metadata:predicting OR All Metadata:predictive OR All Metadata:predictor OR All Metadata:predictors OR All Metadata:predicts OR All Metadata:predictability OR All Metadata:predictable OR All Metadata:predictably OR All Metadata:predictively OR All Metadata:predictiveness))) OR ((All Metadata:sensitivity OR All Metadata:sensitively OR All Metadata:sensitiveness OR All Metadata:sensitive OR All Metadata:sensitivities))) OR ((All Metadata:diagnose OR All Metadata:diagnosis OR All Metadata:diagnosed OR All Metadata:diagnoses OR All Metadata:diagnostic OR All Metadata:diagnosing OR All Metadata:diagnosable OR All Metadata:diagnostics OR All Metadata:diagnoseable OR All Metadata:diagnostical OR All Metadata:diagnostician OR All Metadata:diagnosticians OR All Metadata:diagnostically))) AND ((No Keywords Specified))) AND ((No Keywords Specified))) AND ((Index Terms:EEG) OR (Index Terms:Electroencephalograph*) OR (Index Terms: "electr* encephalograph*") OR (Index Terms: "brain wave") OR (Index Terms:"brain waves"))) OR ((Document Title:EEG) OR (Document Title:Electroencephalograph*) OR (Document Title:"electr* encephalograph*") OR (Document Title:"brain wave") OR (Document Title:"brain waves"))) AND ((Index Terms:epilep*) OR (Document Title:seizure OR Document Title:seizures OR Document Title:convulsion OR Document Title:convulsions OR Document Title:"infantile spasm" OR Document Title:"infantile spasms"))	2492

Google Scholar (using Publish or Perish)

<executed on December 21>

Electroencephalogram epilepsy [title], machine learning algorithm* diagnos* [keywords]	32 selected articles out of 32
Electroencephalography epilepsy [title], machine learning algorithm* diagnos* [keywords]	21 selected article out of 21
EEG epilepsy [title], machine learning algorithm* diagnos* [keywords]	433 sur 433

Grey literature

Alberta: Health evidence reviews

https://www.alberta.ca/health-evidence-reviews.aspx

Electroencephalography	0 selected articles out of 1
EEG	0 selected articles out of 3

Canadian Agency for Drug and Technologies in Health

https://www.cadth.ca/search?keywords

Electroencephalography	0 selected articles out of 1
EEG	0 selected articles out of 4

Health Quality Council of Alberta

https://hqca.ca/studies-and-reviews/

Electroencephalography	0 selected articles out of 0
EEG	0 selected articles out of 0

Health Quality Ontario: Health Technology Assessment

Quality Standards - Health Quality Ontario (HQO) (hqontario.ca)

Electroencephalography	1 selected article out of 7
EEG	1 selected article out of 5

INESS

https://www.inesss.qc.ca/en/publications/publications.html?tx_solr%5Bq%5D=EEG

électroencéphalographie	0 selected articles out of 5
EEG	0 selected articles out of 0

McGill University Health Centre (MUHC). Technology Assessment Unit Reports

https://muhc.ca/tau/page/tau-reports

Electroencephalography	0 selected article out of 0
EEG	0 selected articles out of 3

Newfoundland & Labrador Centre For Applied Health Research

http://www.nlcahr.mun.ca/CHRSP/CompletedCHRSP.php

Electroencephalography AND epilepsy	0 selected articles out of 37
Electroencephalogram AND epilepsy	0 selected articles out of 34
EEG AND epilepsy	0 selected articles out of 28

The Ottawa Hospital Research institute: Knowledge Synthesis Group

http://www.ohri.ca/ksgroup/

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG AND epilepsy	0 selected articles out of 7

Programs for Assessment of Technology in Health

https://www.path-hta.com/research-1

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

The International Network of Agencies for Health Technology Assessment

Publications - INAHTA

Electroencephalography	0 selected articles out of 1
Electroencephalogram	0 selected articles out of 4
EEG	0 selected articles out of 4

Horizon Scanning

Horizon Scanning - Australia and New Zealand Horizon Scanning Network - Technologies Assessed

Electroencephalography	0 selected articles out of 1
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

Austrian Academy of Sciences

https://www.oeaw.ac.at/en/

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 2

Austrian Institute Of Health Technology Assessment

Welcome to Repository of AIHTA GmbH - Repository of AIHTA GmbH (lbg.ac.at)

Electroencephalography	0 selected articles out of 4
Electroencephalogram	0 selected articles out of 0

EEG	0 selected articles out of 2

KCE: Belgian health Knowledge Center

All reports - KCE (fgov.be)

Electroencephalography	0 selected articles out of 1
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 1
électroencéphalographie	0 selected article out of 1

CEDIT, the Hospital-Based HTA Agency Of AP-HP

Recommendations and Reports | Cedit (aphp.fr)

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 1
électroencéphalographie	0 selected article out of 0

Haute Autorité de Santé

Haute Autorité de Santé - Résultat de recherche (has-sante.fr)

EEG	1 selected article out of 218
électroencéphalographie	0 selected article out of 27

Health Information and Quality Autority

Health Technology Assessments | HIQA

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

Irish Health Repository

Lenus the Irish Health Repository

Title: Electroencephalography AND epilepsy	1 selected article out of 51
Electroencephalogram	0 selected articles out of 3
Title: EEG AND epilepsy	0 selected articles out of 51

Norwegian Institute of Public Health

Norwegian Institute of Public Health - NIPH (fhi.no)

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 3

Swedish Agency for Health Technology Assessment And Assessment Of Social Services Home (sbu.se)

Electroencephalography	0 selected articles out of 2
Electroencephalogram	0 selected articles out of 2
EEG	0 selected articles out of 4

Healthcare Improvement Scotland

Healthcare Improvement Scotland

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

National Institute for Health and Care Excellence

NICE | The National Institute for Health and Care Excellence

electroencephalography AND epilepsy	0 selected articles out of 2
Electroencephalogram AND epilepsy	1 selected article out of 5
EEG	0 selected articles out of 9

NIHR Innovation Observatory

Innovation Observatory | Next generation search tools for the next generation. (nihr.ac.uk)

Electroencephalography	1 selected article out of 2
Electroencephalogram	0 selected articles out of 1
EEG	0 selected articles out of 5

National institute for health Research

Research Programmes (nihr.ac.uk)

electroencephalography AND epilepsy	1 selected article out of 67
Electroencephalogram AND epilepsy	0 selected articles out of 67
EEG	0 selected articles out of 67

Agency for Healthcare Research and Quality : Technology Assessment Program

Technology Assessment Program | Agency for Healthcare Research and Quality (ahrq.gov)

Electroencephalography AND epilepsy AND diagnosis	0 selected articles out of 1
Electroencephalogram AND epilepsy AND diagnosis	0 selected articles out of 78
EEG AND epilepsy AND diagnosis	0 selected articles out of 83

Agency for Healthcare Research and Quality : Evidence-Based Reports

Search Evidence-Based Reports | Agency for Healthcare Research and Quality (ahrq.gov)

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG AND epilepsy	0 selected articles out of 4

Google

intitle: Electroencephalography AND epilepsy AND machine learning AND diagnosis	3 selected articles out of 9
intitle: Electroencephalogram AND epilepsy AND machine learning AND diagnosis	0 selected articles out of 9
intitle: EEG AND epilepsy AND machine learning AND diagnosis	1 selected articles out of 9
intitle: Electroencephalography AND epilepsy AND algorithm AND diagnosis	0 selected articles out of 9
intitle: Electroencephalogram AND epilepsy AND algorithm AND diagnosis	0 selected articles out of 9
intitle: EEG AND epilepsy AND algorithm AND diagnosis	0 selected articles out of 9

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☐	24
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	265 – 270
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	265 – 270
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	265 – 270
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	265 – 270
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	29 – 70
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	71 – 75

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	82 – 106
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	107 – 116
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	App. 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	111 – 116
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	111 – 116
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	111 – 116
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	118 – 154
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	149 – 152
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	156 – 182
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	184 – 188
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	198 – 221
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	198 – 221
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	189 – 196
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☒	☐	220 – 227

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	NA

BMJ Open

Computer-assisted analysis of routine electroencephalogram to identify hidden biomarkers of epilepsy: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-066932.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Dec-2022
Complete List of Authors:	Lemoine, Émile; University of Montreal, Department of Neurosciences; Ecole Polytechnique de Montreal, Institute of Biomedical Engineering Neves Briard, Joel; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Rioux, Bastien; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Podbielski, Renata; University of Montreal Hospital Centre Research Centre Nauche, Bénédicte; University of Montreal Hospital Centre Research Centre Toffa, Denahin; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Keezer, Mark; University of Montreal, Department of Neurosciences; Stichting Epilepsie Instellingen Nederland Lesage, Frederic; Ecole Polytechnique de Montreal, Institute of Biomedical Engineering Nguyen, Dang ; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre Bou Assi, Elie; University of Montreal, Department of Neurosciences; University of Montreal Hospital Centre Research Centre
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Epidemiology, Diagnostics, Health informatics
Keywords:	Epilepsy < NEUROLOGY, Neurophysiology < NEUROLOGY, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, NEUROLOGY

Title: Computer-assisted analysis of routine electroencephalogram to identify hidden biomarkers of epilepsy: protocol for a systematic review

Authors

Émile Lemoine[1, 2, 3]
Joel Neves Briard[1, 3]
Bastien Rioux[1, 3]
Renata Podbielski[3]
Bénédicte Nauche[3]
Denahin Toffa[1,3]
Mark Keezer[1,3-5]
Frédéric Lesage[2]
Dang K. Nguyen[1,3]
Elie Bou Assi[1,3]

[1]Department of Neurosciences, University of Montreal, Canada
[2]Institute of biomedical engineering, Polytechnique Montreal, Canada
[3]University of Montreal Hospital Center's Research Center, Canada
[4]School of Public Health, University of Montreal, Canada
[5]Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

Corresponding author

Émile Lemoine, emile.lemoine@umontreal.ca
1051 rue Sanguinet, Montréal, Québec. H2X 3E4

Abstract

Introduction: The diagnosis of epilepsy frequently relies on the visual interpretation of the electroencephalogram (EEG) by a neurologist. The hallmark of epilepsy on EEG is the interictal epileptiform discharge (IED). This marker lacks sensitivity: it is only captured in a small percentage of 30-minute routine EEGs in patients with epilepsy. In the past three decades, there has been growing interest in the use of computational methods to analyze the EEG without relying on the detection of IEDs, but none have made it to the clinical practice. We aim to review the diagnostic accuracy of quantitative methods applied to ambulatory EEG analysis to guide the diagnosis and management of epilepsy.

Methods and analysis: The protocol complies with the recommendations for systematic reviews of diagnostic test accuracy by Cochrane. We will search MEDLINE, EMBASE, EBM reviews, IEEE Explore along with grey literature for articles, conference papers and conference abstracts published after 1961. We will include observational studies that present a computational method to analyze the EEG for the diagnosis of epilepsy in adults or children without relying on the identification of IEDs or seizures. The reference standard is the diagnosis of epilepsy by a physician. We will report the estimated pooled sensitivity and specificity, and receiver operating characteristic area-under-the-curve (ROC AUC) for each marker. If possible, we will perform a meta-analysis of the sensitivity and specificity and ROC AUC for each individual marker. We will assess the risk of bias using an adapted QUADAS-2 tool. We will also describe the algorithms used for signal processing, feature extraction and predictive modeling, and comment on the reproducibility of the different studies.

Ethics and dissemination: Ethical approval was not required. Findings will be disseminated through peer-reviewed publication and presented at conferences related to this field.

PROSPERO registration number: CRD42022292261

Strengths and limitations of this study:

- This systematic review will be the first to critically evaluate the diagnostic accuracy of computational markers of epilepsy on routine EEG, with an emphasis on identifying the barriers towards clinical translation of this technology;
- The publication of this protocol ensures transparency, and evaluation of all studies during screening, selection, and data extraction by independent reviewers reduces the risk of bias in the selection and analysis of included studies;

- High heterogeneity in reporting standards and inclusion criteria is anticipated, possibly preventing the reliable estimation of diagnostic performance metrics;
- Our review will constitute a comprehensive reference of current practices in the automated processing and analysis of routine EEG for epilepsy.

Keywords: Epilepsy – Electroencephalogram – Machine Learning – Diagnosis – Computer-assisted – Biomarker

Word count (abstract): 290

Background

Epilepsy is characterized by an enduring propensity towards epileptic seizures—transient neurological manifestations provoked by a state of abnormal and excessive neuronal activity in the brain[1]. Epilepsy affects over 65 million people worldwide, and 10% of the population will experience at least one seizure in their lifetime[2,3]. Epileptic seizures can lead to fractures, road accidents, isolation, anxiety, cognitive decline, and death[4]. In specialized-care settings, the first anti-seizure medication (ASM) achieves seizure freedom in approximately 47% of patients[5]. A prompt diagnosis is key in the prevention of epilepsy-related morbidity and mortality[4].

A history of epileptic seizures or a high recurrence risk after a single seizure are the basis for the definition of epilepsy by the International League Against Epilepsy (ILAE)[1]. Ancillary tests are often needed to estimate seizure recurrence risk after a single seizure. These include the neurological examination, neuroimaging, and the electroencephalogram (EEG).

An EEG records the electrical activity of the brain. It is recommended that all patients who present with a first unprovoked seizure or with new diagnosis of epilepsy undergo an EEG[6,7]. The initial EEG is generally performed with electrodes applied to the patient's scalp (scalp EEG or *routine EEG*) for a duration of 20–40 minutes[8]. The EEG tracing is then interpreted visually by a neurologist, who attempts to identify interictal epileptiform discharges (IEDs; *aka* spikes). IEDs are brief (20–200ms) sharp discharges, clearly emerging from background oscillations, often negative in polarity and sometimes followed by a typical slow wave[8]. The presence of interictal spikes on the EEG is considered a hallmark of epilepsy, as it represents a strong predictor of seizure recurrence[9,10]. Furthermore, the identification of interictal spikes can help localize an epileptic focus that may be amenable to surgical resection, and can guide the withdrawal of ASMs in patients after a prolonged period of seizure freedom[11,12].

The interictal spike has several limitations. It occurs very sporadically: in patients with epilepsy, only 29 – 55% of routine EEGs will capture these transient abnormalities[8]. After a first unprovoked seizure in

adults, the sensitivity of a single routine EEG for detecting epileptiform abnormalities is only 17%[9]. Furthermore, their identification is somewhat subjective: the percent agreement between EEG experts is around 76%[13]. Many physiological transient discharges can be misinterpreted as epileptiform spikes. This can lead to the erroneous diagnosis of epilepsy, with sometimes important consequences[14,15]. In patients labelled with drug-resistant epilepsy, over 25% may have had an erroneous diagnosis as a result of both inadequate history taking and misinterpretation of the EEG[16]. Despite the abundant information on brain activity recorded by the EEG, no other interictal anomalies have been validated for use in clinical settings[1,17,18].

Compared to other neuroimaging modalities, a scalp EEG is inexpensive, easy to acquire, and confers functional information with high temporal resolution[19,20]. Moreover, great effort was put in the last decade by the ILAE in standardizing the equipment, recording and storage of EEG data[10,21]. Decades of research have suggested that the automated analysis of EEG can identify hidden differences between with epilepsy and non-epileptic subjects in terms of connectivity[22–24], signal predictability and complexity[25,26], spectral power[27,28], and chaoticity[29]. Computational analysis of EEG holds the promise of extracting information that is invisible to the naked eye of the human interpreter, in an objective and reproducible manner. Discovering new, non-visible markers of epilepsy could increase the diagnostic yield of the EEG, improve its accessibility, and reduce costs, especially in settings where the expertise of a fellowship-trained neurophysiologist is unavailable[18,30]. In spite of this, none of the proposed non-visible markers of epilepsy have made it into clinical practice[10,31]. This discrepancy calls attention to the lack of comprehensible and systematic evaluation of these new methods.

We will perform a systematic review of diagnostic test accuracy for automated methods of interictal EEG analysis to distinguish between patients with and without epilepsy, without relying on the detection of spikes. The questions that this review addresses are the following: What is the current evidence on the performances of automatically extracted hidden markers compared to the clinical diagnosis of epilepsy by

a physician? What is the benefit over the visual identification of IEDs on routine EEG? And what are the different algorithms that have been tested and how does their diagnostic accuracy compare?

Methods

Study design

This will be a systematic review and meta-analysis following guidance from the Cochrane Diagnostic Test Accuracy group. We will report the results according to the PRISMA statement for diagnostic test accuracy (PRISMA-DTA)[32].

Study selection criteria

Type of studies

We will include all studies that describe a computed marker of epilepsy on routine (scalp) EEG which does not explicitly rely on the identification of interictal spikes or ictal activity (seizures). Studies must compare the EEG signal of individuals with and without epilepsy. We will include retrospective or prospective comparative studies enabling the assessment of diagnostic accuracy (cohort or case-control studies). We will exclude studies reporting data on non-human animals only, studies that include only intracranial or critical care EEG recordings, studies that do not include both individuals with and without epilepsy, and studies that are focused solely on seizure/spike detection or on short-term (<24h) seizure prediction. For studies that include multiple EEG types, we will only extract data that meet the inclusion criteria. We restricted the search to studies published after 1961 (the first use of digital EEG)[33]. There are no restrictions for language.

Population

Our population of interest is individuals undergoing routine EEG in a clinical or research setting. A routine EEG is defined as a 20- to 60-minute scalp recording using the international 10–20 electrodes system, with or without prior sleep deprivation. There is no restriction for age groups or diagnoses.

Reference standard

We defined the reference standard as the diagnosis of epilepsy by a physician based on criteria specified by the authors (clinical or para-clinical). These criteria must accord with the definition of epilepsy by the ILAE: having had at least one seizure and long-term enduring predisposition to other unprovoked seizures[1,34].

Index test

The index test is a characteristic or feature which is computationally extracted from the EEG signal to identify patients with epilepsy, without relying on detecting IEDs or seizures. These include measures of connectivity, entropy, chaoticity, and power spectrum density[35]. Also included are statistical models that combine several features or models that take as input the raw or processed EEG.

Search strategy

The search strategy (**Appendix 1**) was developed by two medical librarians specialized in systematic reviews (BN and RP), and peer-reviewed by a senior colleague. We will search MEDLINE (Ovid), EMBASE (Ovid), EBM reviews (Ovid), IEEE Explore along with grey literature for articles, conference papers and conference abstracts. We will use the Covidence platform (Melbourne, Australia) to manage our data for eligibility assessment, selection, and data collection. Two independent reviewers (EL, and either JNB or BR) will screen the records for eligibility using their title and abstract. Any item selected by either reviewer will proceed to the next phase. This process will be repeated on the screened items, this time by consulting the items' full text. A third, senior reviewer (EBA) will settle conflicts as necessary during the final selection.

Data items

Data collection will be performed using Covidence by two independent reviewers (EL and JNB/BR), and conflicts will be resolved by a third author (EBA). Authors of the primary study will be contacted if the required data are not available in the original publication. Data collection will include the following information:

1. Title and authors of the study, country of sampling, year of publication;
2. Study type: retrospective vs. prospective, design (cohort, case control);
3. Study sample: exclusion and inclusion criteria, number of screened and included patients;
4. Data collection:
    a. Number of patients, number of EEGs, duration of EEG recordings, use of activation procedures (hyperventilation, photic stimulation, sleep deprivation), setting of recording (hospitalized or ambulatory), whether the same protocol was used for all patients;
    b. Number of electrodes, sampling frequency;
    c. If public dataset: reference to the original dataset, dataset name, exclusion/inclusion criteria used on the EEG segments from the dataset;
    d. Participant characteristics: age, sex, comorbidities, number of ASM, age of first seizure;
5. Reference standard: whether a predefined reference standard was used, definition of reference standard, whether all patients underwent the same reference standard, time lapse between reference standard and EEG;
6. Index test:
    a. Pre-processing: artifact detection and removal (automated or manual), filtering method, filtering frequencies, segmentation protocol (whole EEG vs. EEG segments, window size, overlapping vs. non-overlapping segments, manual vs. automated selection of segments), channel selection;

b. Feature extraction and selection: multi-channel vs. single channel, number of channels selected, whether feature selection was performed, feature extraction algorithm, feature selection method, whether feature selection was applied to data before vs. after excluding testing data;

c. Classification: algorithm(s) used for classification, testing methodology (cross-validation vs. held out testing set);

d. Metric used to report diagnostic performances: ROC AUC, accuracy/sensibility/specificity, F_1-score, reporting of confidence intervals (CI);

7. Diagnostic performances: number of true positives, number of true negatives, number of false positives, number of false negatives, reported accuracy, reported sensitivity, reported specificity, reported F_1-score, reported ROC AUC (if more than one index test is performed on the same patient, we will only consider the first test);
8. Reproducibility: whether every data processing step is detailed, whether methods can be reproduced easily, data availability, code availability, open-source computer libraries referenced.

Risk of bias

The risk of bias of all included studies will be assessed through an adapted version of the QUADAS-2 tool[36]. Risk of bias for each of the following four elements will be evaluated by two independent reviewers (EL and JNB/BR) as low, high, or unclear. Conflicts will be resolved by a third author (EBA). In addition, all publicly available datasets used by at least one of the included studies will be evaluated with the same tool. The following items will be assessed:

1. Patient selection
    a. Is the population representative of clinical practice?
    b. Are inclusion and exclusion criteria identical for cases (patients with epilepsy) and controls?

c. Are withdrawals explained and appropriate? If individual EEG segments were excluded, were the same criteria used for all segments?

2. Index test
   a. Were the protocols used for recording the EEG identical in all patients, irrespective of the epilepsy diagnosis?
   b. Was the index test validated on an independent sample of patients (patients which were not used to identify the index test's threshold or train the learning algorithm)?
3. Reference standard
   a. Are the criteria used for the diagnosis of epilepsy specified and acceptable (likely to correctly classify the target condition)?
   b. Was the reference standard assessment independent and blinded to the index test?
4. Flow and timing
   a. Did the whole sample undergo the reference standard?
   b. Did the whole sample undergo the same reference standard?
   c. Was the time lapse between reference standard and EEG acceptable?
   d. Was the same data used in the index method available at the time of the reference standard?
   e. Were all EEGs included in the analysis?

Data synthesis

We will provide a table summarizing every published study included in the review, comparing the studies' design, population, reference standard, dataset size, data processing methods, and diagnostic accuracy. We will also provide a figure that summarizes the risk of bias for each item in the adapted QUADAS-2 tool, comparing 1) every individual article included in the review, and 2) every public dataset that is used in ≥ 2 studies.

We will describe the number of patients, number of EEGs, duration of EEGs, and the EEG-duration-per-patient ratio across all included studies. We will report the pooled proportion of patients with focal vs. generalized epilepsy, adult vs. children, structural vs. non-structural epilepsy, IEDs on EEG, and with specific epilepsy syndromes. For every publicly available dataset identified during the review, we will report the number of studies that used that dataset in their work.

We will summarize in a table the methods used by the different articles during the pipeline's algorithm (pre-processing, feature extraction, feature selection, and classification algorithm), along with the proportion of studies that used each method.

Analyses

We will estimate the specificity and sensitivity for each study, using the Wilson score to compute 95% CI. For studies with varying thresholds, we will estimate the ROC AUC and 95% CI.

If there are sufficient (≥ 5) studies that report the number of true/false positives and true/false negatives, we will estimate the pooled sensitivity and specificity of each individual marker using a hierarchical, bivariate generalized linear mixed model[37]. This allows us to account for the correlation between specificity and sensitivity in a single study. If ≥ 5 studies report these numbers for varying thresholds, we will estimate the pooled ROC curve using the Rutter and Gatsonis HSROC model[38]. All analyses will be implemented with the R statistical language. A p-value <0.05 will be considered statistically significant. Given insufficient data for the pooled estimates, we will only describe the diagnostic performances (sensitivity, specificity, ROC AUC) narratively. We will present the results of the analyses with forest plots. We will compare the performance of the computational markers for the diagnosis of epilepsy to the visual identification of IEDs on EEG.[9]

We will quantify heterogeneity using the variances of the logit specificity and sensitivity, as well as the median odds ratio (median OR)[39]. The median OR is a measure of inter-study variance translated on the OR scale. It corresponds to the increase in the odds of being true positive/negative in a patient/control going from a study with lower sensitivity/specificity to a study with higher sensitivity/specificity. For

heterogeneity in the ROC plane, we will compute the area of the 95% prediction ellipse and present the results on a scatterplot in the ROC plane.[39] The median OR and the area of the 95% prediction ellipse are easily obtained and interpreted, and take into account the correlation between a single study's specificity and sensitivity in contrast to univariate methods like Cochrane's Q and I^2[37,40]. We will perform subgroup analysis for the following variables: epilepsy type (focal, generalized), epilepsy etiology (structural vs. non-structural), presence of IEDs, age groups (children (< 18 y.o.), adults (≥ 18 y.o.)), epilepsy syndromes, extracted marker, and dataset used. We will also perform a subgroup analysis for populations with a higher prevalence of IEDs without epilepsy (cerebral palsy, autism spectrum disorder, attention deficit disorder)[41] and for extra-temporal vs. temporal focal epilepsy. We will assess heterogeneity for all subgroup analyses. We will consider a study as belonging to a particular subgroup if ≥80% of the studied population belongs to that subgroup. Sensitivity analysis will be conducted for the main analyses by excluding studies with overall high/unclear risk of bias.

Some studies use multiple markers to classify patients with epilepsy from controls (*e.g.,* as input features for a machine learning algorithm). For each marker that is used in ≥ 2 of such studies, we will evaluate the number of studies for which these markers were identified as "important" (selected for the classification task or statistically significant in separating the two classes) and the ratio between the number of studies in which this marker was extracted vs. identified as important.

Reporting bias for sensitivity and specificity will be evaluated by visual inspection of funnel plots.

Patient and public involvement

No patients will be involved for this study.

Discussion

The interictal EEG is key in informing the diagnosis of epilepsy, solely based on the visual identification of interictal spikes.[42] Despite years of research on computational biomarkers of epilepsy, only these

spikes are currently used in clinical settings.[1,17,18] This review aims to systematically evaluate the performances of hidden interictal markers of epilepsy on EEG against the clinical diagnosis by a physician, describe the data processing pipelines favored by the researchers to classify the EEG for epilepsy diagnosis, and identify the pitfalls that prevent clinical translation of these algorithms.

Algorithms have gained growing interest in medicine for their potential to assist diagnosis and guide clinical decision-making.[43] EEG analysis is well-suited for this application due to the complex nature of the EEG signal. Automated extraction of new epilepsy markers on routine EEG could lead to reduced rate of misdiagnosis, increased availability in areas without access to an expert neurophysiologist, and more efficient clinical trials. Research on automatic analysis of EEG data is thriving, in part assisted by the recent increase in computational capacities.[44–51] However, automatic analysis of EEG is not mentioned in any of the high-quality clinical practice guidelines systematically reviewed by the ILAE.[17]

In recent years, increased computational capacities have allowed the development of powerful algorithms that can learn complex representations such as medical images and EEG signals.[44,52,53] A growing number of algorithms have now been approved by the United States Food and Drug Administration for assisting in the diagnosis of several diseases.[54] Recent systematic reviews have found that most of the studies on automated diagnosis using artificial intelligence have high risk of bias, mostly due to patient selection methodology and absence of validation on external data.[55–57] Systematic reviews on computer-based clinical-decision support systems also highlight the need for more robust patient selection.[58–63]

Translation of technology to clinical practice requires strong evidence based on high quality research. This review is important because it will establish the potential of automatic analysis of EEG as a diagnostic tool for epilepsy, and if evidence to support its use is lacking, it will identify the pitfalls that need to be overcome in future research. Also, by systematically describing current practices that are used by research groups, it will serve as a reference for new researchers in the field. Upon completion of this review, we will have a better understanding of the potential ways that automated analysis of EEG could

be integrated into the clinical workflow; this information will be valuable to anyone designing clinical studies on clinical-decision support systems for epilepsy.

We anticipate that diagnostic accuracy of automatic analysis of EEG for epilepsy will be hard to estimate because of the high heterogeneity between the different dataset used and between the data processing methodology. We also anticipate high risk of bias in many studies, because of the high volume of "proof-of-concept" studies that emphasize computation performances and algorithm development over rigorous diagnostic study methodology. In these cases, we hope to produce recommendations that will assist in bridging the gap between the development of new automated markers and validation in appropriate populations, for ultimate implementation into clinical practice.

List of abbreviations

ASM: anti-seizure medication; CI: confidence interval; EEG: electroencephalogram; IED: interictal epileptiform discharge; ILAE: International League Against Epilepsy; ROC AUC: receiver operating-characteristic area-under-the-curve.

Funding

MRK and DKN report unrestricted educational grants from UCB and Eisai, and research grants for investigator-initiated studies from UCB and Eisai. Émile Lemoine is supported by a scholarship from the Canadian Institute of Health Research. Dang Nguyen is supported by the Canada Research Chairs Program, the Canadian Institutes of Health Research, and Natural Sciences and Engineering Research Council of Canada.

Authors' contributions

EL planned the study, drafted the protocol, reviewed the search strategy, and is the guarantor of the review. DT, FL, DKN, and EBA participated in the design of the study. JNB, BR, DT, MRK, FL, DKN,

and EBA provided content expertise and critically reviewed the manuscript and the search strategy. BN and RP designed the search strategy. All authors read and approved the final manuscript.

Competing interests

None of the authors have any competing interest to declare.

Data sharing statement

Data collected for this study will be available upon reasonable request.

Ethics and dissemination statement

Ethics approval is not required as this is a review of published evidence. Findings will be disseminated through publication in a peer-review journal and presentations at conferences related to this field.

References

1. Fisher, R. S. *et al.* ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia* **55**, 475–482 (2014).
2. Ngugi, A. K., Bottomley, C., Kleinschmidt, I., Sander, J. W. & Newton, C. R. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia* **51**, 883–890 (2010).
3. Hauser, W. A. & Beghi, E. First seizure definitions and worldwide incidence and mortality. *Epilepsia* **49 Suppl 1**, 8–12 (2008).
4. Devinsky, O., Spruill, T., Thurman, D. & Friedman, D. Recognizing and preventing epilepsy-related mortality: A call for action. *Neurology* **86**, 779–786 (2016).
5. Kwan, P. & Brodie, M. J. Early identification of refractory epilepsy. *N Engl J Med* **342**, 314–319 (2000).

6. Krumholz, A. *et al.* Practice Parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* **69**, 1996–2007 (2007).

7. Hirtz, D. *et al.* Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. *Neurology* **55**, 616–623 (2000).

8. Pillai, J. & Sperling, M. R. Interictal EEG and the Diagnosis of Epilepsy. *Epilepsia* **47**, 14–22 (2006).

9. Bouma, H. K., Labos, C., Gore, G. C., Wolfson, C. & Keezer, M. R. The diagnostic accuracy of routine electroencephalography after a first unprovoked seizure. *European Journal of Neurology* **23**, 455–463 (2016).

10. Tatum, W. O. *et al.* Clinical utility of EEG in diagnosing and monitoring epilepsy in adults. *Clinical Neurophysiology* **129**, 1056–1082 (2018).

11. Lamberink, H. J. *et al.* Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. *Lancet Neurol* **16**, 523–531 (2017).

12. West, S. *et al.* Surgery for epilepsy. *Cochrane Database of Systematic Reviews* (2019) doi:10.1002/14651858.CD010541.pub3.

13. Jing, J. *et al.* Interrater Reliability of Experts in Identifying Interictal Epileptiform Discharges in Electroencephalograms. *JAMA Neurology* **77**, 49–57 (2020).

14. Amin, U. & Benbadis, S. R. The Role of EEG in the Erroneous Diagnosis of Epilepsy. *J Clin Neurophysiol* **36**, (2019).

15. Kang, J. Y. & Krauss, G. L. Normal Variants Are Commonly Overread as Interictal Epileptiform Abnormalities. *J Clin Neurophysiol* **36**, 257–263 (2019).

16. Smith, D., Defalla, B. A. & Chadwick, D. W. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM* **92**, 15–23 (1999).

17. Sauro, K. M. *et al.* The current state of epilepsy guidelines: A systematic review. *Epilepsia* **57**, 13–23 (2016).

18. Engel Jr, J., Bragin, A. & Staba, R. Nonictal EEG biomarkers for diagnosis and treatment. *Epilepsia Open* **3**, 120–126 (2018).

19. DellaBadia Jr, J., Bell, W. L., Keyes Jr, J. W., Mathews, V. P. & Glazier, S. S. Assessment and cost comparison of sleep-deprived EEG, MRI and PET in the prediction of surgical treatment for epilepsy. *Seizure* **11**, 303–309 (2002).

20. Abdelhady, S., Shokri, H., Fathy, M. & wahid el din, mona M. Evaluation of the direct costs of epilepsy in a sample of Egyptian patients following up in Ain Shams University Hospital. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery* **56**, 112 (2020).

21. Velis, D., Plouin, P., Gotman, J., Da Silva, F. L., & members of the ILAE DMC Subcommittee on Neurophysiology. Recommendations Regarding the Requirements and Applications for Long-term Recordings in Epilepsy. *Epilepsia* **48**, 379–384 (2007).

22. Schmidt, H. *et al.* A computational biomarker of idiopathic generalized epilepsy from resting state EEG. *Epilepsia* **57**, e200–e204 (2016).

23. Lopes, M. A. *et al.* Revealing epilepsy type using a computational analysis of interictal EEG. *Scientific Reports* **9**, 10169 (2019).

24. Verhoeven, T. *et al.* Automated diagnosis of temporal lobe epilepsy in the absence of interictal spikes. *NeuroImage: Clinical* **17**, 10–15 (2018).

25. Ouyang, C.-S., Yang, R.-C., Wu, R.-C., Chiang, C.-T. & Lin, L.-C. Determination of Antiepileptic Drugs Withdrawal Through EEG Hjorth Parameter Analysis. *Int. J. Neur. Syst.* **30**, 2050036 (2020).

26. Zhang, J.-H. *et al.* Personalized prediction model for seizure-free epilepsy with levetiracetam therapy: a retrospective data analysis using support vector machine. *Br J Clin Pharmacol* **84**, 2615–2624 (2018).

27. Oliva, J. T. & Rosa, J. L. G. Differentiation between Normal and Interictal EEG Using Multitaper Spectral Classifiers. in *2018 International Joint Conference on Neural Networks (IJCNN)* 1–8 (2018). doi:10.1109/IJCNN.2018.8489503.

28. Pegg, E. J., Taylor, J. R. & Mohanraj, R. Spectral power of interictal EEG in the diagnosis and prognosis of idiopathic generalized epilepsies. *Epilepsy & Behavior* **112**, 107427 (2020).

29. Jacob, J. E., Sreelatha, V. V., Iype, T., Nair, G. K. & Yohannan, D. G. Diagnosis of epilepsy from interictal EEGs based on chaotic and wavelet transformation. *Analog Integrated Circuits and Signal Processing* **89**, 131–138 (2016).

30. Wahl, B., Cossy-Gantner, A., Germann, S. & Schwalbe, N. R. Artificial intelligence (AI) and global health: how can AI contribute to health in resource-poor settings? *BMJ Global Health* **3**, e000798 (2018).

31. Pitkänen, A. *et al.* Advances in the development of biomarkers for epilepsy. *The Lancet Neurology* **15**, 843–856 (2016).

32. McInnes, M. D. F. *et al.* Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. *JAMA* **319**, 388–396 (2018).

33. November, J. Biomedical computing: Digitizing life in the United States. *Biomedical Computing: Digitizing Life in the United States* 1–344 (2012).

34. Fisher, R. S. *et al.* Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* **46**, 470–472 (2005).

35. Supriya, S., Siuly, S., Wang, H. & Zhang, Y. Automated epilepsy detection techniques from electroencephalogram signals: a review study. *Health Information Science and Systems* **8**, 33 (2020).

36. Whiting, P. F. *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* **155**, 529–536 (2011).

37. Reitsma, J. B. *et al.* Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology* **58**, 982–990 (2005).

38. Rutter, C. M. & Gatsonis, C. A. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* **20**, 2865–2884 (2001).

39. Plana, M. N., Pérez, T. & Zamora, J. New measures improved the reporting of heterogeneity in diagnostic test accuracy reviews: a metaepidemiological study. *Journal of Clinical Epidemiology* **131**, 101–112 (2021).

40. Rücker, G., Schwarzer, G., Carpenter, J. R. & Schumacher, M. Undue reliance on I2 in assessing heterogeneity may mislead. *BMC Medical Research Methodology* **8**, 79 (2008).

41. So, E. L. Interictal Epileptiform Discharges in Persons Without A History of Seizures: What Do They Mean? *Journal of Clinical Neurophysiology* **27**, 229–238 (2010).

42. Smith, S. J. M. EEG in the diagnosis, classification, and management of patients with epilepsy. *J Neurol Neurosurg Psychiatry* **76**, ii2–ii7 (2005).

43. Obermeyer, Z. & Emanuel, E. J. Predicting the Future - Big Data, Machine Learning, and Clinical Medicine. *N Engl J Med* **375**, 1216–1219 (2016).

44. Roy, Y. *et al.* Deep learning-based electroencephalography analysis: a systematic review. *Journal of Neural Engineering* **16**, 051001 (2019).

45. Craik, A., He, Y. & Contreras-Vidal, J. L. Deep learning for electroencephalogram (EEG) classification tasks: a review. *J. Neural Eng.* **16**, 031001 (2019).

46. Rasheed, K. *et al.* Machine Learning for Predicting Epileptic Seizures Using EEG Signals: A Review. *IEEE Rev. Biomed. Eng.* **14**, 139–155 (2020).

47. Gemein, L. A. W. *et al.* Machine-learning-based diagnostics of EEG pathology. *NeuroImage* **220**, 117021 (2020).

48. Mesraoua, B. *et al.* Electroencephalography in epilepsy: look for what could be beyond the visual inspection. *Neurological Sciences* **40**, 2287–2291 (2019).

49. van Diessen, E. *et al.* Brain Network Organization in Focal Epilepsy: A Systematic Review and Meta-Analysis. *PLOS ONE* **9**, e114606 (2014).

50. Faiman, I., Smith, S., Hodsoll, J., Young, A. H. & Shotbolt, P. Resting-state EEG for the diagnosis of idiopathic epilepsy and psychogenic nonepileptic seizures: A systematic review. *Epilepsy & Behavior* **121**, 108047 (2021).

51. Pegg, E. J., Taylor, J. R., Keller, S. S. & Mohanraj, R. Interictal structural and functional connectivity in idiopathic generalized epilepsy: A systematic review of graph theoretical studies. *Epilepsy & Behavior* **106**, (2020).

52. Esteva, A. *et al.* A guide to deep learning in healthcare. *Nature Medicine* **25**, 24–29 (2019).

53. Litjens, G. *et al.* A survey on deep learning in medical image analysis. *Medical Image Analysis* **42**, 60–88 (2017).

54. FDA Cleared AI Algorithms. *American College of Radiology Data Science Institute* https://models.acrdsi.org.

55. Aggarwal, R. *et al.* Diagnostic accuracy of deep learning in medical imaging: a systematic review and meta-analysis. *npj Digital Medicine* **4**, 65 (2021).

56. Liu, X. *et al.* A comparison of deep learning performance against health-care professionals in detecting diseases from medical imaging: a systematic review and meta-analysis. *The Lancet Digital Health* **1**, e271–e297 (2019).

57. Nagendran, M. *et al.* Artificial intelligence versus clinicians: systematic review of design, reporting standards, and claims of deep learning studies. *BMJ* vol. 368 m689 (2020).

58. Riches, N. *et al.* The Effectiveness of Electronic Differential Diagnoses (DDX) Generators: A Systematic Review and Meta-Analysis. *PLoS One* **11**, e0148991 (2016).

59. Bright, T. J. *et al.* Effect of clinical decision-support systems: a systematic review. *Ann Intern Med* **157**, 29–43 (2012).

60. Jaspers, M. W. M., Smeulers, M., Vermeulen, H. & Peute, L. W. Effects of clinical decision-support systems on practitioner performance and patient outcomes: a synthesis of high-quality systematic review findings. *J Am Med Inform Assoc* **18**, 327–334 (2011).

61. Garg, A. X. *et al.* Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* **293**, 1223–1238 (2005).

62. Varghese, J., Kleine, M., Gessner, S. I., Sandmann, S. & Dugas, M. Effects of computerized decision support system implementations on patient outcomes in inpatient care: a systematic review. *J Am Med Inform Assoc* **25**, 593–602 (2018).

63. Vasey, B. *et al.* Association of Clinician Diagnostic Performance With Machine Learning–Based Decision Support Systems: A Systematic Review. *JAMA Network Open* **4**, e211276–e211276 (2021).

Appendix 1: Search strategy

Medline [OVID]

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 13, 2021>

#	Searches	Results
1	exp Electroencephalography/	173584
2	(EEG* or Electroencephalograph* or "electr* encephalograph*" or "brain wave*").tw,kf.	111352
3	1 or 2	201652
4	exp Epilepsy/	118716
5	Epilep*.tw,kf.	152323
6	(seizure* or convulsion* or infantile spasm*).tw,kf.	147989
7	(BCECTS or BECTS).tw,kf.	346
8	(panayiotopoulos adj2 syndrome*).tw,kf.	166
9	((Nodding or dravet or doose or may white or fukhura) adj2 (disease* or syndrome*)).tw,kf.	1407
10	(myoencephalopathy ragged red fiber* disease* or MERRF).tw,kf.	530
11	((Lafora or Unverricht or Landau-Kleffner or Lennox Gastaut) adj2 (disease* or syndrome* or disorder* or seizure*)).tw,kf.	2534
12	or/4-11	244612
13	exp Algorithms/	375058
14	Machine learning.tw,kf.	54804
15	((Deep or hierarchical) adj1 learning).tw,kf.	25347
16	((transfer* or representation* or network*) adj2 learning).tw,kf.	7945
17	((artificial or machine or computer or computational) adj2 intelligence).tw,kf.	19275
18	algorithm*.tw,kf.	299232
19	((data or binary or multiclass or multilabel) adj2 classification).tw,kf.	4758

20	((artificial or computational or computer* or convolutional or connectionist or mathematical) adj2 neur* network*).tw,kf.	28375
21	exp Pattern Recognition, Automated/	26085
22	(Automat* adj2 pattern* adj2 recognition*).tw,kf.	155
23	(Back* propagation* or backpropagation*).tw,kf.	4397
24	exp Bayes Theorem/	40554
25	(Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kf.	21469
26	(feature* adj2 (detecti* or extracti* or learning* or ranking* or selection*)).tw,kf.	21577
27	(Fuzzy or neurofuzzy).tw,kf.	13240
28	exp Markov chains/	15485
29	(Markov adj2 (model* or chain$1 or process*)).tw,kf.	21918
30	K nearest neighbor*.tw,kf.	3529
31	(Kernel$1 adj2 (method* or algorithm* or approach or correlation or estim* or regression or model* or string or tree)).tw,kf.	3950
32	exp Knowledge discovery/	130
33	(Knowledge adj2 discover*).tw,kf.	1589
34	exp Multifactor Dimensionality Reduction/	226
35	Dimensionality reduction*.tw,kf.	3836
36	(predicti* adj2 model*).tw,kf.	79862
37	connectom*.tw,kf.	4980
38	neur* decod*.tw,kf.	361
39	(outlier* adj2 detection*).tw,kf.	893
40	Neural networks, computer/	35265
41	(neural adj2 network*).tw,kf.	70371
42	perceptron*.tw,kf.	3390
43	radial basis function*.tw,kf.	2359
44	random forest*.tw,kf.	13717

45	recursive feature* elimination*.tw,kf.	688
46	recursive partition*.tw,kf.	2380
47	exp Support Vector Machine/	8553
48	(vector* adj2 (machine* or classifi* or network* or regression)).tw,kf.	22248
49	support vector*.tw,kf.	21483
50	rough set*.tw,kf.	397
51	((automat* or electron* or comput* or information or analytic*) adj2 (processing or reasoning)).tw,kf.	38719
52	(quantitative adj2 analys*).tw,kf.	90324
53	(Peak* adj2 (alpha* or frequenc*)).tw,kf.	5453
54	Entrop*.tw,kf.	45494
55	Lyapunov exponent*.tw,kf.	2179
56	Hjorth*.tw,kf.	184
57	Sub-band energ*.tw,kf.	18
58	exp fourier Analysis/	17272
59	(Fourier* or (cyclic adj2 (analys* or series or transform* or approach*)) or FFT).tw,kf.	87439
60	(Hilbert* adj2 transform*).tw,kf.	1008
61	(dimension* adj2 (fractal* or correlation*)).tw,kf.	8106
62	(Hurst adj2 exponent*).tw,kf.	575
63	exp wavelet analysis/	2541
64	(Wavelet* adj2 (analysis or processing or transform*)).tw,kf.	7248
65	phase locking value*.tw,kf.	311
66	Fisher information*.tw,kf.	870
67	Dynamic network*.tw,kf.	1839
68	Principal component* analys*.tw,kf.	47819
69	Independant component* analys*.tw,kf.	2
70	Functional connectivit*.tw,kf.	22171

71	(gradient* boost* or Adaboost*).tw,kf.	3337
72	(QEEG or Quantitative Electroencephalogra*).tw,kf.	1750
73	(chaotic feature* or chaos).tw,kf.	9755
74	comput*.tw,kf.	958508
75	quantitative.tw,kf.	689806
76	or/13-75	2378446
77	(sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp.	11325259
78	di.fs.	2760821
79	or/77-78	11325259
80	3 and 12 and 76 and 79	5990
81	(Animals/ or Models, animal/ or Disease models, animal/) not Humans/	4900078
82	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient* or women or men)).tw,kf.	3315730
83	81 or 82	5542727
84	80 not 83	5627
85	limit 84 to yr="1961 -Current"	5627

EMBASE [OVID]

Embase <1974 to 2021 December 13>

#	Searches	Results
1	exp electroencephalography/	124495
2	(EEG* or Electroencephalograph* or "electr* encephalograph*" or "brain wave*").tw,kf.	146325
3	1 or 2	206929
4	exp epilepsy/	251058
5	Epilep*.tw,kf.	214171
6	(seizure* or convulsion* or infantile spasm*).tw,kf.	216888
7	(BCECTS or BECTS).tw,kf.	509

8	(panayiotopoulos adj2 syndrome*).tw,kf.	249
9	((Nodding or dravet or doose or may white or fukhura) adj2 (disease* or syndrome*)).tw,kf.	2324
10	(myoencephalopathy ragged red fiber* disease* or MERRF).tw,kf.	711
11	((Lafora or Unverricht or Landau-Kleffner or Lennox Gastaut) adj2 (disease* or syndrome* or disorder* or seizure*)).tw,kf.	3984
12	or/4-11	371364
13	Machine learning/	49774
14	Machine learning.tw,kf.	63858
15	((Deep or hierarchical) adj1 learning).tw,kf.	28566
16	exp network learning/	886
17	((transfer* or representation* or network*) adj2 learning).tw,kf.	8790
18	exp artificial intelligence/	55153
19	((artificial or machine or computer or computational) adj2 intelligence).tw,kf.	23056
20	exp algorithm/	465121
21	algorithm*.tw,kf.	381089
22	((data or binary or multiclass or multilabel) adj2 classification).tw,kf.	6087
23	exp artificial neural network/	62826
24	((artificial or computational or computer* or convolutional or connectionist or mathematical) adj2 neur* network*).tw,kf.	33889
25	exp pattern recognition/ or exp automated pattern recognition/	68427
26	(Automat* adj2 pattern* adj2 recognition*).tw,kf.	199
27	exp back propagation/	2553
28	(Back* propagation* or backpropagation*).tw,kf.	5107
29	exp Bayesian learning/	4303
30	(Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kf.	24116
31	exp Feature detection/ or exp feature extraction/ or exp feature learning/ or exp feature ranking/ or exp feature selection/	31030

32	((feature* or representation) adj2 (detecti* or extracti* or learning* or ranking* or selection*)).tw,kf.	28097
33	exp fuzzy system/	4077
34	(fuzzy or neurofuzzy).tw,kf.	16138
35	exp Markov chain/ or exp Markov state model/	12093
36	(Markov adj2 (model* or chain$1 or process*)).tw,kf.	29000
37	exp k nearest neighbor/	4553
38	K nearest neighbor*.tw,kf.	4260
39	kernel method/	6720
40	(Kernel$1 adj2 (method* or algorithm* or approach or correlation or estim* or regression or model* or string or tree)).tw,kf.	4389
41	exp Knowledge discovery/	727
42	(Knowledge adj2 discover*).tw,kf.	1804
43	exp multifactor dimensionality reduction/	864
44	Dimension* reduction*.tw,kf.	7086
45	(predicti* adj2 model*).tw,kf.	105404
46	connectom*.tw,kf.	6225
47	neur* decod*.tw,kf.	433
48	exp Outlier detection/	470
49	(outlier* adj2 detection*).tw,kf.	1010
50	exp artificial neural network/	62826
51	exp Perceptron/	2478
52	perceptron*.tw,kf.	3962
53	(neural adj2 network*).tw,kf.	84786
54	exp radial basis function/	942
55	radial bas* function*.tw,kf.	2927
56	exp random forest/	14358
57	(random adj2 forest*).tw,kf.	17752

58	exp recursive feature elimination/	393
59	recursive feature* elimination*.tw,kf.	860
60	exp recursive partitioning/	462
61	recursive partition*.tw,kf.	3567
62	exp relevance vector machine/ or exp support vector machine/	28522
63	(vector* adj2 (machine* or classifi* or network* or regression)).tw,kf.	27021
64	support vector*.tw,kf.	26266
65	exp rough set/	248
66	rough set*.tw,kf.	531
67	exp online analytical processing/	187
68	((automat* or electron* or comput* or information or analytic*) adj2 (processing or reasoning)).tw,kf.	44254
69	Quantitative analysis/	367570
70	(quantitative adj2 analys*).tw,kf.	113093
71	(Peak* adj2 (alpha* or frequenc*)).tw,kf.	6315
72	Entrop*.tw,kf.	43483
73	Lyapunov exponent*.tw,kf.	1600
74	Hjorth*.tw,kf.	264
75	Sub-band energ*.tw,kf.	23
76	exp Fourier analysis/	10056
77	(Fourier* or (cyclic adj2 (analys* or series or transform* or approach*)) or FFT).tw,kf.	89584
78	Hilbert transform/	183
79	(Hilbert* adj2 transform*).tw,kf.	1253
80	(dimension* adj2 (fractal* or correlation*)).tw,kf.	8947
81	(Hurst adj2 exponent*).tw,kf.	555
82	exp wavelet transform/	2217
83	(Wavelet* adj2 (analysis or processing or transform*)).tw,kf.	9182

84	phase locking value*.tw,kf.	425
85	Fisher information*.tw,kf.	746
86	Dynamic network*.tw,kf.	1972
87	Principal component* analys*.tw,kf.	58526
88	Independent component* analys*.tw,kf.	7493
89	Functional connectivity/	21903
90	Functional connectivit*.tw,kf.	30389
91	(gradient* boost* or Adaboost*).tw,kf.	4097
92	(QEEG or Quantitative Electroencephalogra*).tw,kf.	2861
93	(chaotic feature* or chaos).tw,kf.	8412
94	comput*.tw,kf.	1156500
95	quantitative.tw,kf.	852081
96	or/13-95	2994032
97	(sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp.	14413096
98	di.fs.	3343316
99	or/97-98	14413096
100	3 and 12 and 96 and 99	8362
101	(exp animal/ or animal experiment/ or nonhuman/) not (exp human/ or human experiment/)	6801969
102	(animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey ormonkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.	2062187
103	101 or 102	6872024
104	100 not 103	7906
105	limit 104 to yr="1961 -Current"	7890
106	limit 105 to embase	5134

EBM Reviews [OVID]

All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCA, CCTR, CMR, HTA, and NHSEED <executed on December 14>

#	Searches	Results
1	(EEG* or Electroencephalograph* or "electr* encephalograph*" or "brain wave*").tw,kw,sh.	12245
2	Epilep*.tw,kw,sh.	10099
3	(seizure* or convulsion* or infantile spasm*).tw,kw,sh.	11675
4	(BCECTS or BECTS).tw,kw,sh.	31
5	(panayiotopoulos adj2 syndrome*).tw,kw,sh.	5
6	((Nodding or dravet or doose or may white or fukhura) adj2 (disease* or syndrome*)).tw,kw,sh.	413
7	(myoencephalopathy ragged red fiber* disease* or MERRF).tw,kw,sh.	5
8	((Lafora or Unverricht or Landau-Kleffner or Lennox Gastaut) adj2 (disease* or syndrome* or disorder* or seizure*)).tw,kw,sh.	339
9	or/2-8	16595
10	algorithm*.tw,kw.	16401
11	Machine learning.tw,kw,sh.	1918
12	((Deep or hierarchical) adj1 learning).tw,kw,sh.	708
13	((transfer* or representation* or network*) adj2 learning).tw,kw,sh.	691
14	((artificial or machine or computer or computational) adj2 intelligence).tw,kw,sh.	827
15	algorithm*.tw,kw,sh.	18549
16	((data or binary or multiclass or multilabel) adj2 classification).tw,kw,sh.	335
17	((artificial or computational or computer* or connectionist or convolutional or mathematical) adj2 neur* network*).tw,kw,sh.	782
18	(Automat* adj2 pattern* adj2 recognition*).tw,kw,sh.	15
19	(Back* propagation* or backpropagation*).tw,kw,sh.	66
20	(Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kw,sh.	1841
21	(feature* adj2 (detecti* or extracti* or learning* or ranking* or selection*)).tw,kw,sh.	607

22	(fuzzy or neurofuzzy).tw,kw,sh.	197
23	(Markov adj2 (model* or chain$1 or process*)).tw,kw,sh.	4373
24	K nearest neighbor*.tw,kw,sh.	73
25	(Kernel$1 adj2 (method* or algorithm* or approach or correlation or estim* or regression or model* or string or tree)).tw,kw,sh.	90
26	(Knowledge adj2 discover*).tw,kw,sh.	26
27	Dimensionality reduction*.tw,kw,sh.	73
28	(predicti* adj2 model*).tw,kw,sh.	5378
29	connectom*.tw,kw,sh.	308
30	neur* decod*.tw,kw,sh.	2
31	(outlier* adj2 detection*).tw,kw,sh.	14
32	perceptron*.tw,kw,sh.	76
33	(neural adj2 network*).tw,kw,sh.	1672
34	radial basis function*.tw,kw,sh.	39
35	random forest*.tw,kw,sh.	615
36	recursive feature* elimination*.tw,kw,sh.	30
37	recursive partition*.tw,kw,sh.	282
38	(vector* adj2 (machine* or classifi* or network* or regression)).tw,kw,sh.	555
39	support vector*.tw,kw,sh.	544
40	rough set*.tw,kw,sh.	3
41	((automat* or electron* or comput* or information or analytic*) adj2 (processing or reasoning)).tw,kw,sh.	7510
42	(quantitative adj2 analys*).tw,kw,sh.	8960
43	(Peak* adj2 (alpha* or frequenc*)).tw,kw,sh.	357
44	Entrop*.tw,kw,sh.	951
45	Lyapunov exponent*.tw,kw,sh.	37
46	Hjorth*.tw,kw,sh.	29
47	Sub-band energ*.tw,kw,sh.	0

48	(Fourier* or (cyclic adj2 (analys* or series or transform* or approach*)) or FFT).tw,kw,sh.	1043
49	(Hilbert* adj2 transform*).tw,kw,sh.	19
50	(dimension* adj2 (fractal* or correlation*)).tw,kw,sh.	184
51	(Hurst adj2 exponent*).tw,kw,sh.	14
52	(Wavelet* adj2 (analysis or processing or transform*)).tw,kw,sh.	126
53	phase locking value*.tw,kw,sh.	11
54	Fisher information*.tw,kw,sh.	7
55	Dynamic network*.tw,kw,sh.	12
56	Principal component* analys*.tw,kw,sh.	1207
57	Independant component* analys*.tw,kw,sh.	0
58	Functional connectivit*.tw,kw,sh.	2220
59	(gradient* boost* or Adaboost*).tw,kw,sh.	168
60	(QEEG or Quantitative Electroencephalogra*).tw,kw,sh.	448
61	(chaotic feature* or chaos).tw,kw,sh.	141
62	comput*.tw,kw,sh.	80820
63	quantitative.tw,kw,sh.	33706
64	or/10-63	145496
65	(sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp.	810011
66	di.tw,kw,sh.	17162
67	65 or 66	811399
68	1 and 9 and 64 and 67	350
69	((animal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or veterinar*) not (human* or patient* or women or men)).tw,kw,sh.	5147
70	68 not 69	346
71	limit 70 to yr="1961 -Current" [Limit not valid in DARE; records were retained]	321
72	remove duplicates from 71	315

IEEE Xplore

<executed on December 14>

(((((((((All Metadata:predicted OR All Metadata:prediction OR All Metadata:predictions OR All Metadata:predicting OR All Metadata:predictive OR All Metadata:predictor OR All Metadata:predictors OR All Metadata:predicts OR All Metadata:predictability OR All Metadata:predictable OR All Metadata:predictably OR All Metadata:predictively OR All Metadata:predictiveness))) OR ((All Metadata:sensitivity OR All Metadata:sensitively OR All Metadata:sensitiveness OR All Metadata:sensitive OR All Metadata:sensitivities))) OR ((All Metadata:diagnose OR All Metadata:diagnosis OR All Metadata:diagnosed OR All Metadata:diagnoses OR All Metadata:diagnostic OR All Metadata:diagnosing OR All Metadata:diagnosable OR All Metadata:diagnostics OR All Metadata:diagnoseable OR All Metadata:diagnostical OR All Metadata:diagnostician OR All Metadata:diagnosticians OR All Metadata:diagnostically))) AND ((No Keywords Specified))) AND ((No Keywords Specified))) AND ((Index Terms:EEG) OR (Index Terms:Electroencephalograph*) OR (Index Terms: "electr* encephalograph*") OR (Index Terms: "brain wave") OR (Index Terms:"brain waves"))) OR ((Document Title:EEG) OR (Document Title:Electroencephalograph*) OR (Document Title:"electr* encephalograph*") OR (Document Title:"brain wave") OR (Document Title:"brain waves"))) AND ((Index Terms:epilep*) OR (Document Title:seizure OR Document Title:seizures OR Document Title:convulsion OR Document Title:convulsions OR Document Title:"infantile spasm" OR Document Title:"infantile spasms"))	2492

Google Scholar (using Publish or Perish)

<executed on December 21>

Electroencephalogram epilepsy [title], machine learning algorithm* diagnos* [keywords]	32 selected articles out of 32
Electroencephalography epilepsy [title], machine learning algorithm* diagnos* [keywords]	21 selected article out of 21
EEG epilepsy [title], machine learning algorithm* diagnos* [keywords]	433 sur 433

Grey literature

Alberta: Health evidence reviews

https://www.alberta.ca/health-evidence-reviews.aspx

Electroencephalography	0 selected articles out of 1
EEG	0 selected articles out of 3

Canadian Agency for Drug and Technologies in Health

https://www.cadth.ca/search?keywords

Electroencephalography	0 selected articles out of 1
EEG	0 selected articles out of 4

Health Quality Council of Alberta

https://hqca.ca/studies-and-reviews/

Electroencephalography	0 selected articles out of 0
EEG	0 selected articles out of 0

Health Quality Ontario: Health Technology Assessment

Quality Standards - Health Quality Ontario (HQO) (hqontario.ca)

Electroencephalography	1 selected article out of 7
EEG	1 selected article out of 5

INESS

https://www.inesss.qc.ca/en/publications/publications.html?tx_solr%5Bq%5D=EEG

électroencéphalographie	0 selected articles out of 5
EEG	0 selected articles out of 0

McGill University Health Centre (MUHC). Technology Assessment Unit Reports

https://muhc.ca/tau/page/tau-reports

Electroencephalography	0 selected article out of 0
EEG	0 selected articles out of 3

Newfoundland & Labrador Centre For Applied Health Research

http://www.nlcahr.mun.ca/CHRSP/CompletedCHRSP.php

Electroencephalography AND epilepsy	0 selected articles out of 37
Electroencephalogram AND epilepsy	0 selected articles out of 34
EEG AND epilepsy	0 selected articles out of 28

The Ottawa Hospital Research institute: Knowledge Synthesis Group

http://www.ohri.ca/ksgroup/

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG AND epilepsy	0 selected articles out of 7

Programs for Assessment of Technology in Health

https://www.path-hta.com/research-1

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

The International Network of Agencies for Health Technology Assessment

Publications - INAHTA

Electroencephalography	0 selected articles out of 1
Electroencephalogram	0 selected articles out of 4
EEG	0 selected articles out of 4

Horizon Scanning

Horizon Scanning - Australia and New Zealand Horizon Scanning Network - Technologies Assessed

Electroencephalography	0 selected articles out of 1
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

Austrian Academy of Sciences

https://www.oeaw.ac.at/en/

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 2

Austrian Institute Of Health Technology Assessment

Welcome to Repository of AIHTA GmbH - Repository of AIHTA GmbH (lbg.ac.at)

Electroencephalography	0 selected articles out of 4
Electroencephalogram	0 selected articles out of 0

EEG	0 selected articles out of 2

KCE: Belgian health Knowledge Center

All reports - KCE (fgov.be)

Electroencephalography	0 selected articles out of 1
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 1
électroencéphalographie	0 selected article out of 1

CEDIT, the Hospital-Based HTA Agency Of AP-HP

Recommendations and Reports | Cedit (aphp.fr)

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 1
électroencéphalographie	0 selected article out of 0

Haute Autorité de Santé

Haute Autorité de Santé - Résultat de recherche (has-sante.fr)

EEG	1 selected article out of 218
électroencéphalographie	0 selected article out of 27

Health Information and Quality Autority

Health Technology Assessments | HIQA

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

Irish Health Repository

Lenus the Irish Health Repository

Title: Electroencephalography AND epilepsy	1 selected article out of 51
Electroencephalogram	0 selected articles out of 3
Title: EEG AND epilepsy	0 selected articles out of 51

Norwegian Institute of Public Health

Norwegian Institute of Public Health - NIPH (fhi.no)

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 3

Swedish Agency for Health Technology Assessment And Assessment Of Social Services Home (sbu.se)

Electroencephalography	0 selected articles out of 2
Electroencephalogram	0 selected articles out of 2
EEG	0 selected articles out of 4

Healthcare Improvement Scotland

Healthcare Improvement Scotland

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG	0 selected articles out of 0

National Institute for Health and Care Excellence

NICE | The National Institute for Health and Care Excellence

electroencephalography AND epilepsy	0 selected articles out of 2
Electroencephalogram AND epilepsy	1 selected article out of 5
EEG	0 selected articles out of 9

NIHR Innovation Observatory

Innovation Observatory | Next generation search tools for the next generation. (nihr.ac.uk)

Electroencephalography	1 selected article out of 2
Electroencephalogram	0 selected articles out of 1
EEG	0 selected articles out of 5

National institute for health Research

Research Programmes (nihr.ac.uk)

electroencephalography AND epilepsy	1 selected article out of 67
Electroencephalogram AND epilepsy	0 selected articles out of 67
EEG	0 selected articles out of 67

Agency for Healthcare Research and Quality : Technology Assessment Program

Technology Assessment Program | Agency for Healthcare Research and Quality (ahrq.gov)

Electroencephalography AND epilepsy AND diagnosis	0 selected articles out of 1
Electroencephalogram AND epilepsy AND diagnosis	0 selected articles out of 78
EEG AND epilepsy AND diagnosis	0 selected articles out of 83

Agency for Healthcare Research and Quality : Evidence-Based Reports

Search Evidence-Based Reports | Agency for Healthcare Research and Quality (ahrq.gov)

Electroencephalography	0 selected articles out of 0
Electroencephalogram	0 selected articles out of 0
EEG AND epilepsy	0 selected articles out of 4

Google

intitle: Electroencephalography AND epilepsy AND machine learning AND diagnosis	3 selected articles out of 9
intitle: Electroencephalogram AND epilepsy AND machine learning AND diagnosis	0 selected articles out of 9
intitle: EEG AND epilepsy AND machine learning AND diagnosis	1 selected articles out of 9
intitle: Electroencephalography AND epilepsy AND algorithm AND diagnosis	0 selected articles out of 9
intitle: Electroencephalogram AND epilepsy AND algorithm AND diagnosis	0 selected articles out of 9
intitle: EEG AND epilepsy AND algorithm AND diagnosis	0 selected articles out of 9

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	Title page
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☐	24
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	Title page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	265 – 270
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	265 – 270
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	265 – 270
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	265 – 270
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	29 – 70
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	71 – 75

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	82 – 106
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	107 – 116
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	App. 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	111 – 116
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	111 – 116
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	111 – 116
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	118 – 154
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	149 – 152
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	156 – 182
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	184 – 188
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	198 – 221
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	198 – 221
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	189 – 196
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective	☒	☐	220 – 227

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		reporting within studies)			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☐	NA