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

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

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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;

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| 2 | 31 | • High heterogeneity in reporting standards and inclusion criteria is anticipated, possibly preventing |
| 4 5 | 32 | the reliable estimation of diagnostic performance metrics; |
| 6 7 | 33 | • Our review will constitute a comprehensive reference of current practices in the automated |
| 8 9 | 34 | processing and analysis of routine EEG for epilepsy. |
| 10 | 35 | |
| 12 | | |
| 13 14 | 36 | ${\bf Keywords:}\ {\rm Epilepsy-Electroencephalogram-Machine\ Learning-Diagnosis-Computer-assisted-}$ |
| 15 16 | 37 | Biomarker |
| $\begin{array}{c} 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 9\\ 50\\ 51\\ 52\\ 53\\ \end{array}$ | 38 | Word count (abstract): 290 |
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39 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 brain¹. 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 death⁴. In specialized-care settings, the first anti-seizure medication (ASM) achieves seizure freedom in approximately 47% of patients⁵. A prompt diagnosis is key in the prevention of epilepsy-related morbidity and mortality⁴. 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 minutes⁸. 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 wave⁸. 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

62 - 55% of routine EEGs will capture these transient abnormalities⁸. After a first unprovoked seizure in

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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 EEG¹⁶. 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 chaoticity²⁹. 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?

87 Methods

88 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.

92 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

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

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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}.

113 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 density³⁵. Also included are statistical models that combine several features or models that take as input the raw or processed EEG.

118 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.

128 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

| 1 | | |
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| 2 3 4 | 131 | required data are not available in the original publication. Data collection will include the following |
| 5 6 | 132 | information: |
| 7 8 9 | 133 | 1. Title and authors of the study, country of sampling, year of publication; |
|) 10 11 | 134 | 2. Study type: retrospective vs. prospective, design (cohort, case control); |
| 11 12 13 | 135 | 3. Study sample: exclusion and inclusion criteria, number of screened and included patients; |
| 14 15 | 136 | 4. Data collection: |
| 16 17 | 137 | a. Number of patients, number of EEGs, duration of EEG recordings, use of activation |
| 18 19 | 138 | procedures (hyperventilation, photic stimulation, sleep deprivation), setting of recording |
| 20 21 | 139 | (hospitalized or ambulatory), whether the same protocol was used for all patients; |
| 22 23 | 140 | b. Number of electrodes, sampling frequency; |
| 24 25 | 141 | c. If public dataset: reference to the original dataset, dataset name, exclusion/inclusion |
| 26 27 28 29 30 31 32 | 142 | criteria used on the EEG segments from the dataset; |
| | 143 | d. Participant characteristics: age, sex, comorbidities, number of ASM, age of first seizure; |
| | 144 | 5. Reference standard: whether a predefined reference standard was used, definition of reference |
| 32 33 34 | 145 | standard, whether all patients underwent the same reference standard, time lapse between |
| 35 36 | 146 | reference standard and EEG; |
| 37 38 | 147 | 6. Index test: |
| 39 40 | 148 | a. Pre-processing: artifact detection and removal (automated or manual), filtering method, |
| 41 42 | 149 | filtering frequencies, segmentation protocol (whole EEG vs. EEG segments, window |
| 43 44 | 150 | size, overlapping vs. non-overlapping segments, manual vs. automated selection of |
| 45 46 | 151 | segments), channel selection; |
| 47 48 | 152 | b. Feature extraction and selection: multi-channel vs. single channel, number of channels |
| 49 50 | 153 | selected, whether feature selection was performed, feature extraction algorithm, feature |
| 51 52 | 154 | selection method, whether feature selection was applied to data before vs. after excluding |
| 55 55 | 155 | testing data; |
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Page 9 of 40

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| - 3 4 | 156 | c. Classification: algorithm(s) used for classification, testing methodology (cross-validation |
| 5 6 | 157 | vs. held out testing set); |
| 7 8 | 158 | d. Metric used to report diagnostic performances: ROC AUC, |
| 9 10 | 159 | accuracy/sensibility/specificity, F1-score, reporting of confidence intervals (CI); |
| 11 12 | 160 | 7. Diagnostic performances: number of true positives, number of true negatives, number of false |
| 13 14 | 161 | positives, number of false negatives, reported accuracy, reported sensitivity, reported specificity, |
| 15 16 | 162 | reported F ₁ -score, reported ROC AUC (if more than one index test is performed on the same |
| 17 18 | 163 | patient, we will only consider the first test); |
| 19 20 21 | 164 | 8. Reproducibility: whether every data processing step is detailed, whether methods can be |
| 21 22 23 | 165 | reproduced easily, data availability, code availability, open-source computer libraries referenced. |
| 24 25 | 166 | Disk of hiss |
| 26 27 | 166 | Risk of blas |
| 28 29 | 167 | The risk of bias of all included studies will be assessed through an adapted version of the QUADAS-2 |
| 29 30 31 32 33 34 35 36 37 | 168 | tool ³⁶ . Risk of bias for each of the following four elements will be evaluated by two independent |
| | 169 | reviewers (EL and JNB/BR) as low, high, or unclear. Conflicts will be resolved by a third author (EBA). |
| | 170 | In addition, all publicly available datasets used by at least one of the included studies will be evaluated |
| | 171 | with the same tool. The following items will be assessed: |
| 38 39 | 172 | 1. Patient selection |
| 40 41 | 173 | a. Is the population representative of clinical practice? |
| 42 43 | 174 | b. Are inclusion and exclusion criteria identical for cases (patients with epilepsy) and |
| 44 45 | 175 | controls? |
| 46 47 | 176 | c. Are withdrawals explained and appropriate? If individual EEG segments were excluded, |
| 48 49 | 177 | were the same criteria used for all segments? |
| 50 51 | 178 | 2. Index test |
| 52 53 | 179 | a. Were the protocols used for recording the EEG identical in all patients, irrespective of the |
| 54 55 | 180 | epilepsy diagnosis? |
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Page 10 of 40

BMJ Open

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| 3 4 | 181 | b. Was the index test validated on an independent sample of patients (patients which were |
| 5 6 | 182 | not used to identify the index test's threshold or train the learning algorithm)? |
| 7 8 | 183 | 3. Reference standard |
| 9 10 | 184 | a. Are the criteria used for the diagnosis of epilepsy specified and acceptable (likely to |
| 11 12 | 185 | correctly classify the target condition)? |
| 13 14 | 186 | b. Was the reference standard assessment independent and blinded to the index test? |
| 15 16 | 187 | 4. Flow and timing |
| 17 18 | 188 | a. Did the whole sample undergo the reference standard? |
| 19 20 | 189 | b. Did the whole sample undergo the same reference standard? |
| 21 22 22 | 190 | c. Was the time lapse between reference standard and EEG acceptable? |
| 25 24 25 | 191 | d. Was the same data used in the index method available at the time of the reference |
| 25 26 27 | 192 | standard? |
| 28 29 | 193 | e. Were all EEGs included in the analysis? |
| 30 31 32 | 194 | Data synthesis |
| 33 34 | 195 | We will provide a table summarizing every published study included in the review, comparing the |
| 35 36 27 | 196 | studies' design, population, reference standard, dataset size, data processing methods, and diagnostic |
| 37 38 30 | 197 | accuracy. We will also provide a table summarizing the risk of bias for all items in the adapted |
| 40 41 | 198 | QUADAS-2 tool, comparing 1) every individual article included in the review, and 2) every public |
| 42 43 | 199 | dataset that is used in ≥ 2 studies. |
| | 177 | |
| 44 45 | 200 | We will describe the number of patients, number of EEGs, duration of EEGs, and the EEG-duration-per- |
| 44 45 46 47 | 200 201 | 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. |
| 44 45 46 47 48 49 | 200 201 202 | 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 |
| 44 45 46 47 48 49 50 51 | 200 201 202 203 | 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 |
| 44 45 46 47 48 49 50 51 52 53 54 | 200 201 202 203 204 | 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. |
| 44 45 46 47 48 49 50 51 52 53 54 55 56 | 200 201 202 203 204 | 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. |
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| 2 | 205 | We will successive the model descend by the difference with her descine the minute size in the descine (and |
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| 4 5 6 7 8 9 10 11 | 205 | We will summarize the methods used by the different articles during the pipeline's algorithm (pre- |
| | 206 | processing, feature extraction, feature selection, and classification algorithm), along with the proportion |
| | 207 | of studies that used each method. |
| | 208 | Analyses |
| 12 13 | 209 | We will estimate the specificity and sensitivity for each study, using the Wilson score to compute 95% |
| 14 15 16 | 210 | CI. For studies with varying thresholds, we will estimate the ROC AUC and 95% CI. |
| 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 | 211 | If there are sufficient (\geq 5) studies that report the number of true/false positives and true/false negatives, |
| | 212 | we will estimate the pooled sensitivity and specificity of each individual marker using a hierarchical, |
| | 213 | bivariate generalized linear mixed model ³⁷ . This allows us to account for the correlation between |
| | 214 | specificity and sensitivity in a single study. If \geq 5 studies report these numbers for varying thresholds, we |
| | 215 | will estimate the pooled ROC curve using the Rutter and Gatsonis HSROC model ³⁸ . All analyses will be |
| | 216 | implemented with the R statistical language. A <i>p</i> -value <0.05 will be considered statistically significant. |
| | 217 | Given insufficient data for the pooled estimates, we will only describe the diagnostic performances |
| | 218 | (sensitivity, specificity, ROC AUC) narratively. We will present the results of the analyses with forest |
| | 219 | plots. |
| | 220 | We will quantify heterogeneity using the variances of the logit specificity and sensitivity, as well as the |
| | 221 | median odds ratio (median OR) ³⁹ . The median OR is a measure of inter-study variance translated on the |
| | 222 | OR scale. It corresponds to the increase in the odds of being true positive/negative in a patient/control |
| 42 43 | 223 | going from a study with lower sensitivity/specificity to a study with higher sensitivity/specificity. For |
| 44 45 46 | 224 | heterogeneity in the ROC plane, we will compute the area of the 95% prediction ellipse ³⁹ . The median OR |
| 40 47 48 | 225 | and the area of the 95% prediction ellipse are easily obtained and interpreted, and take into account the |
| 49 50 | 226 | correlation between a single study's specificity and sensitivity in contrast to univariate methods like |
| 51 52 | 227 | Cochrane's Q and $P^{237,40}$. We will perform subgroup analysis for the following variables: epilepsy type |
| 53 54 | 228 | (focal, generalized), epilepsy etiology (structural vs. non-structural), age groups (children (< 18 y.o.), |
| 55 56 57 | 229 | adults (\geq 18 y.o.)), epilepsy syndromes, extracted marker, and dataset used. We will assess heterogeneity |
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> for all subgroup analyses. We will consider a study as belonging to a particular subgroup if \geq 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.

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

239 **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

Page 13 of 40

BMJ Open

| 3 4 | 253 | In recent years, increased computational capacities have allowed the development of powerful algorithms |
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| 5 6 | 254 | that can learn complex representations such as medical images and EEG signals. ^{43,51,52} A growing number |
| 7 8 | 255 | of algorithms have now been approved by the United States Food and Drug Administration for assisting |
| 9 10 | 256 | in the diagnosis of several diseases. ⁵³ Recent systematic reviews have found that most of the studies on |
| 11 12 | 257 | automated diagnosis using artificial intelligence have high risk of bias, mostly due to patient selection |
| 13 14 | 258 | methodology and absence of validation on external data.54-56 Systematic reviews on computer-based |
| 15 16 17 | 259 | clinical-decision support systems also highlight the need for more robust patient selection. ^{57–62} |
| 17 18 19 | 260 | Translation of technology to clinical practice requires strong evidence based on high quality research. |
| 20 21 | 261 | This review is important because it will establish the potential of automatic analysis of EEG as a |
| 22 23 | 262 | diagnostic tool for epilepsy, and if evidence to support its use is lacking, it will identify the pitfalls that |
| 24 25 | 263 | need to be overcome in future research. Also, by systematically describing current practices that are used |
| 26 27 | 264 | by research groups, it will serve as a reference for new researchers in the field. |
| 28 29 20 | 265 | We anticipate that diagnostic accuracy of automatic analysis of EEG for epilepsy will be hard to estimate |
| 30 31 32 | 266 | because of the high heterogeneity between the different dataset used and between the data processing |
| 33 34 | 267 | methodology. We also anticipate high risk of bias in many studies, because of the high volume of "proof- |
| 35 36 | 268 | of-concept" studies that emphasize computation performances and algorithm development over rigorous |
| 37 38 | 269 | diagnostic study methodology. In these cases, we hope to produce recommendations that will assist in |
| 39 40 | 270 | bridging the gap between the development of new automated markers and validation in appropriate |
| 41 42 43 44 45 | 271 | populations, for ultimate implementation into clinical practice. |

272 List of abbreviations

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

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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

·2007 Data collected for this study will be available upon reasonable request.

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BMJ Open

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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 (grad | lient* boost* or Adaboost*).tw,kf. | 3337 |
|---------------------------------------|--|----------|
| 72 (QEE | EG or Quantitative Electroencephalogra*).tw,kf. | 1750 |
| 73 (chao | otic feature* or chaos).tw,kf. | 9755 |
| 74 comp | put*.tw,kf. | 958508 |
| 75 quant | titative.tw,kf. | 689806 |
| 76 or/13 | -75 | 2378446 |
| 77 (sens | itiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp. | 11325259 |
| 78 di.fs. | | 2760821 |
| 79 or/77 | '-78 | 11325259 |
| 80 3 and | 1 12 and 76 and 79 | 599(|
| 81 (Anir | mals/ or Models, animal/ or Disease models, animal/) not Humans/ | 4900078 |
| 82 ((anir lamb piglet veteri | mal or animals or canine* or cat or cats or dog or dogs or feline or hamster* or or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or t* or porcine or primate* or rabbit* or rats or rat or rodent* or sheep* or inar*) not (human* or patient* or women or men)).tw,kf. | 3315730 |
| 83 81 or | · 82 | 5542727 |
| 84 80 no | ot 83 | 5627 |
| 85 limit | 84 to yr="1961 -Current" | 5627 |

EMBASE [OVID]

| EM | IBASE [OVID] | |
|-----|---|---------|
| Emb | base <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 |

Page 25 of 40

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| 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 |

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| 58 | exp recursive feature elimination/ | 393 |
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| 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 |

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| 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 |
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| 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>

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| 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")) | | |
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| Google Scholar (using Publish or Perish) | | |
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| Electroencephalogram epilepsy [title], machine learning algorithm* diagnos* [keywords] | 32 selected articles out of 32 |
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| 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 |
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| EEG | 0 selected articles out of 3 |

Canadian Agency for Drug and Technologies in Health

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

| Electroencephalography | 0 selected articles out of 1 |
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| 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 |
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| 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 |
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KCE: Belgian health Knowledge Center

All reports - KCE (fgov.be)

| Electroencephalography | 0 selected articles out of 1 |
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| 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 |
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| 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 |
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| électroencéphalographie | 0 selected article out of 27 |
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| Health Information and Quality Autority | |
| Health Technology Assessments HIQA | |

Health Information and Quality Autority

Health Technology Assessments | HIQA

| Electroencephalography | 0 selected articles out of 0 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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

| Santian/tania | щ | | Informatio | Line | |
|------------------------|------|---|------------|------|------------|
| Section/topic | # | | Yes | No | number(s) |
| ADMINISTRATIVE INFO | RMAT | ION | | | |
| 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 | За | 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 |



| Saction/topia | # | Checklist item | Information reported | | Line | |
|---------------------------------------|-----|---|----------------------|----|-----------|--|
| Section/topic | # | | Yes | No | number(s) | |
| 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 | | | Арр. 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 | | | | | | |
| | 15a | Describe criteria under which study data will be quantitatively synthesized | \square | | 184 – 188 | |
| Synthesis | 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>I</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 | |

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un of the body of evidence will be assessed (e.g.



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BMJ Open

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

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BMJ Open

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

Authors

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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;

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| 2 3 | 31 | • High heterogeneity in reporting standards and inclusion criteria is anticipated, possibly preventing |
| 4 5 | 32 | the reliable estimation of diagnostic performance metrics; |
| 6 7 | 33 | • Our review will constitute a comprehensive reference of current practices in the automated |
| 8 | 34 | processing and analysis of routine EEG for epilepsy. |
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| 11 12 | 35 | |
| 13 | 36 | Keywords: Epilepsy – Electroencephalogram – Machine Learning – Diagnosis – Computer-assisted – |
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39 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 brain¹. 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 death⁴. In specialized-care settings, the first anti-seizure medication (ASM) achieves seizure freedom in approximately 47% of patients⁵. A prompt diagnosis is key in the prevention of epilepsy-related morbidity and mortality⁴. 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 minutes⁸. 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 wave⁸. 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 abnormalities⁸. After a first unprovoked seizure in

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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 EEG¹⁶. 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 connectivity²²⁻²⁴, signal predictability and complexity^{25,26}, spectral power^{27,28}, and chaoticity²⁹. 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

87 a physician? What is the benefit over the visual identification of IEDs on routine EEG? And what are the

88 different algorithms that have been tested and how does their diagnostic accuracy compare?

89 Methods

90 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.

94 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.

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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

109 system, with or without prior sleep deprivation. There is no restriction for age groups or diagnoses.

110 **Reference standard**

Population

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}.

115 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 density³⁵. Also included are statistical models that combine several features or models that take as input the raw or processed EEG.

120 Search strategy

21 The search strategy (Appendix 1) was developed by two medical librarians specialized in systematic 22 reviews (BN and RP), and peer-reviewed by a senior colleague. We will search MEDLINE (Ovid), 23 EMBASE (Ovid), EBM reviews (Ovid), IEEE Explore along with grey literature for articles, conference 24 papers and conference abstracts. We will use the Covidence platform (Melbourne, Australia) to manage 25 our data for eligibility assessment, selection, and data collection. Two independent reviewers (EL, and 26 either JNB or BR) will screen the records for eligibility using their title and abstract. Any item selected by 27 either reviewer will proceed to the next phase. This process will be repeated on the screened items, this 28 time by consulting the items' full text. A third, senior reviewer (EBA) will settle conflicts as necessary 29 during the final selection.

| 3 4 | 130 | Data items |
|----------------------|-----|---|
| 5 6 7 | 131 | Data collection will be performed using Covidence by two independent reviewers (EL and JNB/BR), and |
| / 8 | 132 | conflicts will be resolved by a third author (EBA). Authors of the primary study will be contacted if the |
| 9 10 11 | 133 | required data are not available in the original publication. Data collection will include the following |
| 12 13 | 134 | information: |
| 14 15 | 135 | 1. Title and authors of the study, country of sampling, year of publication; |
| 16 17 | 136 | 2. Study type: retrospective vs. prospective, design (cohort, case control); |
| 18 19 | 137 | 3. Study sample: exclusion and inclusion criteria, number of screened and included patients; |
| 20 21 22 | 138 | 4. Data collection: |
| 22 23 24 | 139 | a. Number of patients, number of EEGs, duration of EEG recordings, use of activation |
| 25 26 | 140 | procedures (hyperventilation, photic stimulation, sleep deprivation), setting of recording |
| 27 28 | 141 | (hospitalized or ambulatory), whether the same protocol was used for all patients; |
| 29 30 | 142 | b. Number of electrodes, sampling frequency; |
| 31 32 | 143 | c. If public dataset: reference to the original dataset, dataset name, exclusion/inclusion |
| 33 34 | 144 | criteria used on the EEG segments from the dataset; |
| 35 36 | 145 | d. Participant characteristics: age, sex, comorbidities, number of ASM, age of first seizure; |
| 37 38 | 146 | 5. Reference standard: whether a predefined reference standard was used, definition of reference |
| 39 40 41 | 147 | standard, whether all patients underwent the same reference standard, time lapse between |
| 42 43 | 148 | reference standard and EEG; |
| 44 45 | 149 | 6. Index test: |
| 46 47 | 150 | a. Pre-processing: artifact detection and removal (automated or manual), filtering method, |
| 48 49 | 151 | filtering frequencies, segmentation protocol (whole EEG vs. EEG segments, window |
| 50 51 | 152 | size, overlapping vs. non-overlapping segments, manual vs. automated selection of |
| 52 53 54 55 | 153 | segments), channel selection; |
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| 2 3 4 | 154 | b. Feature extraction and selection: multi-channel vs. single channel, number of channels |
| 5 6 | 155 | selected, whether feature selection was performed, feature extraction algorithm, feature |
| 7 8 | 156 | selection method, whether feature selection was applied to data before vs. after excluding |
| 9 10 | 157 | testing data; |
| 11 12 | 158 | c. Classification: algorithm(s) used for classification, testing methodology (cross-validation |
| 13 14 | 159 | vs. held out testing set); |
| 15 16 | 160 | d. Metric used to report diagnostic performances: ROC AUC, |
| 17 18 | 161 | accuracy/sensibility/specificity, F ₁ -score, reporting of confidence intervals (CI); |
| 19 20 | 162 | 7. Diagnostic performances: number of true positives, number of true negatives, number of false |
| 21 22 | 163 | positives, number of false negatives, reported accuracy, reported sensitivity, reported specificity, |
| 23 24 25 | 164 | reported F ₁ -score, reported ROC AUC (if more than one index test is performed on the same |
| 25 26 27 | 165 | patient, we will only consider the first test); |
| 27 28 20 | 166 | 8. Reproducibility: whether every data processing step is detailed, whether methods can be |
| 30 31 | 167 | reproduced easily, data availability, code availability, open-source computer libraries referenced. |
| 32 33 | | |
| 34 35 | 168 | Risk of bias |
| 36 37 | 169 | The risk of bias of all included studies will be assessed through an adapted version of the QUADAS-2 |
| 38 39 | 170 | tool ³⁶ . Risk of bias for each of the following four elements will be evaluated by two independent |
| 40 41 | 171 | reviewers (EL and JNB/BR) as low, high, or unclear. Conflicts will be resolved by a third author (EBA). |
| 42 43 | 172 | In addition, all publicly available datasets used by at least one of the included studies will be evaluated |
| 44 45 | 173 | with the same tool. The following items will be assessed: |
| 46 47 | 174 | 1. Patient selection |
| 48 49 | 175 | a. Is the population representative of clinical practice? |
| 50 51 | 176 | b. Are inclusion and exclusion criteria identical for cases (patients with epilepsy) and |
| 52 53 | 177 | controls? |
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| 3 4 | 178 | c. Are withdrawals explained and appropriate? If individual EEG segments were excluded, |
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| 5 6 | 179 | were the same criteria used for all segments? |
| 7 8 | 180 | 2. Index test |
| 9 10 | 181 | a. Were the protocols used for recording the EEG identical in all patients, irrespective of the |
| 11 12 | 182 | epilepsy diagnosis? |
| 13 14 | 183 | b. Was the index test validated on an independent sample of patients (patients which were |
| 15 16 | 184 | not used to identify the index test's threshold or train the learning algorithm)? |
| 17 18 | 185 | 3. Reference standard |
| 19 20 | 186 | a. Are the criteria used for the diagnosis of epilepsy specified and acceptable (likely to |
| 21 22 22 | 187 | correctly classify the target condition)? |
| 23 24 25 | 188 | b. Was the reference standard assessment independent and blinded to the index test? |
| 25 26 27 | 189 | 4. Flow and timing |
| 28 29 | 190 | a. Did the whole sample undergo the reference standard? |
| 30 31 | 191 | b. Did the whole sample undergo the same reference standard? |
| 32 33 | 192 | c. Was the time lapse between reference standard and EEG acceptable? |
| 34 35 | 193 | d. Was the same data used in the index method available at the time of the reference |
| 36 37 | 194 | standard? |
| 38 39 | 195 | e. Were all EEGs included in the analysis? |
| 40 41 | | |
| 42 43 | 196 | Data synthesis |
| 44 45 | 197 | We will provide a table summarizing every published study included in the review, comparing the |
| 46 47 | 198 | studies' design, population, reference standard, dataset size, data processing methods, and diagnostic |
| 48 49 | 199 | accuracy. We will also provide a figure that summarizes the risk of bias for each item in the adapted |
| 50 51 | 200 | QUADAS-2 tool, comparing 1) every individual article included in the review, and 2) every public |
| 52 53 | 201 | dataset that is used in ≥ 2 studies. |
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| 3 4 | 202 | We will describe the number of patients, number of EEGs, duration of EEGs, and the EEG-duration-per- |
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| 5 6 | 203 | patient ratio across all included studies. We will report the pooled proportion of patients with focal vs. |
| 7 8 | 204 | generalized epilepsy, adult vs. children, structural vs. non-structural epilepsy, IEDs on EEG, and with |
| 9 10 | 205 | specific epilepsy syndromes. For every publicly available dataset identified during the review, we will |
| 11 12 13 | 206 | report the number of studies that used that dataset in their work. |
| 14 15 | 207 | We will summarize in a table the methods used by the different articles during the pipeline's algorithm |
| 16 17 | 208 | (pre-processing, feature extraction, feature selection, and classification algorithm), along with the |
| 18 19 20 | 209 | proportion of studies that used each method. |
| 21 22 22 | 210 | Analyses |
| 23 24 | 211 | We will estimate the specificity and sensitivity for each study, using the Wilson score to compute 95% |
| 25 26 27 | 212 | CI. For studies with varying thresholds, we will estimate the ROC AUC and 95% CI. |
| 28 29 | 213 | If there are sufficient (\geq 5) studies that report the number of true/false positives and true/false negatives, |
| 30 31 | 214 | we will estimate the pooled sensitivity and specificity of each individual marker using a hierarchical, |
| 32 33 | 215 | bivariate generalized linear mixed model ³⁷ . This allows us to account for the correlation between |
| 34 35 | 216 | specificity and sensitivity in a single study. If \geq 5 studies report these numbers for varying thresholds, we |
| 36 37 | 217 | will estimate the pooled ROC curve using the Rutter and Gatsonis HSROC model ³⁸ . All analyses will be |
| 38 39 40 | 218 | implemented with the R statistical language. A <i>p</i> -value <0.05 will be considered statistically significant. |
| 40 41 42 | 219 | Given insufficient data for the pooled estimates, we will only describe the diagnostic performances |
| 43 44 | 220 | (sensitivity, specificity, ROC AUC) narratively. We will present the results of the analyses with forest |
| 45 46 | 221 | plots. We will compare the performance of the computational markers for the diagnosis of epilepsy to the |
| 47 48 | 222 | visual identification of IEDs on EEG. ⁹ |
| 49 50 | 223 | We will quantify heterogeneity using the variances of the logit specificity and sensitivity, as well as the |
| 52 53 | 224 | median odds ratio (median OR) ³⁹ . The median OR is a measure of inter-study variance translated on the |
| 54 55 | 225 | OR scale. It corresponds to the increase in the odds of being true positive/negative in a patient/control |
| 56 57 | 226 | going from a study with lower sensitivity/specificity to a study with higher sensitivity/specificity. For |
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227 heterogeneity in the ROC plane, we will compute the area of the 95% prediction ellipse and present the 228 results on a scatterplot in the ROC plane.³⁹ The median OR and the area of the 95% prediction ellipse are 229 easily obtained and interpreted, and take into account the correlation between a single study's specificity 230 and sensitivity in contrast to univariate methods like Cochrane's Q and $I^{237,40}$. We will perform subgroup 231 analysis for the following variables: epilepsy type (focal, generalized), epilepsy etiology (structural vs. 232 non-structural), presence of IEDs, age groups (children (< 18 y.o.), adults (> 18 y.o.)), epilepsy 233 syndromes, extracted marker, and dataset used. We will also perform a subgroup analysis for populations 234 with a higher prevalence of IEDs without epilepsy (cerebral palsy, autism spectrum disorder, attention 235 deficit disorder)⁴¹ and for extra-temporal vs. temporal focal epilepsy. We will assess heterogeneity for all 236 subgroup analyses. We will consider a study as belonging to a particular subgroup if $\geq 80\%$ of the studied 237 population belongs to that subgroup. Sensitivity analysis will be conducted for the main analyses by 238 excluding studies with overall high/unclear risk of bias. 239 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

242 classification task or statistically significant in separating the two classes) and the ratio between the

243 number of studies in which this marker was extracted vs. identified as important.

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

- **Patient and public involvement**
 - 246 No patients will be involved for this study.

247 **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

Page 13 of 41

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250 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 251 252 physician, describe the data processing pipelines favored by the researchers to classify the EEG for 253 epilepsy diagnosis, and identify the pitfalls that prevent clinical translation of these algorithms. 254 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 255 256 the EEG signal. Automated extraction of new epilepsy markers on routine EEG could lead to reduced rate 257 of misdiagnosis, increased availability in areas without access to an expert neurophysiologist, and more 258 efficient clinical trials. Research on automatic analysis of EEG data is thriving, in part assisted by the 259 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.¹⁷ 260 261 In recent years, increased computational capacities have allowed the development of powerful algorithms 262 that can learn complex representations such as medical images and EEG signals.^{44,52,53} A growing number 263 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 264 265 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 266 267 clinical-decision support systems also highlight the need for more robust patient selection.^{58–63} 268 Translation of technology to clinical practice requires strong evidence based on high quality research. 269 This review is important because it will establish the potential of automatic analysis of EEG as a 270 diagnostic tool for epilepsy, and if evidence to support its use is lacking, it will identify the pitfalls that 271 need to be overcome in future research. Also, by systematically describing current practices that are used 272 by research groups, it will serve as a reference for new researchers in the field. Upon completion of this 273 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 "proofof-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.

283 List of abbreviations

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

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293 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,

| 2 | | |
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| 3 4 | 296 | and EBA provided content expertise and critically reviewed the manuscript and the search strategy. BN |
| 5 6 7 8 | 297 | and RP designed the search strategy. All authors read and approved the final manuscript. |
| 9 10 11 | 298 | Competing interests |
| 11 12 13 14 | 299 | None of the authors have any competing interest to declare. |
| 16 17 | 300 | Data sharing statement |
| 18 19 20 | 301 | Data collected for this study will be available upon reasonable request. |
| 20 21 22 | | |
| 23 24 | 302 | Ethics and dissemination statement |
| 25 26 | 303 | Ethics approval is not required as this is a review of published evidence. Findings will be disseminated |
| 27 28 29 30 | 304 | through publication in a peer-review journal and presentations at conferences related to this field. |
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| $\begin{array}{c} 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 56\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 56\\ 57\\ 58\end{array}$ | 448 | |
| 59 60 | | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml |

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 |
| | nondom fornatik try lef | 12717 |

| 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 |

| 1 (gradient* boost* or Adaboost*).tw,kf. | 3337 |
|---|----------|
| ⁷ 2 (QEEG or Quantitative Electroencephalogra*).tw,kf. | 1750 |
| ⁷ 3 (chaotic feature* or chaos).tw,kf. | 9755 |
| /4 comput*.tw,kf. | 958508 |
| 75 quantitative.tw,kf. | 689800 |
| 76 or/13-75 | 2378440 |
| 7 (sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp. | 11325259 |
| 78 di.fs. | 276082 |
| 79 or/77-78 | 11325259 |
| 30 3 and 12 and 76 and 79 | 599 |
| 31 (Animals/ or Models, animal/ or Disease models, animal/) not Humans/ | 490007 |
| 32 ((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. | 331573 |
| 33 81 or 82 | 554272 |
| 34 80 not 83 | 562 |
| 35 limit 84 to yr="1961 -Current" | 562 |

EMBASE [OVID]

| EM | BASE [OVID] | | | | |
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| Emb | 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. | 24 |
|----|--|--------|
| 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. | 71 |
| 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. | 6385 |
| 15 | ((Deep or hierarchical) adj1 learning).tw,kf. | 2856 |
| 16 | exp network learning/ | 88 |
| 17 | ((transfer* or representation* or network*) adj2 learning).tw,kf. | 879 |
| 18 | exp artificial intelligence/ | 55153 |
| 19 | ((artificial or machine or computer or computational) adj2 intelligence).tw,kf. | 2305 |
| 20 | exp algorithm/ | 46512 |
| 21 | algorithm*.tw,kf. | 38108 |
| 22 | ((data or binary or multiclass or multilabel) adj2 classification).tw,kf. | 608 |
| 23 | exp artificial neural network/ | 6282 |
| 24 | ((artificial or computational or computer* or convolutional or connectionist or mathematical) adj2 neur* network*).tw,kf. | 3388 |
| 25 | exp pattern recognition/ or exp automated pattern recognition/ | 6842 |
| 26 | (Automat* adj2 pattern* adj2 recognition*).tw,kf. | 19 |
| 27 | exp back propagation/ | 255 |
| 28 | (Back* propagation* or backpropagation*).tw,kf. | 510 |
| 29 | exp Bayesian learning/ | 430 |
| 30 | (Bayes* adj2 (theorem or learning or analysis or approach* or forecast* or method* or prediction*)).tw,kf. | 2411 |
| 31 | exp Feature detection/ or exp feature extraction/ or exp feature learning/ or exp feature ranking/ or exp feature selection/ | 3103 |

Page 27 of 41

| 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. | 1613 |
| 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/ | 72 |
| 42 | (Knowledge adj2 discover*).tw,kf. | 1804 |
| 43 | exp multifactor dimensionality reduction/ | 864 |
| 44 | Dimension* reduction*.tw,kf. | 708 |
| 45 | (predicti* adj2 model*).tw,kf. | 105404 |
| 46 | connectom*.tw,kf. | 622 |
| 47 | neur* decod*.tw,kf. | 43 |
| 48 | exp Outlier detection/ | 47 |
| 49 | (outlier* adj2 detection*).tw,kf. | 101 |
| 50 | exp artificial neural network/ | 6282 |
| 51 | exp Perceptron/ | 2473 |
| 52 | perceptron*.tw,kf. | 396 |
| 53 | (neural adj2 network*).tw,kf. | 8478 |
| 54 | exp radial basis function/ | 942 |
| 55 | radial bas* function*.tw,kf. | 292 |
| 56 | exp random forest/ | 1435 |
| 57 | (random adj2 forest*).tw,kf. | 1775 |

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| 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 |

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| 84 | phase locking value*.tw,kf. | 425 |
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| 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 |

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| 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. | 18 |
| 51 | (Hurst adj2 exponent*).tw,kw,sh. | 14 |
| 52 | (Wavelet* adj2 (analysis or processing or transform*)).tw,kw,sh. | 12 |
| 53 | phase locking value*.tw,kw,sh. | 1 |
| 54 | Fisher information*.tw,kw,sh. | , |
| 55 | Dynamic network*.tw,kw,sh. | 12 |
| 56 | Principal component* analys*.tw,kw,sh. | 1207 |
| 57 | Independant component* analys*.tw,kw,sh. | (|
| 58 | Functional connectivit*.tw,kw,sh. | 2220 |
| 59 | (gradient* boost* or Adaboost*).tw,kw,sh. | 168 |
| 60 | (QEEG or Quantitative Electroencephalogra*).tw,kw,sh. | 44 |
| 61 | (chaotic feature* or chaos).tw,kw,sh. | 14 |
| 62 | comput*.tw,kw,sh. | 80820 |
| 63 | quantitative.tw,kw,sh. | 33700 |
| 64 | or/10-63 | 14549 |
| 65 | (sensitiv* or diagnos* or predict*).mp. or scor*.tw. or observ*.mp. | 81001 |
| 66 | di.tw,kw,sh. | 1716 |
| 67 | 65 or 66 | 81139 |
| 68 | 1 and 9 and 64 and 67 | 35 |
| 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. | 514 |
| 70 | 68 not 69 | 34 |
| 71 | limit 70 to yr="1961 -Current" [Limit not valid in DARE; records were retained] | 32 |
| 72 | remove duplicates from 71 | 31 |

IEEE Xplore

<executed on December 14>

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| (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")) | | |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| Electroencephalogram | 0 selected articles out of 0 |

| EEG | 0 selected articles out of 2 |
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KCE: Belgian health Knowledge Center

All reports - KCE (fgov.be)

| Electroencephalography | 0 selected articles out of 1 |
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| 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 |
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| 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 |
| | 4 |
| Health Information and Quality Autority | |
| Health Technology Assessments HIQA | |

Health Information and Quality Autority

Health Technology Assessments | HIQA

| Electroencephalography | 0 selected articles out of 0 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
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| 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 |
| | 4 |

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/tonic # | | Chacklist item | Information | Line | | |
|------------------------|----------------------------|---|-------------|------|------------|--|
| Section/topic | # | | Yes | No | number(s) | |
| ADMINISTRATIVE INFO | 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 | За | 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 | |



| Soction/tonio # | | | Information reported | | Line | |
|---------------------------------------|-----|---|----------------------|----|-----------|--|
| Section/topic | # | | Yes | No | number(s) | |
| 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 | | | Арр. 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 | | | | | | |
| | 15a | Describe criteria under which study data will be quantitatively synthesized | | | 184 – 188 | |
| Synthesis | 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>I</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 | |

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

and the body of evidence will be assessed (e.g., GRADE)



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