Check for updates

REVIEW

Overview of methods and available tools used in complex brain disorders

[version 1; peer review: 2 approved]

Loukas Ilias, George Doukas, Michael Kontoulis, Konstantinos Alexakis, Ariadni Michalitsi-Psarrou, Christos Ntanos, Dimitris Askounis

Decision Support Systems Laboratory, School of Electrical and Computer Engineering, National Technical University of Athens, Athens, 15773, Greece

v1 **First published:** 19 Sep 2023, **3**:152
https://doi.org/10.12688/openreseurope.16244.1
Latest published: 19 Sep 2023, **3**:152
https://doi.org/10.12688/openreseurope.16244.1

Abstract

Complex brain disorders, including Alzheimer's dementia, sleep disorders, and epilepsy, are chronic conditions that have high prevalence individually and in combination, increasing mortality risk, and contributing to the socioeconomic burden of patients, their families and, their communities at large. Although some literature reviews have been conducted mentioning the available methods and tools used for supporting the diagnosis of complex brain disorders and processing different files, there are still limitations. Specifically, these research works have focused primarily on one single brain disorder, i.e., sleep disorders or dementia or epilepsy. Additionally, existing research initiatives mentioning some tools, focus mainly on one single type of data, i.e., electroencephalography (EEG) signals or actigraphies or Magnetic Resonance Imaging, and so on. To tackle the aforementioned limitations, this is the first study conducting a comprehensive literature review of the available methods used for supporting the diagnosis of multiple complex brain disorders, i.e., Alzheimer's dementia, sleep disorders, epilepsy. Also, to the best of our knowledge, we present the first study conducting a comprehensive literature review of all the available tools, which can be exploited for processing multiple types of data, including EEG, actigraphies, and MRIs, and receiving valuable forms of information which can be used for differentiating people in a healthy control group and patients suffering from complex brain disorders. Additionally, the present study highlights both the benefits and limitations of the existing available tools.

Keywords

neurocognitive disorders, sleep disorders, epilepsy, data analytics, machine learning, data analytics tools

Open Peer Review

Approval Status ✓ ✓

	1	2
version 1 19 Sep 2023	✓ view	✓ view

1. **George Tsihrintzis**, University of Piraeus, Piraeus, Greece

2. **Euripidis Loukis**, University of the Aegean, Samos, Greece

Any reports and responses or comments on the article can be found at the end of the article.



This article is included in the Horizon 2020 gateway.



This article is included in the Brain Dysfunction and Degeneration collection.

Corresponding author: Loukas Ilias (lilias@epu.ntua.gr)

Author roles: Ilias L: Conceptualization, Formal Analysis, Investigation, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Doukas G**: Conceptualization, Formal Analysis, Methodology, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Kontoulis M**: Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Alexakis K**: Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Michalitsi-Psarrou A**: Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Ntanos C**: Conceptualization, Funding Acquisition, Project Administration, Supervision, Writing – Review & Editing; **Askounis D**: Conceptualization, Funding Acquisition, Project Administration, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This project has received funding from the European Union's Horizon 2020 research and innovation programme, in the context of the MES-CoBraD (Multidisciplinary Expert System for the Assessment \& Management of Complex Brain Disorders) project, under grant agreement No GA 965422.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2023 Ilias L *et al*. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Ilias L, Doukas G, Kontoulis M *et al.* **Overview of methods and available tools used in complex brain disorders [version 1; peer review: 2 approved]** Open Research Europe 2023, **3**:152 https://doi.org/10.12688/openreseurope.16244.1

First published: 19 Sep 2023, **3**:152 https://doi.org/10.12688/openreseurope.16244.1

1 Introduction

The Multidisciplinary Expert System for the Assessment & Management of Complex Brain Disorders (MES-CoBraD) is an interdisciplinary project combining real-world data (RWD) from multiple clinical and consumer sources towards improving diagnostic accuracy and therapeutic outcomes in people with complex brain disorders (CoBraD), as reflected in neurocognitive (dementia), sleep, and seizure (epilepsy) disorders and their interdependence. CoBraD, as represented in neurocognitive (e.g., Alzheimer's dementia), sleep, and seizure (i.e., epilepsy) disorders, are chronic conditions that have high prevalence individually and in combination, leading to disability that interferes with activities of daily living (ADLs) and worsens quality of life. According to the World Health Organization (WHO), more than 55 million people have dementia worldwide, while every year there are nearly 10 million new cases. Similarly, WHO states that around 50 million people worldwide have epilepsy. According to estimates, 50 to 70 million people in the U.S. have ongoing sleep disorders (www.sleepfoundation.org).

The MES-CoBraD project exploits real-world data, including questionnaires / structured examinations, neuropsychological tests, imaging data, electroencephalogram (EEG)/polysomnography (PSG), biosamples of blood and cerebrospinal fluid biomarkers, medical device data, and consumer technology data. Several methods have been proposed using the aforementioned data for supporting the diagnosis of complex brain disorders. At the same time, many tools have been introduced which process these data to extract valuable forms of information.

Our main contributions are two-fold. Specifically, we present the first review study, which presents the most common methods used for processing different kinds of data, including PSG, magnetic resonance imaging (MRI), actigraphies, targeted at supporting the diagnosis of multiple complex brain disorders. On the contrary, other research works focus either on one type of data or one single brain disorder. Next, to the best of our knowledge this is the first study listing all the available tools (along with the benefits and drawbacks per tool), which can be used for supporting the diagnosis of complex brain disorders.

This paper is organized as follows: Section 2 presents the related work. Specifically, in Section 2.1, we mention some existing research initiatives using PSG signals along with data analytics and machine learning techniques for supporting the diagnosis of neurocognitive, epilepsy, and sleep disorders. Section 2.2 and Section 2.3 present the research conducted in terms of actigraphies and MRI respectively. In Section 3, we mention some tools, which can be used for performing experiments using all the aforementioned data, namely PSG, MRIs, actigraphies, questionnaires, and so on. Finally, concluding remarks are provided in Section 4.

2 Related work

2.1 Polysomnography (PSG)

EEG was first recorded on the animal brain in 1875 by Richard Caton and on the human brain in 1929 by Hans Berger[1]. The EEG signal displays the brain's electrical activity as recorded by placing metal electrodes over the scalp. A 10–20 electrode placement system has been devised by the International Federation of Societies for Electroencephalography to specify the location of the electrodes with respect to the underlying area of the cerebral cortex. The neuronal activities are measured as electric currents generated by the synchronized activity of a group of specialized pyramidal cells inside the brain. Voltage variations observed in the EEG measurements demonstrate the occurrence of neuronal activity.

EEG signals are non-linear and non-stationary in nature[2,3]. Abnormal brain activity can be distinguished without difficulty from a normal one using signal processing methods since EEG traces tend to differ. Therefore, in clinical practice, EEG signals can be used as a reliable, non-invasive indicator for the observation of mental states and the diagnosis and treatment of brain disorders. EEG signals, with the support of computer-aided technologies, assist in diagnosing various neurological and neuropsychiatric disorders, such as epilepsy[4–7], dementia[8,9], depression[10–13], alcoholism[14–16], sleep disorders[17,18], concussions[19], strokes[20], and problems associated with trauma[21,22].

EEG signals may indicate the following brain rhythms: delta (0.1–3.5) waves, theta (4–7.5 Hz) waves, alpha (8–13 Hz) waves, beta (14–30Hz) and gamma (>30 Hz) waves. Brain rhythms are related to occurrence regions and specific characteristics, and therefore support inferring a patient's mental state[23]. Any small changes in these waves' patterns support the identification of neuronal activity or the diagnosis of neurological disorders.

Despite the significance of EEG signals, it is difficult and time-consuming to get useful information just by observation. In this context, machine learning approaches are increasingly being applied in EEG signal processing and analysis providing preliminary results to neurologists for further assessment. The processing and analysis of EEG signals consist of specific steps[3,24–26], as the academic literature suggests, as follows: signal acquisition, signal preprocessing and enhancement, feature extraction, feature selection or dimensionality reduction and finally machine learning training and testing and results analysis. Signal acquisition methods should ensure the quality of the acquired data, while publicly available EEG datasets, specifying the devices used for the collection, the sampling rate and the number of subjects participating, are frequently used in research studies. The second step, signal preprocessing and enhancement involves the removal of noise and artefacts from the signals. Artefacts may generally fall into two classes, based on their origin[27]: technical artefacts, which arise from

external, technical issues due to the data collection process, such as power line interferences, and physiological artefacts, which are generated by the human body, such as eye blinks, eye

movements (EOG artefacts), muscle activities (EMG artefacts), and heartbeat (ECG artefacts). Various artefact removal methods have been proposed for the handling of all these artefacts. Some of the most common ones encountered in the literature are independent component analysis (ICA), principal component analysis (PCA), common average referencing (CAR), common spatial patterns (CSP), surface Laplacian (SL), adaptive filtering and the wavelet method, each one having its advantages and disadvantages, its preferred use for the removal of a specific type of artefacts and its application for filtering on specific problem types[3,24,25,28]. For example, PCA and ICA seem to be more effective for EOG artifact removal[28], while on their deficiencies PCA is not as powerful as ICA, but ICA requires more computational power for decomposition[24].

After clean signal data have been obtained, feature extraction follows to obtain essential features from the brain signals. Features are parameters providing information about the signal structure and it is in most cases a necessary step for an efficient EEG analysis. The types of features used in EEG analysis are mainly categorized into time-domain features (TDFs), frequency-domain features (FDFs) and time-frequency-domain features (TFDFs). The first, TDFs, are computed on raw, non-processed EEG signals or on preprocessed in the time domain ones. FDFs are calculated on the discrete-Fourier transform of raw EEG signals. Finally, TFDFs are determined on processed EEG signals that contain both time and frequency domain characteristics, such as short-time Fourier transform (STFT) or discrete wavelet transform (DWT)[29]. There have been many techniques proposed in the literature for feature extraction from EEG signals. In 3, feature extraction methods have been analysed in three categories: spectral estimation methods, family of transforms, and time decomposition methods. In spectral estimation methods the Welch method is one of the most popular ones[30], while in the family of transforms methods[31,32], Fourier transform (FT), STFT, continuous wavelet transform (CWT), DWT and wavelet packet decomposition (WPD) should be mentioned. In the time decomposition methods, empirical mode decomposition (EMD)[33] is the most characteristic example. Each method can be used for the computation of different features. In 34, fast Fourier transform (FFT) has been used for computing the normalized band power, while in 35, the gravity frequency, power percentage and frequency variability. DWT is also frequently used in many research papers for the computation of several statistical, wavelet, spectral and non-linear features, such as mean, median and standard deviation[36,37], wavelet coefficients[38,39], band power[40] and entropy[40,41]. In many cases, different bandpass filters are used for the decomposition of the signal into sub-bands and the extraction of features for them. Feature selection and dimensionality reduction are optional steps to improve the quality of results in case many features have arisen from the previous steps. In the study for epilepsy, for instance, the Kruskal Wallis test and the ANOVA test are encountered in the literature for feature selection[42,43], and PCA, ICA, linear discriminant analysis (LDA), Laplacian eigenmaps (LE), kernel principal component analysis (KPCA) for dimensionality reduction. All features extracted are usually arranged into a vector, known as a feature vector.

Finally, the machine learning and testing phase involves mainly classification techniques aiming to classify the results into two or more classes. Indicatively, in epilepsy, researchers may want to classify the dataset instances to seizure/non-seizure[40,44], or to control/interictal/ictal[30,36]. Different types of classifiers have been used by researchers in the field, including linear classifiers, such as support vector machine (SVM)[42], linear and logistic regression[45,46] and LDA[36,47], as well as artificial neural networks (ANN) based classifiers[48–50], nearest neighbor classifiers, such as K-nearest neighbor (KNN)[9,51] and decision trees and random forests[4,52]. In general, since there is a vivid and acute interest in the academic literature for EEG classification and analysis, all the primary methods and techniques in machine learning have been applied with diverse results based on their application field. Therefore, there is no straightforward way to conclude which are better techniques than others horizontally. Supervised learning methods are, however, considered in general more accurate than unsupervised alternative methods. Every method though has its advantages and disadvantages. For example, the ANN method provides high-accuracy results, but it is highly dependent on the number of neurons chosen in the hidden layer, of which their best number and combination is a result of a lot of trial and error. The KNN method is an easy-to-use and understandable method but requires careful and robust feature selection for high performance. After the application of the machine learning phase, the classification results are converted to decisions in the hands of physicians.

2.2 Actigraphies

According to 53, actigraphies are a valuable form of information, which can be used for estimating a range of sleep parameters and thus reveal some sleep disorders. Actigraphies have been proven to be an alternative solution to PSG due to their low-cost[54]. Several machine learning approaches have been used for processing actigraphy data[54]. Specifically, several sleep metrics can be computed through processing actigraphy files, which are mentioned briefly below:

- Time in bed (TIB)
- Sleep period
- Mean activity during TIB
- Sleep minutes during TIB
- Sleep onset latency
- Latency to persistent sleep
- Sleep efficiency
- Episodes of continuous sleep during TIB
- Sleep fragmentation index
- Wake after sleep onset

2.3 MRI

Several machine learning approaches have been introduced for supporting the diagnosis of dementia by using MRIs[55–57]. For processing the MRIs, several preprocessing steps are required, including motion correction, skull strip, white matter segmentation, tessellation, smooth1, inflate1, and so on. For instance, the work proposed in 58 used first recon-all from the FreeSurfer software package and then trained a deep learning model consisting of convolutional neural networks (CNNs).

Also, methods for measuring the brain cortical thickness have been introduced[59]. This can be justified by the fact that assessing cortical brain properties and white matter atrophy has given complementary information about the Alzheimer's disease (AD) process[60]. Additionally, the authors in 61 used three-dimensional (3D) T1-weighted anatomical images and calculate the cortical thickness and volume. In terms of the preprocessing steps, the authors applied the following: brain extraction and intensity normalization, non-rigid registration n to a spherical template atlas, and implementation of the cortical parcellation exploiting the Desikan-Killiany atlas. For performing the experiments, the authors employed the FreeSurfer software package. Finally, a general linear model was used.

Structural equation modeling is also used as a statistical method and is exploited in 62 for teasing out the causal relationships among all these contributors to Alzheimer's disease.

3 List of available tools

In this section, we describe the most common tools, which are used for performing all the experiments mentioned in Section 2.

NumPy (RRID:SCR_008633). NumPy is an open-source Python library[63]. Several libraries are using NumPy, including scikit-learn, SciPy, statsmodels, etc. Below, we mention the benefits and limitations of this Python library:

- Benefits:
  - NumPy provides many functionalities, including indexing, broadcasting, or applying reduction operations. To be more precise, the user can have access to elements of a NumPy array via indexing, can apply multiplications or summations between arrays of different dimensions via broadcasting, and apply reduction operations, i.e., summation, mean, maximum, etc.
  - Statistical functions are provided through this library, including maximum, minimum, q-th percentile of the data, histograms, correlations, etc.
- Limitations:
  - NumPy does not offer many functionalities for pure statistical purposes. On the contrary, the statsmodels and SciPy libraries in Python offer many statistical functions.

Pandas (RRID:SCR_018214). Pandas is an open-source Python library used for working with structured datasets[64].

- Benefits:
  - In big data and especially medical data, datasets contain a lot of missing values. For performing statistical analysis and machine learning techniques, it is imperative that these missing values be imputed. The Pandas library offers functionalities for imputing missing data, including dropna and fillna. In terms of the fillna method, the user is able to apply some interpolation methods for propagating the values backward and forward.
  - The Pandas library provides the groupby function, where the user is capable of grouping the data by some identifiers and then applying statistical analyses. Also, the describe method is used, where the user can get descriptive statistics of all the columns and the rows of a dataset.
  - Similar to SQL, datasets can be combined, merged, and joined.
  - Correlation functions are provided through this library, including the Pearson correlation, Spearman rank correlation, and Kendall Tau correlation.
- Limitations:
  - As mention6ed in the documentation, if one works with very large datasets and a tool like PostgreSQL fits the needs and requirements of the project, then this tool may be the right choice. Also, the documentation recommends the usage of other libraries, including Dask, which can operate more efficiently with larger datasets in parallel.
  - The methods for missing values imputation provided by this library are very simple. The sklearn library offers more algorithms for imputing missing values, including Nearest neighbors imputation and many more.

DASK. The DASK library is a Python library and is used for parallel computing[65]. DASK comprises two parts, namely the dynamic task scheduling and the big data collections.

- Benefits:
  - DASK provides most of the functionalities offered by the NumPy library, including the reduction operations, arithmetic and scalar mathematics, slicing, and many more. Through the blocked algorithms, computations on arrays larger than memory can be performed.
  - DASK can use multiple threads or processes on a single machine, or a cluster of machines to process data in parallel.

  - The DASK DataFrame provides most of the utilities offered by the Pandas library, including the pearson correlation, drop duplicates, row-wise selections, etc.

- Limitations:
  - Some of the utilities offered by the NumPy library are not supported by DASK. Examples are operations like sort or tolist.
  - Some of the utilities offered by the Pandas library are not supported by DASK. To be more precise, setting a new index from an unsorted column is expensive and as a consequence performing operations like groupbyapply and join on unsorted columns is expensive too.

SciPy (RRID:SCR_008058). SciPy[66] constitutes an open-source Python library providing algorithms for many tasks, including optimization, integration, interpolation, differential equations, signal or image processing, etc. SciPy uses functions provided by the NumPy library and is being used by other libraries, such as scikit-learn.

- Benefits:
  - SciPy provides algorithms for signal processing, including convolutions, splines, filters, peak finding, spectral analysis, and many more. Through the fft module, the user is capable of applying the fast Fourier transform, including 1-D, 2, and N-D discrete Fourier transforms, the discrete cosine/sine transforms, and the fast Hankel transform.
  - Statistical functions are also provided by the SciPy library through the stats module. Specifically, one can apply statistical tests, including the t-test, Mann-Whitney U rank test, Wilcoxon signed-rank test, Kruskal-Wallis H-test, etc. Also, one can plot cumulative frequency histograms and compute summary statistics, i.e., mean, variance, skewness, kurtosis, etc. In terms of the correlation functions, the point-biserial, the Spearman, and the Pearson are provided.
  - In terms of the image processing, one can use the module *ndimage* and perform linear and non-linear filtering, region labelling and processing, B-spline interpolation, etc.
- Limitations:
  - Although Scipy provides implementations of statistical tests, it does not provide the functionality of the adjustment/correction of the p-values through multiple comparisons. On the contrary, this functionality is provided by the statsmodels library.

Sklearn (RRID:SCR_019053). Scikit-learn is an open-source Python library[67] offering many functionalities of machine learning techniques, clustering, preprocessing data, and more.

- Benefits:
  - The scikit-learn library provides methods of missing data imputation, including univariate-multivariate imputation, nearest neighbours imputation, etc.
  - Functionalities for clustering and dimensionality reduction techniques are also provided, including the principal component analysis (PCA), t-SNE, etc. These methods are also used for visualization purposes.
- Limitations:
  - Despite the fact that scikit-learn provides methods, which can be used for neuroimaging and time-series data, there are libraries, including Nilearn, MNE, etc. which provide more functionalities.

statsmodel (RRID:SCR_016074). Statsmodels is a library for statistical and econometric analysis in Python[68].

- Benefits:
  - This library provides access to time-series analysis, including univariate autoregressive models (AR), vector autoregressive models (VAR), and univariate autoregressive moving average models (ARMA). These methods can be used for time-series forecasting. Also, autocorrelation, partial autocorrelation, periodogram, etc. are supported.
  - Compared with the SciPy library, the statsmodels library implements more statistical packages. Also, methods for the adjustment/correction of the p-values with multiple tests are also supported, including the Bonferroni, Benjamini-Hochberg[69], Simes-Hochberg, Holm-Sidak, etc.
  - Missing values imputation methods are also supported, including the multiple imputation with chained equations (MICE), and the Bayesian imputation using a Gaussian model.
- Limitations:
  - Some of the functionalities provided via the SciPy library are not available in the statsmodels library. For instance, multidimensional image processing, peak finding, or spectral analysis of signals are some of these methods.

pmdarima. pmdarima is a Python library providing implementations of ARIMA estimators to the user[70].

- Benefits:
  - The most important contribution of the pmdarima library is the implementation of the AutoArima method, which automatically discovers the optimal order for an ARIMA model. It is the implementation of the R programming language.

  - pmdarima provides implementations of the ARIMA estimator and statistical tests, including OCSB test of seasonality, CH test for seasonality, KPSS test for stationarity, PP test for stationarity, and ADF test for stationarity.

  - Also, pmdarima provides a number of transformer classes for pre-processing time series or exogenous arrays, including the Box-Cox transformation and the log transformation.

- Limitations:

  - The statsmodels library implements more statistical tests. However, one should not overlook the implementation of the AutoArima.

sktime. sktime constitutes a scikit-learn compatible Python library with a unified interface for machine learning with time series[71,72].

- Benefits:

  - The sktime library provides algorithms for time-series forecasting, annotation, classification, regression, clustering, and transformations.

  - Regarding time-series forecasting, reduction forecasters that use sklearn regressors or sktime time series regressors to make forecasts, exponential smoothing based forecasters, AR(I)MA type forecasters, ensembles, stacking, etc. are supported by the library.

  - In terms of clustering, clusteing models are provided, including time series K-mean implementation, time series K-medoids implementation, K-shape algorithm wrapper tslearns implementation, and Kernel algorithm wrapper tslearns implementation.

- Limitations:

  - The time series annotation API is still experimental.

Pingouin (RRID:SCR_022261). Pingouin is an open-source Python library, which provides implementations of statistical tests and is based on Pandas and NumPy[73].

- Benefits:

  - Statistical tests are supported, including ANOVA, t-test, bayes factors, multivariate tests, and many more. Also, the functionality of correcting the p-values is supported.

  - The t-test function of Pingouin returns the T-value, the p-value, the degrees of freedom, the effect size (Cohen's d), the 95% confidence intervals of the difference in means, the statistical power and the Bayes factor (BF10) of the test. On the contrary, the SciPy library returns only the T-value and the p-value.

- Limitations:

  - The statsmodels implements more statistical tests.

Nitime (RRID:SCR_002504). Nitime is a Python library and is being used for neuroimaging data (especially functional magnetic resonance imaging data)[74].

- Benefits:

  - The nitime library provides the module called algorithms. This module provides implementations of spectral transforms, coherency, regularized coherency, and event-related analysis.

  - For instance, in terms of spectral transforms the calculation of a standard periodogram and cross-spectral density estimates based on both the regular and multi-taper periodograms are provided.

  - In terms of coherency, this technique is used in order to calculate the functional connectivity between time-series derived from different voxels in the brain, or different ROIs.

  - With regards to the event-related analysis, univariate statistics, which are calculated separately for the time-series in each voxel or each ROI, are provided.

- Limitations:

  - The nitime library provides limited support for preprocessing the data.

MNE software (RRID:SCR_005972). MNE constitutes an open-source Python package for exploring, visualizing, and analyzing human neurophysiological data: magnetoencephalography (MEG), EEG, stereoelectroencephalography (sEEG), electrocorticography (ECoG), near-infrared spectroscopy (NIRS), and more[75].

- Benefits:

  - The MNE library provides many functions for reading data in several formats, including BrainVision (.vhdr, .vmrk, .eeg), European data format (.edf), BioSemi data format (.bdf), general data format (.gdf), Neuroscan CNT (.cnt), and more.

  - Methods for processing data are provided, including filtering (notch), detection and removal of artifacts (ICA and SSP), spectral analysis, making montages, etc.

  - The MNE library provides plots of data.

  - In terms of MRI processing, the MNE library implements some methods, including the coregistration for subjects with structural MRI.

- Limitations:

  - The MNE library provides limited support for MRIs in comparison with other libraries.

YASA. Yet Another Spindle Algorithm (YASA) is a sleep analysis toolbox in Python[76].

- Benefits:
  - This library provides the functionality of the automatic sleep stating of polysomnography data. Also, it provides methods for event detection. Such events are the following: sleep spindles, slow-waves, rapid eye movements on single or multi-channel EEG data.
  - The library supports also methods for artifact rejection, spectral analyses, including bandpower, IRASA method, spectrogram, overnight coupling between EEG bandpower and heart rate variability, and many more.
  - Finally, YASA provides hypnogram analysis, i.e., sleep statistics and stage transitions.
- Limitations:
  - MNE can be used for reading data and preprocessing stages.

WONAMBI (https://wonambi-python.github.io/). WONAMBI is a package used for the analysis of EEG, ECoG and other electrophysiology modalities.

- Benefits:
  - This library provides the functionality of reading files of the following formats: Axon (.abf, ABF2 only), Brain Vision (.vhdr, .vmrk, .eeg / .dat), EEGLAB (.set, .set / .fdt), European data format (.edf), etc.
  - An interface for sleep scoring is also supported.
  - Computes frequency analysis (spectrogram), time-frequency analysis (short-time spectrogram, Morlet wavelet), and detects spindles and slow waves.
- Limitations:
  - YASA offers more functionalities than WONAMBI.

SleepPy. SleepPy constitutes an open source python package prividing functions for the assessment of sleep quantity and quality[77].

- Benefits:
  - This library can process multi-day streams of raw accelerometer data (X, Y & Z) from wrist-worn wearable devices. Sleep reports and visualizations for each recording day are produced.
  - This package derives activity index, identifies major rest period, performs sleep/wake classification, and calculates sleep measures.
- Limitations:
  - SleepPy can work with data generated by the GeneActiv wrist-worn devices (GeneActiv.bin files). It can also support .csv files generated by GeneActiv's software.

Visbrain. Visbrain is an open-source Python package used for the visualization of the brain signals[78].

- Benefits:
  - This package provides the *Signal* module, which implements functionalities, such as de-trending and demeaning, filtering (lowpass, highpass, bandpass, bandstop), extracting the amplitude, phase or power in specific frequency bands.
  - The *Sleep* module provides time-frequency methods, including the fourier-based spectrogram, the morlet's wavelet, and the multitaper-based Wigner spectrogram.
  - Detection of events is also supported, including sleep spindles, K-complexes, rapid-eye movements, slow waves, muscle twitches, and peaks.
  - The *Brain* module provides interface with many functionalities, including connecting deep sources, adding time series, pictures, region of interest, etc.
- Limitations:
  - Visbrain does not provide data analysis functions, which are provided by other libraries.

Neuropycon. Neuropycon is a Python open-source multi-modal brain data analysis toolkit[79]. It includes two different packages, namely the ephypype and the graphpype.

- Benefits:
  - The ephypype package is based on the MNE library and provides pipelines and analyses for electrophysiology data. Specifically, one can apply the ICA algorithm for removing the eyes and heart related artifacts, can compute the power spectral density, the inverse solution starting from raw data, and perform connectivity analysis in sensor or source space.
  - The graphpype package includes graph-theoretical tools for connectivity matrices. In addition, the pipeline called *inv_ts_to_graph* is capable of running the spectral connectivity and the graph computation over time series. Also, the computation of connectivity matrices from preprocessed functional MRI is supported.
- Limitations:
  - Difficulties pertaining to the creation of the workflows.

NiLearn (RRID:SCR_001362). Nilearn constitutes a Python library used for neuroimaging data and provides both statistical and machine learning tools[80].

- Benefits:
  - Nilearn provides the implementation of generalized linear models accompanied with examples in terms of both the first level and second level analysis. Also functionalities for manipulating brain image volumes are supported, including smoothing an image, comparing the means of two images, breaking an atlas of labels in separated regions, resampling an image to a template, etc.
  - Advanced statistical analysis of brain images is supported, including advanced decoding using scikit-learn, multivariate decomposition, and many more.
  - Nilearn provides functionalities for visualizing MRI data in an interactive way.
- Limitations:
  - Nilearn does not support functionalities for reading MRI data.

Dipy (RRID:SCR_000029). Diffusion imaging in Python (Dipy) is an open-source Python library used for the analysis of diffusion magnetic resonance imaging (dMRI) data[81].

- Benefits:
  - DIPY provides algorithms for statistical analysis, reconstruction, registration, tractography, denoising, visualization, and preprocessing.
  - Several methods are available for denoising, including Patch2Self[82], Non-Local Means, local PCA via empirical thresholds, Marcenko-Pastur PCA algorithm, and the supression of Gibbs artifacts.
  - With regards to the registration, the following methods are supported: Affine Registration in 3D, Affine Registration with Masks, Symmetric Diffeomorphic Registration in 2D, Symmetric Diffeomorphic Registration in 3D, Diffeomorphic Registration with binary and fuzzy images, and Streamline-based Registration.
- Limitations:
  - No significant limitations.

Antropy. AntroPy is a Python 3 package providing several time-efficient algorithms for computing the complexity of time-series. It can be used for example to extract features from EEG signals.

- Benefits:
  - This library provides many algorithms, including Approximate Entropy, Hjorth mobility and complexity, Number of zero-crossings, Permutation Entropy, Sample Entropy, Spectral Entropy, Singular Value Decomposition entropy, Detrended fluctuation analysis (DFA), Higuchi Fractal Dimension, Katz Fractal Dimension, and Petrosian fractal dimension.
- Limitations:
  - As mentioned in the documentation, the results need to be double-checked.

UK Biobank accelerometer analysis. UK biobank accelerometer analysis is a tool used for the extraction of information from large accelerometer datasets. It can be installed via Python and also needs Java to be installed[83–86].

- Benefits:
  - This package can process data from raw GENEActiv. Bin files, raw Actigraph .gt3x files (both versions 1 and 2), raw gzipped CSV files. Moreover, this package provides the opportunity for processing hundreds of accelerometer files.
- Limitations:
  - Limited support for various data formats.

PyEEG. PyEEG is an open-source Python library providing functionalities for extracting features from EEG data[87].

- Benefits:
  - Many features can be computed, including the Power Spectral Intensity (PSI) and Relative Intensity Ratio (RIR), Petrosian Fractal Dimension (PFD), Higuchi Fractal Dimension (HFD), Hjorth mobility and complexity, Spectral Entropy (Shannon's entropy of RIRs), SVD Entropy, etc
- Limitations:
  - PyEEG does not provide support for reading data.

Eeglib. eeglib is an open-source Python library used for feature extraction from EEG signals and is based on sliding windows[88].

- Benefits:
  - This library can read data from three formats, namely csv, EDF, and NumPy arrays.
  - It provides functionalities of bandpass filter, ICA, and z-scores normalization to the raw EEG data.
  - FFT, DWT, Power Spectral Density, Band Power, Hjorth Parameters, Detrented Fluctuation Analysis, Sample Entropy, and many more are supported.
- Limitations:
  - MNE can import data in more file formats than Eeglib.

NiBabel (RRID:SCR_002498). Nibabel is a Python library used for reading neuroimaging data[89].

- Benefits:
  - Nibabel provides access to the most common medical and neuroimaging file formats, including ANALYZE (plain, SPM99, SPM2 and later), GIFTI, NIfTI1, NIfTI2, MINC1, MINC2, MGH and ECAT as well as Philips PAR/REC.
  - Access to head information and the image data is supported.
  - Easy-to-read documentation with many examples.
- Limitations:
  - Limited support for DICOM.

AcqKnowledge Software (RRID:SCR_014279) (https://www.biopac.com/)

- Benefits:
  - Offers integrated functionality to control the data acquisition process using the associated hardware device.
  - Reports and displays all data gathered by actigraphy devices and displays sleep and actigraphy metrics.
  - Has many display options and analytics functions, relating to both actigraphies and eeg data.
  - Automated analysis for ECG, HRV, EEG, EMG, EGG, and many more.
- Limitations:
  - Proprietary application designed to work in tandem with specific devices

MotionWare (RRID:SCR_022253)[90]

- Benefits:
  - Reports and displays all data gathered by actigraphy devices and offer sleep and actigraphy analytics, including automatic sleep scoring, circadian rhythm NPCRA analysis and physical activity analysis.
  - Offers detailed view and plot options.
  - Has cloud integration for the handling of data.
- Limitations:
  - Proprietary application designed to work in tandem with specific devices.

Respironics Actiware (RRID:SCR_016440)[91]

- Benefits:
  - Reports and displays all data gathered by actigraphy devices and offer sleep and actigraphy analytics, including automatic sleep scoring.
  - Offers detailed view and plot options.
- Limitations:
  - Proprietary application designed to work in tandem with specific devices (Actiwatch), but it at least supports using data from older legacy versions of the devices.
  - Actiwatch, the associated device has been reportedly recently discontinued and new ones aren't offered in clinician or research markets, making the future and usability of Actiware uncertain[92].

MedPy (http://loli.github.io/medpy/).

- Benefits:
  - Open-source application with code available in public code repositories.
  - Can handle many different formats of medical files including large files with multidimensional features.
  - Offers several two dimensional image filters in a n-dimensional version appropriate for medical imaging.
  - Offers image feature extractors such as histograms, means, indices.
  - Can create DIMACS graphs from sources by using aribtrary energy n-dimensional images.
- Limitations:
  - No major release the last years but fixes and minor development seems to continue to this day.
  - Its a library focused on specific and bare bone functionality that needs effort from non technical users to implement in applications.

Skimage. scikit-image is a collection of algorithms for image processing[93].

- Benefits:
  - This package provides algorithms for the detection of edges and lines, geometrical transformations and registration, filtering and restoration, detection of features and objects, segmentation of objects, and more.
- Limitations:
  - Skimage does not provide many functionalities for medical images.

OpenCV (RRID:SCR_015526). OpenCV is a library available in C++, Java, and Python and is used for image processing[94].

- Benefits:
  - OpenCV provides many functionalities, including image filtering, feature and object detection, image segmentation, motion analysis, object tracking, Canny edge detector, Hough Line/Circle Transform, and Affine Transformations, histogram equalisation, calculation, and comparison.
  - OpenCV provides a forum, where one could seek for help.
- Limitations:
  - Compared to other libraries, i.e., Nilearn, this library offers general functions.

fMRIPrep (RRID:SCR_016216). Fmriprep is a functional magnetic resonance imaging (fMRI) data preprocessing pipeline[95].

- Benefits:
  - The fMRIPrep pipeline uses a combination of tools from well-known software packages, including FSL, ANTs, FreeSurfer and AFNI.
  - Optimal data processing quality is achieved, preprocessing quality reports are generated, processing steps are automated.
- Limitations:
  - Fmriprep is not easily customizable, meaning that changes to the steps of a pipeline may be difficult.

Nipype (RRID:SCR_002502). Nipype is a Python project providing interface to existing neurimaging softwares[96].

- Benefits:
  - Nipype provides interfaces for many tools, including AFNI, ANTs, dcm2nii, DIPY, FreeSurfer, FSL, MIPAV, MNE, Statistical Parametric Mapping (SPM), 3D Slicer, etc.
  - Nipype provides a forum, where one can seek for assistance.
- Limitations:
  - Although it provides access to neuroimaging tools, it does not support all the functionalities offered by these tools. For instance, SAMSEG of FreeSurfer is not supported via Nipype.
  - One can use FreeSurfer, instead of the interface of nipype, since FreeSurfer is dockerized.

NLTools. NLTools is a Python package for analyzing neuroimaging data[97].

- Benefits:
  - NLTools provides a wide number of functionalities, including the identification of spikes from time-series data, getting the median of each voxel or image, applying Fisher's r to z transformation, extracting brain connected regions into separate regions, running a mass-univariate regression across voxels, applying spatial smoothing, and many more.
- Limitations:
  - No significant limitations.

ActiLife. ActiLife is ActiGraph's premier actigraphy data analysis software platform.[98]

- Benefits:
  - Developed specifically for advanced sleep research and clinical applications
  - Includes a variety of sophisticated sleep analysis and reporting tools.
  - Representation of graphical sleep/wake activity and calculate sleep statistics such as onset, sleep latency, amount of sleep, and sleep efficiency using several validated scoring algorithms
- Limitations:
  - The full functionality of the software requires activation licenses.

PyActigraphy. PyActigraphy constitutes an open-source Python library used for actigraphy data visualization and analysis[99].

- Benefits:
  - PyActigraphy can read data from many formats, including:
    * Actigraph: wGT3X-BT
    * CamNtech: Actiwatch 4 and MotionWatch 8
    * Condor Instrument: ActTrust 2
    * Daqtix: Daqtometer
    * Respironics: Actiwatch 2 and Actiwatch Spectrum (plus)
    * Tempatilumi (CE Brasil)
  - Algorithms for detecting resting periods are supported, including the Cole-Kripke's[100], Sadeh's[101], Crespo's[102], and Roenne-berg's[103].
  - Advanced signal processing functions are provided, including the Cosinor Analysis[104], Detrended

Fluctuation Analysis[105,106], Functional Linear Modelling[107], Locomotor Inactivity during sleep[108], Singular Spectrum Analysis[109].

- Limitations:
  - PyActigraphy package is currently under development and many more features are expected to be implemented.

FactorAnalyzer (https://factor-analyzer): FactorAnalyzer constitutes an open-source Python library used for performing exploratory factor analysis (EFA) and confirmatory factor analysis (CFA).

- Benefits:
  - Includes class to perform exploratory and factor analysis, with several optional rotations.
  - Includes class to perform confirmatory factor analysis, with certain pre-defined constraints.
  - In exploratory factor analysis, factor extraction can be performed using a variety of estimation techniques.
- Limitations:
  - The Confirmatory Factor Analyzer class is very experimental at this point.

lifelines: lifelines constitutes an open-source Python library used as a complete survival analysis library[110].

- Benefits:
  - Incorporates the most popular parametric, semi-parametric and non-parametric models
  - Can handle right, left and interval censored data
  - Provides internal plotting methods
  - Facilitates an easy and intuitive way of use
- Limitations:
  - No significant limitations.

zEpid (https://zepid): zEpid constitutes an open-source Python toolkit used for epidemiology analysis.

- Benefits:
  - Provides basic epidemiology calculations and summary measure calculations from summary data
  - Supports several different graphics generated using matplotlib.
  - Provides sensitivity analyses to determine the robustness of findings against certain assumptions or unmeasured factors.
- Limitations:
  - No significant limitations.

semopy: semopy (Structural Equation Models Optimization in Python) is designed to help statisticians that employ SEM techniques to handle their research using Python[111,112].

- Benefits:
  - Provides a User-friendly syntax for specifying SEM models.
  - Provides Random Effects model (or Linear Mixed Models/LMM) with SEM to take population structure into account when necessary.
  - Supports the prediction of data, the imputation of missing values and the estimation of factor scores.
  - Incorporates some utilities to perform EFA to extract measurement structure from the data.
  - Supports random models generation to test semopy or other SEM packages features
  - Excellent performance when applied to big datasets.
  - Active community with issue tracking and updates
- Limitations:
  - No significant limitations.

lavaan: The lavaan package is developed to provide users, researchers and teachers a free open-source, but commercialquality package for latent variable modeling[113].

- Benefits:
  - Provides the estimation of large variety of multivariate statistical models, including path analysis, confirmatory factor analysis, structural equation modeling and growth curve models
  - It is deemed as reliable, open and extensible
  - Facilitates an easy and intuitive way of use
  - Active community with issue tracking and frequent new releases
- Limitations:
  - No significant limitations.

scikit-survival: scikit-survival is a Python module for survival analysis built on top of scikit-learn[114].

- Benefits:
  - Enhance understanding of predictions in Survival Analysis

  - Provides evaluating Survival Models, Gradient Boosted and Penalized Cox Models
  - Active community with issue tracking and frequent new releases

- Limitations:
  - No significant limitations.

EPViz: EPViz (EEG Prediction Visualizer) is a tool to aid researchers in developing, validating, and reporting their predictive modeling outputs[115].

- Benefits:
  - Provides a basic functionality for EEG signals visualisation, with average reference and longitudinal bipolar montages and an annotation editor
  - Allows researchers to load a PyTorch deep learning model.
  - Computing basic signal statistics
  - Incorporates spectrogram computation and analysis

- Limitations:
  - Simple signal viewer good for research purposes, but lacks the needed resolution for clinical diagnosis.

EEGraph: EEGraph is a Python library to model electroencephalograms (EEGs) as graphs, so the connectivity between different brain areas could be analyzed[116].

- Benefits:
  - Incorporates several different connectivity measures in EEGraph, like correlations, coherence, WPLI, PLV, etc.
  - Supports the export of the graph as a NetworkX graph-like object or/and as graphically visualised object.

- Limitations:
  - No significant limitations.

EDFbrowser (https://www.teuniz.net/):

- Benefits:
  - EDFBrowser offers many visualisation options, such as filtering, saving montages with all the parameterisation, including the option to calibrate according the users screen and set the timescale of EDF channels per centimeters of the screen, useful for many neurologists, a functionality not usually present in most open source tools.
  - Allows annotation of file, combined with storing and displaying hypnograms in annotation form.
  - Provides many analysis functions such as power spectral analysis, color density spectral array, amplitude integrated electroencephalography, waveform averaging[117].
  - Offers capabilities to repair, edit or anonymise files.

- Limitations:
  - While remote control capabilities exist through a direct TCP connect, very few options are available.

FreeSurfer (RRID:SCR_001847) (https://surfer.nmr.mgh.harvard.edu/): FreeSurfer is an open source neuroimaging toolkit for processing, analysing, and visualising human brain MR images.

- Benefits:
  - FreeSurfer can be used for the analysis and visualisaton of structural, functional, and diffusion neuroimaging data from cross-sectional and longitudinal studies.
  - FreeSurfer provides the algorithm of recon-all, which includes 31 processing stages, including motion correction and conform, skull strip, spherical mapping/registration, and many more.
  - FreeSurfer supports the functionality of SAMSEG, which is a tool to robustly segment dozens of brain structures from head MRI scans without preprocessing.

- Limitations:
  - The running time of recon-all may range from some hours to days.

Neurodesk (RRID:SCR_023714) (https://www.neurodesk.org/): NeuroDesk constitutes a flexible, scalable and browser-based data analysis environment for reproducible neuroimaging.

- Benefits:
  - NeuroDesk provides analyses of electrophysiological and neuroimaging data, including functional imaging, hippocampus, image reconstruction/registration/segmentation, structural imaging, spine, statistics, etc.
  - With regards to the electrophysiological data, NeuroDesk provides access to brainstorm, eeglab, fieldtrip, and MNE.
  - Regarding neuroimaging data, the FreeSurfer is supported. All the analyses supported by FreeSurfer, including visualisation approaches, are provided in NeuroDesk.
  - 3D Slicer is also supported.
  - Documentation for using docker containers is supported.

  - NeuroDesk applications can be also exploited in Google Colab.

- Limitations:
  - No significant limitations

4 Conclusions

In contrast with other studies, which examined some methods and tools used for supporting the diagnosis of one disorder, this study reviewed advanced analytics and ML methods for neurocognitive disorders (dementia), sleep disorders, and epilepsy. Additionally, this is the first study reviewing all the available tools, which can be used for processing different types of data, including PSG, actigraphies, MRIs, and simple tabular data (questionnaire data). At the same time, all the available tools are accompanied by some benefits and limitations. We hope that this current study will be helpful for AI and ML researchers working towards the diagnosis of complex brain disorders, including dementia, epilepsy, and sleep disorders. Additionally, these methods and tools can be used for other brain disorders as well using actigraphies, PSG, and MRIs.

Ethics and consent statement

Ethical approval and consent were not required.

Data availability

No data are associated with this article.

References

1. Wolpaw JR, Birbaumer N, Heetderks WJ, *et al.*: **Brain-computer interface technology: a review of the first international meeting.** *IEEE Trans Rehabil Eng.* 2000; **8**(2): 164–173.
PubMed Abstract | Publisher Full Text
2. Subha DP, Joseph PK, Acharya UR, *et al.*: **Eeg signal analysis: a survey.** *J Med Syst.* 2010; **34**(2): 195–212.
PubMed Abstract | Publisher Full Text
3. Khosla A, Khandnor P, Chand T: **A comparative analysis of signal processing and classification methods for different applications based on eeg signals.** *Biocybern Biomed Eng.* 2020; **40**(2): 649–690.
Publisher Full Text
4. Zhang T, Chen W, Li M: **Generalized stockwell transform and svd-based epileptic seizure detection in eeg using random forest.** *Biocybern Biomed Eng.* 2018; **38**(3): 519–534.
Publisher Full Text
5. Wu J, Zhou T, Li T: **Detecting epileptic seizures in eeg signals with complementary ensemble empirical mode decomposition and extreme gradient boosting.** *Entropy (Basel).* 2020; **22**(2): 140.
PubMed Abstract | Publisher Full Text | Free Full Text
6. Alickovic E, Kevric J, Subasi A: **Performance evaluation of empirical mode decomposition, discrete wavelet transform, and wavelet packed decomposition for automated epileptic seizure detection and prediction.** *Biomed Signal Process Control.* 2018; **39**: 94–102.
Publisher Full Text
7. Ilias L, Askounis D, Psarras J: **Multimodal detection of epilepsy with deep neural networks.** *Expert Syst Appl.* 2023; **213**(Part B): 119010.
Publisher Full Text
8. Ruiz-Gómez SJ, Gómez C, Poza J, *et al.*: **Automated multiclass classification of spontaneous eeg activity in alzheimer's disease and mild cognitive impairment.** *Entropy (Basel).* 2018; **20**(1): 35.
PubMed Abstract | Publisher Full Text | Free Full Text
9. Yu H, Lei X, Song Z, *et al.*: **Supervised network-based fuzzy learning of eeg signals for alzheimer's disease identification.** *IEEE Transactions on Fuzzy Systems.* 2020; **28**(1): 60–71.
Publisher Full Text
10. Yang J, Zhang Z, Fu Z, *et al.*: **Cross-subject classification of depression by using multiparadigm eeg feature fusion.** *Comput Methods Programs Biomed.* 2023; **233**: 107360.
PubMed Abstract | Publisher Full Text
11. Sharma M, Achuth PV, Deb D, *et al.*: **An automated diagnosis of depression using three-channel bandwidth-duration localized wavelet filter bank with eeg signals.** *Cogn Syst Res.* 2018; **52**: 508–520.
Publisher Full Text
12. Bachmann M, Päeske L, Kalev K, *et al.*: **Methods for classifying depression in single channel EEG using linear and nonlinear signal analysis.** *Comput Methods Programs Biomed.* 2018; **155**: 11–17.
PubMed Abstract | Publisher Full Text
13. Acharya UR, Oh SL, Hagiwara Y, *et al.*: **Automated eeg-based screening of depression using deep convolutional neural network.** *Comput Methods Programs Biomed.* 2018; **161**: 103–113.
PubMed Abstract | Publisher Full Text
14. Anuragi A, Sisodia DS: **Alcohol use disorder detection using eeg signal features and flexible analytical wavelet transform.** *Biomed Signal Process Control.* 2019; **52**: 384–393.
Publisher Full Text
15. Acharya UR, Vidya S, Bhat S, *et al.*: **Computer-aided diagnosis of alcoholism-related eeg signals.** *Epilepsy Behav.* 2014; **41**: 257–263.
PubMed Abstract | Publisher Full Text
16. Rodrigues JDC, Filho PPR, Peixoto E **Jr,** *et al.*: **Classification of EEG signals to detect alcoholism using machine learning techniques.** *Pattern Recognit Lett.* 2019; **125**: 140–149.
Publisher Full Text
17. Sharma M, Tiwari J, Acharya UR: **Automatic sleep-stage scoring in healthy and sleep disorder patients using optimal wavelet filter bank technique with eeg signals.** *Int J Environ Res Public Health.* 2021; **18**(6): 3087.
PubMed Abstract | Publisher Full Text | Free Full Text
18. Siddiqui MM, Rahman S, Saeed SH, *et al.*: **Eeg signals play major role to diagnose sleep disorder.** *Int J Electr Comput Sci Eng.* 2013; **2**(2): 503–505.
Reference Source
19. Corbin-Berrigan LA, Teel E, Vinet SA, *et al.*: **The use of electroencephalography as an informative tool in assisting early clinical management after sport-related concussion: a systematic review.** *Neuropsychol Rev.* 2023; **33**(1): 144–159.
PubMed Abstract | Publisher Full Text
20. Qureshi AA, Zhang C, Zheng R, *et al.*: **Ischemic stroke detection using EEG signals**. In *Proceedings of the 28th Annual International Conference on Computer Science and Software Engineering*. CASCON '18, USA, IBM Corp, 2018; 301–308.
Reference Source
21. Fisher SF, Lanius RA, Frewen PA: **Eeg neurofeedback as adjunct to psychotherapy for complex developmental trauma-related disorders: Case study and treatment rationale.** *Traumatology.* 2016; **22**(4): 255–260.
Publisher Full Text
22. Howells F, Stein D, Russell V: **Childhood trauma is associated with altered cortical arousal: Insights from an eeg study.** *Front Integr Neurosci.* 2012; **6**: 120.
PubMed Abstract | Publisher Full Text | Free Full Text
23. Novik O, Smirnov K, Volgin M, *et al.*: **Structures of the brain**. *Electromagnetic Geophysical Fields: Precursors to Earthquakes and Tsunamis; Impacts on the Brain and Heart*. 2019; 69–89.
Publisher Full Text
24. Xie Y, Oniga S: **A review of processing methods and classification algorithm for eeg signal.** *Carpathian J Electr Comp Eng.* 2020; **13**(1): 23–29.
Publisher Full Text
25. Lakshmi MR, Prasad TV, Prakash VC: **Survey on eeg signal processing methods.** *Int J Adv Res Comput Sci Softw Eng.* 2014; **4**(1): 84–91.
Reference Source
26. Hosseini MP, Hosseini A, Ahi K: **A review on machine learning for eeg signal processing in bioengineering.** *IEEE Rev Biomed Eng.* 2021; **14**: 204–218.
PubMed Abstract | Publisher Full Text
27. Jiang X, Bian GB, Tian Z: **Removal of artifacts from EEG signals: A review.** *Sensors (Basel).* 2019; **19**(5): 987.
PubMed Abstract | Publisher Full Text | Free Full Text
28. Roy V, Shukla PK, Gupta AK, *et al.*: **Taxonomy on eeg artifacts removal**

methods, issues, and healthcare applications. *J Organ End User Comput.* 2021; **33**(1): 19–46.
Publisher Full Text

29. Boonyakitanont P, Lek-uthai A, Chomtho K, *et al.*: **A review of feature extraction and performance evaluation in epileptic seizure detection using eeg.** *Biomed Signal Process Control.* 2020; **57**: 101702.
Publisher Full Text

30. Faust O, Acharya RU, Allen AR, *et al.*: **Analysis of eeg signals during epileptic and alcoholic states using ar modeling techniques.** *IRBM.* 2008; **29**(1): 44–52.
Publisher Full Text

31. Al-Fahoum AS, Al-Fraihat AA: **Methods of eeg signal features extraction using linear analysis in frequency and time-frequency domains.** *ISRN Neurosci.* 2014; **2014**: 730218.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Borisagar KR, Thanki RM, Sedani BS: **Fourier transform, short-time fourier transform, and wavelet transform**. *Speech Enhancement Techniques for Digital Hearing Aids*. 2019; 63–74.
Publisher Full Text

33. Jiang D, Lu YN, Ma Y, *et al.*: **Robust sleep stage classification with single-channel EEG signals using multimodal decomposition and hmm-based refinement.** *Expert Syst Appl.* 2019; **121**: 188–203.
Publisher Full Text

34. Seo J, Laine TH, Sohn KA: **Machine learning approaches for boredom classification using eeg.** *J Ambient Intell Humaniz Comput.* 2019; **10**: 3831–3846.
Publisher Full Text

35. Chen LL, Zhao Y, Zhang J, *et al.*: **Automatic detection of alertness/drowsiness from physiological signals using wavelet-based nonlinear features and machine learning.** *Expert Syst Appl.* 2015; **42**(21): 7344–7355.
Publisher Full Text

36. Subasi A, Gursoy MI: **EEG signal classification using PCA, ICA, lDA and support vector machines.** *Expert Syst Appl.* 2010; **37**(12): 8659–8666.
Publisher Full Text

37. Wang X, Gong G, Li N: **Automated recognition of epileptic eeg states using a combination of symlet wavelet processing, gradient boosting machine, and grid search optimizer.** *Sensors (Basel).* 2019; **19**(2): 219.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Richhariya B, Tanveer M: **Eeg signal classification using universum support vector machine.** *Expert Syst Appl.* 2018; **106**: 169–182.
Publisher Full Text

39. Pandey P, Seeja KR: **Emotional state recognition with eeg signals using subject independent approach**. In *Data Science and Big Data Analytics: ACM-WIR 2018.* Springer, 2019; **16**: **117–124.**
Publisher Full Text

40. Ibrahim S, Djemal R, Alsuwailem A: **Electroencephalography (eeg) signal processing for epilepsy and autism spectrum disorder diagnosis.** *Biocybern Biomed Eng.* 2018; **38**(1): 16–26.
Publisher Full Text

41. Wang Q, Zhao D, Wang Y, *et al.*: **Ensemble learning algorithm based on multi-parameters for sleep staging.** *Med Biol Eng Comput.* 2019; **57**(8): 1693–1707.
PubMed Abstract | Publisher Full Text

42. Li M, Chen W, Zhang T: **Automatic epilepsy detection using wavelet-based nonlinear analysis and optimized svm.** *Biocybern Biomed Eng.* 2016; **36**(4): 708–718.
Publisher Full Text

43. Bhattacharyya A, Sharma M, Pachori RB, *et al.*: **A novel approach for automated detection of focal eeg signals using empirical wavelet transform.** *Neural Comput & Applic.* 2018; **29**: 47–57.
Publisher Full Text

44. Quintero-Rincón A, Pereyra M, D'Giano C, *et al.*: **Fast statistical model-based classification of epileptic eeg signals.** *Biocybern Biomed Eng.* 2018; **38**(4): 877–889.
Publisher Full Text

45. Dora C, Biswal PK: **Robust ECG artifact removal from EEG using continuous wavelet transformation and linear regression.** In: *2016 International Conference on Signal Processing and Communications (SPCOM).* 2016; 1–5.
Publisher Full Text

46. Struck AF, Ustun B, Ruiz AR, *et al.*: **Association of an electroencephalography-based risk score with seizure probability in hospitalized patients.** *JAMA Neurol.* 2017; **74**(12): 1419–1424.
PubMed Abstract | Publisher Full Text | Free Full Text

47. Ishfaque A, Awan AJ, Rashid N, *et al.*: **Evaluation of ann, lda and decision trees for eeg based brain computer interface.** In: *2013 IEEE 9th International Conference on Emerging Technologies (ICET).* 2013; 1–6.
Publisher Full Text

48. Tagluk ME, Akin M, Sezgin N: **Classıfication of sleep apnea by using wavelet transform and artificial neural networks.** *Expert Syst Appl.* 2010; **37**(2): 1600–1607.
Publisher Full Text

49. Choubey H, Pandey A: **A combination of statistical parameters for the detection of epilepsy and eeg classification using ann and knn classifier.** *SIViP.* 2021; **15**: 475–483.
Publisher Full Text

50. Omidvar M, Zahedi A, Bakhshi H: **Eeg signal processing for epilepsy seizure detection using 5-level db4 discrete wavelet transform, ga-based feature selection and ann/svm classifiers.** *J Ambient Intell Human Comput.* 2021; **12**: 10395–10403.
Publisher Full Text

51. Yuvaraj R, Acharya UR, Hagiwara Y: **A novel parkinson's disease diagnosis index using higher-order spectra features in eeg signals.** *Neural Comput & Applic.* 2018; **30**: 1225–1235.
Publisher Full Text

52. Rajaguru H, Prabhakar SK: **Sparse pca and soft decision tree classifiers for epilepsy classifi cation from EEG signals.** In: *2017 International conference of Electronics, Communication and Aerospace Technology (ICECA).* 2017; **1**: 581–584.
Publisher Full Text

53. Fekedulegn D, Andrew ME, Shi M, *et al.*: **Actigraphy-Based Assessment of Sleep Parameters.** *Ann Work Expo Health.* 2020; **64**(4): 350–367.
PubMed Abstract | Publisher Full Text | Free Full Text

54. Khademi A, EL-Manzalawy Y, Master L, *et al.*: **Personalized sleep parameters estimation from actigraphy: A machine learning approach.** *Nat Sci Sleep.* 2019; **11**: 387–399.
PubMed Abstract | Publisher Full Text | Free Full Text

55. Tohka J, Moradi E, Huttunen H, *et al.*: **Comparison of feature selection techniques in machine learning for anatomical brain mri in dementia.** *Neuroinformatics.* 2016; **14**(3): 279–296.
PubMed Abstract | Publisher Full Text

56. Castellazzi G, Cuzzoni MG, Ramusino MC, *et al.*: **A machine learning approach for the differential diagnosis of alzheimer and vascular dementia fed by mri selected features.** *Front Neuroinform.* 2020; **14**: 25.
PubMed Abstract | Publisher Full Text | Free Full Text

57. Chagué P, Marro B, Fadili S, *et al.*: **Radiological classification of dementia from anatomical mri assisted by machine learning-derived maps.** *J Neuroradiol.* 2021; **48**(6): 412–418.
PubMed Abstract | Publisher Full Text

58. Bäckström K, Nazari M, Gu IYH, *et al.*: **An efficient 3d deep convolutional network for alzheimer's disease diagnosis using mr images.** In: *2018 IEEE 15th International Symposium on Biomedical Imaging (ISBI 2018).* 2018; 149–153.
Publisher Full Text

59. Sattari N, Faeghi F, Shekarchi B, *et al.*: **Assessing the changes of cortical thickness in alzheimer disease with mri using freesurfer software.** *Basic Clin Neurosci.* 2022; **13**(2): 185–192.
PubMed Abstract | Publisher Full Text | Free Full Text

60. Ming J, Harms MP, Morris JC, *et al.*: **Integrated cortical structural marker for alzheimer's disease.** *Neurobiol Aging.* 2015; **36 Suppl 1**: S53–S59.
PubMed Abstract | Publisher Full Text | Free Full Text

61. Mentzelopoulos A, Gkiatis K, Karanasiou I, *et al.*: **Chemotherapy-induced brain effects in small-cell lung cancer patients: a multimodal mri study.** *Brain Topogr.* 2021; **34**(2): 167–181.
PubMed Abstract | Publisher Full Text

62. Ferrari-Souza JP, Lussier FZ, Leffa DT, *et al.*: ***APOEε4* associates with microglial activation independently of aβ plaques and tau tangles.** *Sci Adv.* 2023; **9**(14): eade1474.
PubMed Abstract | Publisher Full Text | Free Full Text

63. Harris CR, Millman KJ, Van Der Walt SJ, *et al.*: **Array programming with numpy.** *Nature.* 2020; **585**(7825): 357–362.
PubMed Abstract | Publisher Full Text | Free Full Text

64. McKinney W: **pandas: a foundational python library for data analysis and statistics.** *Python for High Performance and Scientific Computing.* 2011; **14**(9): 1–9.
Reference Source

65. Rocklin M: **Dask: Parallel computation with blocked algorithms and task scheduling.** In: *Proceedings of the 14th python in science conference.* Citeseer, 2015; **130**: 136.
Publisher Full Text

66. Virtanen P, Gommers R, Oliphant TE, *et al.*: **Scipy 1.0: fundamental algorithms for scientific computing in python.** *Nat Methods.* 2020; **17**(3): 261–272.
PubMed Abstract | Publisher Full Text | Free Full Text

67. Pedregosa F, Varoquaux G, Gramfort A, *et al.*: **Scikit-learn: Machine learning in python.** *J Mach Learn Res.* 2011; **12**: 2825–2830.
Reference Source

68. Seabold S, Perktold J: **Statsmodels: Econometric and statistical modeling with python.** In: *Proceedings of the 9th Python in Science Conference.* Austin, TX, 2010; **57**: 10–25080.
Reference Source

69. Benjamini Y, Hochberg Y: **Controlling the false discovery rate: A practical and powerful approach to multiple testing.** *Journal of the Royal Statistical Society. Series B (Methodological).* 1995; **57**(1): 289–300.
Reference Source

70. Smith TG: **pmdarima: Arima estimators for Python.** 2017.
Reference Source

71. Löning M, Bagnall T, Middlehurst M, *et al.*: **alan-turing-institute/sktime: v0.10.1.** February 2022.
Publisher Full Text

72. Löning M, Bagnall A, Ganesh S, *et al.*: **sktime: A unified interface for machine learning with time series.** *arXiv preprint arXiv: 1909.07872.* 2019.
Reference Source

73. Vallat R: **Pingouin: statistics in python.** *J Open Source Softw.* 2018; **3**(31): 1026.
Publisher Full Text

74. Rokem AS, Trumpis M, Pérez F: **Nitime: time-series analysis for neuroimaging data.** 2009.
Reference Source

75. Gramfort A, Luessi M, Larson E, *et al.*: **MEG and EEG data analysis with MNE-python.** *Front Neurosci.* 2013; **7**: 267.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

76. Vallat R, Walker MP: **An open-source, high-performance tool for automated sleep staging.** *eLife.* 2021; **10**: e70092.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

77. Christakis Y, Mahadevan N, Patel S: **Sleeppy: A python package for sleep analysis from accelerometer data.** *J Open Source Softw.* 2019; **4**(44): 1663.
Publisher Full Text

78. Combrisson E, Vallat R, O'Reilly C, *et al.*: **Visbrain: a multi-purpose gpu-accelerated open-source suite for multimodal brain data visualization.** *Front Neuroinform.* 2019; **13**: 14.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

79. Meunier D, Pascarella A, Altukhov D, *et al.*: **Neuropycon: An open-source python toolbox for fast multi-modal and reproducible brain connectivity pipelines.** *NeuroImage.* 2020; **219**: 117020.
PubMed Abstract | **Publisher Full Text**

80. Abraham A, Pedregosa F, Eickenberg M, *et al.*: **Machine learning for neuroimaging with scikit-learn.** *Front Neuroinform.* 2014; **8**: 14.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

81. Garyfallidis E, Brett M, Amirbekian B, *et al.*: **Dipy, a library for the analysis of diffusion mri data.** *Front Neuroinform.* 2014; **8**: 8.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

82. Fadnavis S, Batson J, Garyfallidis E: **Patch2self: Denoising diffusion mri with self-supervised learning.** *Adv Neural Inf Process Syst.* 2020; **33**: 16293–16303.

83. Doherty A, Jackson D, Hammerla N, *et al.*: **Large scale population assessment of physical activity using wrist worn accelerometers: the uk biobank study.** *PLoS One.* 2017; **12**(2): e0169649.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

84. Doherty A, Smith-Byrne K, Ferreira T, *et al.*: **Gwas identifies 14 loci for device-measured physical activity and sleep duration.** *Nat Commun.* 2018; **9**(1): 5257.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

85. Walmsley R, Chan S, Smith-Byrne K, *et al.*: **Reallocating time from device-measured sleep, sedentary behaviour or light physical activity to moderate-to-vigorous physical activity is associated with lower cardiovascular disease risk.** *MedRxiv.* 2020.
Publisher Full Text

86. Willetts M, Hollowell S, Aslett L, *et al.*: **Statistical machine learning of sleep and physical activity phenotypes from sensor data in 96,220 uk biobank participants.** *Sci Rep.* 2018; **8**(1): 7961.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

87. Bao FS, Liu X, Zhang C: **Pyeeg: an open source python module for eeg/meg feature extraction.** *Comput Intell Neurosci.* 2011; **2011**: 406391.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

88. Cabanero-Gomez L, Hervas R, Gonzalez I, *et al.*: **eeglib: a python module for eeg feature extraction.** *SoftwareX.* 2021; **15**: 100745.
Publisher Full Text

89. Brett M, Markiewicz CJ, Hanke M, *et al.*: **nipy/nibabel: 3.2.1.** 2020.
Publisher Full Text

90. **Motionwatch user guide: Issue 1.4.14 the motionwatch user guide the motionwatch is a class i medical device (eu) please consult motionware software user guide ref 30238 for details of software installation, and data analysis**.
Reference Source

91. **Actiware ® and actiware ® ct software manual actiwatch communication and sleep analysis software ® actiware and actiware ct software manual.** 2008.

92. **American academy of sleep medicine on twitter: This week philips told customers by email that it is "discontinuing offering wrist-worn products in the clinician and research markets." the actiware, actiwatch 2, actiwatch pro, and actiwatch plus products will not be sold after dec. 29**.
Reference Source

93. Van der Walt S, Schönberger JL, Nunez-Iglesias J, *et al.*: **scikit-image: image processing in python.** *PeerJ.* 2014; **2**: e453.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

94. Bradski G: **The opencv library.** *Dr. Dobb's Journal: Software Tools for the Professional Programmer.* 2000; **25**(11): 120–123.
Reference Source

95. Esteban O, Markiewicz CJ, Blair RW, *et al.*: **fmriprep: a robust preprocessing pipeline for functional mri.** *Nat Methods.* 2019; **16**(1): 111–116.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

96. Gorgolewski K, Burns CD, Madison C, *et al.*: **Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python.** *Front Neuroinform.* 2011; **5**: 13.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

97. Chang L, Sam EJ, Cheong JH, *et al.*: **cosanlab/nltools: 0.4.7.** August 2022.
Publisher Full Text

98. Wyatt J: **User's manual actilife 6 user's manual**.

99. Hammad G, Reyt M, Beliy N, *et al.*: ***pyactigraphy*: Open-source python package for actigraphy data visualization and analysis.** *PLoS Comput Biol.* 2021; **17**(10): e1009514.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

100. Cole RJ, Kripke DF, Gruen W, *et al.*: **Automatic sleep/wake identification from wrist activity.** *Sleep.* 1992; **15**(5): 461–469.
PubMed Abstract | **Publisher Full Text**

101. Sadeh A, Sharkey KM, Carskadon MA: **Activity-based sleep-wake identification: an empirical test of methodological issues.** *Sleep.* 1994; **17**(3): 201–207.
PubMed Abstract | **Publisher Full Text**

102. Crespo C, Aboy M, Fernández JR, *et al.*: **Automatic identification of activity-rest periods based on actigraphy.** *Med Biol Eng Comput.* 2012; **50**(4): 329–340.
PubMed Abstract | **Publisher Full Text**

103. Roenneberg T, Keller LK, Fischer D, *et al.*: **Human activity and rest *in situ*.** *Methods Enzymol.* 2015; **552**: 257–283.
PubMed Abstract | **Publisher Full Text**

104. Refinetti R, Lissen GC, Halberg F: **Procedures for numerical analysis of circadian rhythms.** *Biol Rhythm Res.* 2007; **38**(4): 275–325.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

105. Peng CK, Havlin S, Stanley HE, *et al.*: **Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series.** *Chaos.* 1995; **5**(1): 82–87.
PubMed Abstract | **Publisher Full Text**

106. Peng CK, Buldyrev SV, Havlin S, *et al.*: **Mosaic organization of dna nucleotides.** *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics.* 1994; **49**(2): 1685–9.
PubMed Abstract | **Publisher Full Text**

107. Auton T: **Applied functional data analysis: Methods and case studies.** *J R Stat Soc Ser A Stat Soc.* 2004; **167**(2): 378–379.
Publisher Full Text

108. Winnebeck EC, Fischer D, Leise T, *et al.*: **Dynamics and ultradian structure of human sleep in real life.** *Curr Biol.* 2018; **28**(1): 49–59.e5.
PubMed Abstract | **Publisher Full Text**

109. Vautard R, Yiou P, Ghil M: **Singular-spectrum analysis: A toolkit for short, noisy chaotic signals.** *Physica D.* 1992; **58**(1–4): 95–126.
Publisher Full Text

110. Davidson-Pilon C: **lifelines: survival analysis in python.** *J Open Source Softw.* 2019; **4**(40): 1317.
Publisher Full Text

111. Igolkina AA, Meshcheryakov G: **semopy: A python package for structural equation modeling.** *Struct Equ Modeling: A Multidisciplinary Journal.* 2020; **27**(6): 1–12.
Publisher Full Text

112. Meshcheryakov G, Igolkina AA, Samsonova MG: **semopy 2: A structural equation modeling package with random effects in python.** 2021.
Publisher Full Text

113. Rosseel Y: **lavaan: An r package for structural equation modeling.** *J Stat Softw.* 2012; **48**(2): 1–36.
Publisher Full Text

114. Pölsterl S: **scikit-survival: A library for time-to-event analysis built on top of scikit-learn.** *J Mach Learn Res.* 2020; **21**(212): 1–6.
Reference Source

115. Currey D, Craley J, Hsu D, *et al.*: **Epviz: A flexible and lightweight visualizer to facilitate predictive modeling for multi-channel eeg.** *PLoS One.* 2023; **18**(2): e0282268.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

116. Maitin AM, Nogales A, Chazarra P, *et al.*: **Eegraph: An open-source python library for modeling electroencephalograms using graphs.** *Neurocomputing.* 2023; **519**: 127–134.
Publisher Full Text

117. Gurumurthy S, Muppalaneni NB, Sekhar C, *et al.*: **Epilepsy analysis using open source edf tools for information science and data analytics.** *Int J Commun Syst.* 2020; **33**(13): e4095.
Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 1

Reviewer Report 21 February 2024

https://doi.org/10.21956/openreseurope.17538.r36449

© **2024 Loukis E.** This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

✔ **Euripidis Loukis**
University of the Aegean, Samos, Greece

This article provides a comprehensive review of the methods and tools used for supporting the diagnosis of complex brain disorders. Initially it reviews the main methods used for this purpose: polysomnography, actigraphies and MRI. Then it reviews a large number of software tools (libraries) that can be used for the analysis of relevant signals. The authors seem to have a good knowledge of these topics, and the article is quite informative, as it includes a lot of useful information.
However, the article could greatly benefit from some improvements. The most important of them might be the restructuring of section 3, which now includes a lot of quite heterogeneous software tools (libraries), which are not grouped into homogeneous sections: generic tools for statistical processing, more specialised tools for neuroimaging data, for EEG signals, for data from artigraphy devices; also, it includes irrelevant tools that do not concern the diagnosis of mental disorders, such as the ones in pages 12 and 13 that concern survival analysis, epidemiology analysis, SEM, latent variable modeling and predictive modeling (it would be better if these were not included). So it would be good to group these tools in separate sub-sections of section 3.
Also, this article lacks a methodology section, which might describe how these tools have been identified and selected for inclusion, and also how the literature review presented in section 2 ('Related work') was conducted (how the papers on which this review was based were identified - probably through a search in one or more of the well established papers databases using some criteria). So it would be good to include a methodology section (even a short one).
Furthermore, this literature review of section 2 is 'asymmetric': while sub-section 2.1 about polysomnography is quite detailed (having a length of 2,5 page columns), section 2.2 about actigraphies and section 2.3 about MRI are much less detailed (having a length of about 0,5 page column each). So it would be good to increase 2.2 and 2.3 and include similar elements and details with the ones of 2.1.
Finally, the article includes a lot of useful information, as mentioned above, but seems inconclusive - the final conclusions section 4 is quite short. So, it would be good to include more the conclusions that are drawn from the extensive information included in the previous sections.
I believe that the above improvements can be easily done, as the authors seem to have a good knowledge of this area, leading to a substantial improvement of the quality of this quite

interesting article

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: One of my research areas are medical information systems and decision support systems, with main emphasis on systems using advanced medical data processing methods, such as machine learning ones - in general I am conducting research in the wider area of information systems and decision support systems

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 15 February 2024

https://doi.org/10.21956/openreseurope.17538.r37162

© 2024 Tsihrintzis G. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

George Tsihrintzis
University of Piraeus, Piraeus, Greece

In this work, the authors investigate the available literature on complex brain disorders in a comprehensive way. The authors survey includes software tools that are currently available towards processing multimodal data to diagnose and classify complex brain disorders in the population. The text also includes a presentation of the limitations of the various available tools, which is particularly useful in identifying targets for future research and development.

Clearly, the manuscript topic is of particular importance to society, as people live longer and exhibit complex brain disorders more often and more seriously.
The manuscript is very well-organized and written.

A suggestion that may improve the article is to include a (perhaps short) discussion on the potential usefulness of generative AI technologies as assistive tools towards the diagnosis of complex brain disorder.

Is the topic of the review discussed comprehensively in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Yes

Is the review written in accessible language?
Yes

Are the conclusions drawn appropriate in the context of the current research literature?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pattern Recognition, Machine Learning, Data Analytics, AI-empowered Software

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.