Journal of Alzheimer's Disease 80 (2021) 1363–1376
DOI 10.3233/JAD-201455
IOS Press

Review

A Review of Automated Techniques for Assisting the Early Detection of Alzheimer's Disease with a Focus on EEG

Eduardo Perez-Valero[a,b], Miguel A. Lopez-Gordo[c,d,*], Christian Morillas[a,b], Francisco Pelayo[a,b] and Miguel A. Vaquero-Blasco[a,c]
[a]*Research Centre for Information and Communications Technologies (CITIC), University of Granada, Granada, Spain*
[b]*Department of Computer Architecture and Technology, University of Granada, Granada, Spain*
[c]*Department of Signal Theory, Telematics and Communications, University of Granada, Granada, Spain*
[d]*Nicolo Association, Churriana de la Vega, Spain*

Accepted 3 February 2021
Pre-press 5 March 2021

Abstract. In this paper, we review state-of-the-art approaches that apply signal processing (SP) and machine learning (ML) to automate the detection of Alzheimer's disease (AD) and its prodromal stages. In the first part of the document, we describe the economic and social implications of the disease, traditional diagnosis techniques, and the fundaments of automated AD detection. Then, we present electroencephalography (EEG) as an appropriate alternative for the early detection of AD, owing to its reduced cost, portability, and non-invasiveness. We also describe the main time and frequency domain EEG features that are employed in AD detection. Subsequently, we examine some of the main studies of the last decade that aim to provide an automatic detection of AD and its previous stages by means of SP and ML. In these studies, brain data was acquired using multiple medical techniques such as magnetic resonance imaging, positron emission tomography, and EEG. The main aspects of each approach, namely feature extraction, classification model, validation approach, and performance metrics, are compiled and discussed. Lastly, a set of conclusions and recommendations for future research on AD automatic detection are drawn in the final section of the paper.

Keywords: Alzheimer's disease, early diagnosis, electroencephalography, machine learning

INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder that disrupts cognitive functions and eventually leads to death [1]. More than one hundred years after the first case of AD was reported, its etiology remains unknown and a definitive diagnosis can only be established upon analysis of the brain at autopsy [2].

According to the latest World Alzheimer Report, published in 2018, more than 50 million people live with dementia [3], and 60% of those cases correspond to AD. The widespread prevalence of AD and its terminal prognosis represent a heavy economic burden for healthcare and social systems. Indeed, AD is the third most expensive disorder in the United States after cancer and coronary heart disease [4]. However, this cost is not equally distributed worldwide, as in 2010 it was estimated that low, middle, and high income countries accounted for 1%, 10%, and 89% of the global costs, but 14%, 40%, and 46% of the prevalence [5].

*Correspondence to: Miguel A. Lopez-Gordo, Department of Signal Theory, Telematics and Communications, University of Granada, C/ Periodista Daniel Saucedo Aranda, s/n, 18014 Granada, Spain. Tel.: +34 958 249 721; E-mail: malg@ugr.es.

ISSN 1387-2877/$35.00

Conventional techniques to detect AD are costly and distressing. Nonetheless, early accurate detection is crucial to control the progression of the disease and postpone intellectual decline [6–8]. For this reason, automated and affordable diagnosis techniques have become an important subject of research.

The aim of this work is to provide a narrative review of state-of-the-art studies that combined signal processing (SP) and machine learning (ML) for the early detection of AD. Furthermore, we present electroencephalography (EEG) as a suitable technique for AD detection, since it is generally considered a fast, inexpensive, and accessible technique to gather brain data. The rest of the document is organized as follows: first, we briefly present traditional AD detection techniques. Then, we describe the role of SP and ML to assist AD diagnosis. Subsequently, we focus on the potential of EEG to support AD detection. Next, we discuss studies that aimed to detect AD and its prodromal stages through SP and ML. Finally, we draw conclusions and provide a set of recommendations for future research on AD automatic detection.

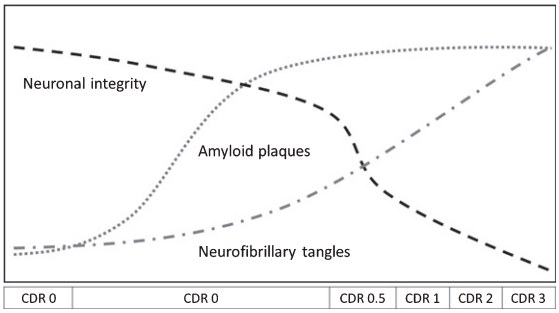

Fig. 1. Progression of the stages of AD regarding the evolution of the hallmark biomarkers and neuronal integrity. The dotted line refers to the appearance of amyloid plaques. The dashed and dotted line corresponds to the accumulation of neurofibrillary tangles and the dashed line represents neuronal integrity. Vertical and horizontal axes correspond to intensity and time. Each stage is assigned a Clinical Dementia Rating (CDR) value according to the severity of the disease in that stage. The first stage corresponds to the Non-AD period and has a CDR score of 0. The second stage refers to Preclinical AD and has a CDR score of 0. In this phase, amyloid plaques start forming in the brain for more than a decade, starting the neuronal decay. The last four stages represent MCI, mild AD, moderate AD and severe AD and have CDR scores of 0.5, 1, 2, and 3 respectively. This graph has been inspired by the work of Perrin et al. [17].

Traditional diagnosis

AD begins with a period devoid of symptoms while the pathological process advances [9]. Then, minor memory losses emerge while cognitive functions remain unaffected. This stage is known as mild cognitive impairment (MCI), and is considered a transitional state between normal aging and AD [10].

The disruption of the healthy functioning of the brain present in AD is caused by a continuous neurodegenerative process defined by two main hallmarks, amyloid plaques and neurofibrillary tangles [11, 12]. The former are deposits of proteins that lose their standard structure and aggregate into plaques around brain cells. The latter are thickened fibrils that surround the nucleus of neurons. In Fig. 1, we have represented the evolution of these hallmarks along with the decay of neuronal integrity. To postpone this decay, classic diagnosis methods aim to detect AD impairments through a diverse set of psychological and medical techniques. Below, we briefly outline these techniques.

- *Cognitive tests.* These assessments evaluate the performance of the patient in different cognitive areas, such as memory, orientation, language, and mood. For instance, general cognitive status is mainly evaluated using the Mini-Mental State Examination (MMSE) [13] and the Montreal Cognitive Assessment (MoCA) [14]. Although these tests are extensively applied, limitations such as lack of sensitivity and high variability have been reported in literature [15, 16].
- *Biomarkers.* In the case of AD, cerebrospinal fluid (CSF) is the most suitable alternative to extract biomarkers from [17]. CSF is a fluid located in the brain and the spinal cord that is extracted via lumbar puncture, a costly, scarce, and painful clinical technique [18]. This procedure evidences the necessity to find approaches that are more comfortable and accessible from the point of view of the patient. Refer to [19] for an in-depth study about AD biomarkers.
- *Medical imaging.* Techniques in this field are applied to render static or functional images of the internal organs of the body. This is achieved through diverse procedures that include strong radio pulses in the case of magnetic resonance imaging (MRI), a radioactive tracer injected into the bloodstream in single photon emission computed tomography (SPECT), or a radiotracer that can be swallowed, inhaled or injected in the case of positron emission tomography (PET).
- *Neurophysiology.* This medical specialty studies the functioning of the nervous system. The two main AD detection techniques in this field are EEG and magnetoencephalography (MEG).

Table 1
Comparison of the medical techniques described in the Introduction section

Technique	Invasive	Costly	Accessibility
MRI	No	Yes	Low
SPECT	Yes	Yes	Low
PET	Yes	Yes	Low
EEG	No	No	High
MEG	No	Yes	Low

EEG monitors the electrical activity in the brain cortex via electrodes placed on the scalp [20, 21]. Alternatively, MEG registers the magnetic fields generated by small currents during postsynaptic potentials using a magnetometer covering the skull [22]. Compared to medical imaging techniques, EEG and MEG provide higher temporal resolution, and conversely to EEG, MEG is not affected by distortion, conductivity changes, or attenuation due to human tissues, as it registers primary electrical activity. However, MEG is a more expensive and less accessible technique compared to EEG.

Table 1 summarizes the main aspects of the detection techniques that we described in this subsection. The results yielded by these techniques rely on time consuming tasks, such as semi quantitative analysis and visual inspection [23]. As a consequence, many studies have taken advantage of SP and ML to develop intelligent models to detect AD and its prodromal stages from clinical trials. These models are appropriate to assist clinicians in the challenging task of early AD detection.

Signal processing and machine learning for AD

Recently, AD detection has been approached as a supervised classification problem through SP and ML. In this kind of task, a model is trained to discriminate brain data from different cohorts (usually controls, MCI, and AD). Data may be presented as a cluster of images (MRI, SPECT, PET, etc.), signals (MEG and EEG), or biomarkers. Before model training, features are extracted from brain data through a process known as feature extraction. Ideally, these features should be independent and discriminative to facilitate classification. Depending upon the acquisition technique, different SP techniques are applied to extract features from brain data. In the case of medical imaging techniques, images are typically segmented into voxels and features are extracted from them [24, 25]. With respect to neurophysiology techniques, features like complexity, coherence, or spectral power are usually extracted from the time and frequency domains. Once feature extraction is completed, training is the subsequent stage in model development. In this process, the classifier learns patterns from the extracted features to obtain generalization capabilities to discriminate unseen data. After training, the performance of the classifier is evaluated through multiple metrics such as accuracy, sensibility, and sensitivity. In the context of AD, multiple classifiers have been successfully applied to discriminate AD data collected through several acquisition techniques. For instance, support vector machines (SVM) [24] and convolutional neural networks [26] have been used to classify subjects into healthy controls (HC), MCI, and AD patients from MRI scans. Similarly, principal component analysis and artificial neural networks [23, 27] have been utilized for the discrimination of those cohorts from SPECT data. Additionally, other studies have addressed the classification of AD cohorts from MEG [28, 29] and EEG data [30–32], and the suitability of these techniques to assist clinical diagnosis has been already demonstrated [33].

In the following section we disclose the most widespread EEG features and processing techniques for AD detection.

EEG PROCESSING FOR AD DETECTION

The suitability of EEG for AD detection is based on its reduced cost, notable accessibility, and non-invasiveness compared to other techniques. Investigations in this field aim to obtain features that correlate with the effects that AD creates in the electrical activity of the brain. These effects include EEG slowing, loss of synchronization, and complexity reduction. For a comprehensive review of the EEG abnormalities caused by AD, refer to [34]. To extract these features, EEG is processed in the time and the frequency domains. Moreover, authors like Ieracitano et al. have stressed the relevance of combining multi-domain features to enhance the discrimination performance of the classifiers [35]. Other authors, like Cassani et al. have evidenced the substantial impact of artifact removal algorithms in EEG-based AD diagnosis. Thereby, in [36] the authors proved that wavelet enhanced independent component analysis outperformed other automated artifact removal algorithms in AD early detection. Over the next two subsections we report some of the most frequent EEG analysis techniques used in AD detection.

Time domain analysis

In this subsection we describe the most extended EEG time domain features for AD detection.

Event-related potentials (ERP)

ERP are electric potentials elicited in the brain as a response to an auditory or visual stimulus. ERP have been utilized to study the morphological differences between AD cohorts, since the potentials in MCI and AD exhibit higher latency and smaller amplitude compared to HC [37]. For this purpose, multiple studies have assessed different cognitive functions like memory [38, 39], oddball recognition [32, 40], and perception [41] for the detection of patients at different stages of AD.

Complexity

Brain activity in MCI and AD patients has lower complexity and irregularity compared to HC [42,43]. Multiple metrics have been used in literature to assess EEG complexity. Most of them are computed from nonlinear analysis, and include Lempel-Ziv complexity, fuzzy entropy, Tsallis entropy, Higuchi fractal dimension, and mutual information [44–46].

Frequency domain analysis

The frequency domain represents the principal source of EEG features for AD detection. Frequency analysis is based on power spectral density, a measure of the power content of a signal with respect to the frequency. In [47], Cassani et al. recommend the use of power spectral density features as baseline. In this subsection we report the most widespread EEG spectral features for AD research.

Coherence

This metric evaluates the synchrony between two signals. More formally, coherence refers to the normalized covariance of two signals in the spectral domain. In the case of EEG, this metric is usually estimated between pairs of electrodes, and quantifies the functional connectivity of the brain. A high coherence represents high synchrony, what indicates strong functional connectivity between brain areas [30]. In literature, authors have reported an increase of coherence in delta and theta rhythms, and a decrease in alpha and beta rhythms in MCI and AD [30, 48]. Other measures of synchrony that have been successfully used to discriminate MCI subjects include the correlation coefficient, Granger causality, and stochastic event synchrony [49].

Relative power

This metric quantifies the proportion of power that is contained in an EEG sub band, compared to the total power of the signal [50]. Studies on relative power have revealed a slowing of brain electrical activity in MCI and AD patients compared to healthy aged [51]. This means that the relative power in the fast rhythms (alpha and beta) decreases, while the relative power in the slow rhythms (delta and theta) increases [7, 37, 52, 53]. Rhythms are typically utilized to analyze the EEG in a particular sub band via filtering, since the activity in each of the different frequency bands is particularly relevant to certain cognitive mechanisms [54–58].

Fourier transform

This transform is used to decompose a time signal into a sum of sines and cosines of different frequencies and infinite length. The Fourier transform has been widely applied in literature [59, 60]. Nonetheless, since EEG is a non-stationary signal, the frequency content of brain activity changes continuously. This implies that the spectral content of the EEG cannot be tracked by the Fourier transform, as the sines and cosines used in this transform are infinite length. Conversely, the wavelet transform represents a suitable alternative to address this issue. This transform decomposes a signal into the combination of functions (wavelets) of finite length and different frequencies. Thus, this technique allows the assessment of the spectral content of the EEG over time. This kind of analysis is also generalized in AD literature [35, 59, 61].

Amplitude modulation

This methodology combines temporal and frequency analysis. To do so, the EEG is filtered in the sub bands of interest and the temporal envelope of each signal is estimated. Then, the temporal dynamics of the envelopes are quantified by performing a second filtering into the modulation sub bands. Amplitude modulation represents an alternative to traditional nonlinear and frequency analysis. This analysis has been validated in the discrimination of AD and healthy cohorts, as well as the characterization of AD severity [62, 63]. Additionally, other studies have presented the changes in the envelope of the slow rhythms as potential indicators for early diagnosis [62].

Lastly, despite the reliability for AD detection of the features outlined in this subsection, authors like Durongbhan et al. have evidenced the potential of

time-frequency-based features (such as the continuous wavelet transform) to improve the results yielded by frequency-based features [64]. Additionally, other authors have recommended the use of both time and frequency metrics to enrich the feature space [45, 65, 66].

DISCUSSION ON RECENT APPROACHES

In this section, we discuss some of the main studies of the last decade that aimed to automatically discriminate AD cohorts through SP and ML.

We summarized the main features of these proposals in Table 2. In particular, *Source* refers to the brain data acquisition technique (for MEG and EEG, the number of channels is indicated in brackets). *Cohorts* represents the different groups of subjects that were considered. *Protocol* describes the procedure followed by the subjects during data acquisition. *Features* stands for the features used to develop the classification model. If reported, feature selection method is also indicated in brackets in this column. *Model* refers to the classifier utilized to discriminate the cohorts. *Validation* indicates the model assessment technique. Finally, *Performance* reports the evaluation of the classifier in terms of accuracy, sensitivity, specificity, or area under receiver operating curve (AUC). We did not include other unusual performance metrics in the table to preserve the homogeneity of the report. Formulae for accuracy, sensitivity, and specificity are provided in equations 1–3, where TP, TN, FP, and FN stand for True Positives, True Negatives, False Positives, and False Negatives, respectively. Over the next paragraphs, we compare the works in Table 2 in terms of these features.

$$A\,(accuracy) = (TP + TN)\,/\,(TP + FP + TN + FN) \quad (1)$$

$$R\,(sensitivity) = TP/\,(TP + FN) \quad (2)$$

$$S\,(specificity) = TN/\,(TN + FP) \quad (3)$$

The studies that we compiled in Table 2 assessed AD detection through predominant clinical trials, including medical imaging (MRI, SPECT, and PET), and neurophysiology techniques (MEG and EEG). Regarding medical imaging, MRI-based studies are more extended in literature than those based on SPECT and PET. This may be due to the invasiveness of the latter techniques compared to MRI. Likewise, in the case of neurophysiology approaches, studies using EEG are more widespread than those using MEG. In this case, the lower cost and higher accessibility of EEG may be the reason behind.

With respect to cohorts, the most common classification problem among the works in Table 2 considered three cohorts: HC, MCI, and AD. This problem has been typically split into two binary classification problems: HC versus MCI and HC versus AD [24, 67, 68]. However, it has also been addressed as a multiclass problem [26, 69]. Less extended approaches considered MCI versus AD [70] and subjective cognitive impairment versus AD [71]. Alternatively, in [72] and [73], the authors trained a model based on data from HC and AD subjects, and then they evaluated it for stable MCI and progressive MCI discrimination. This type of approach is explained in detail in [74]. In this context, note that we have split Table 2 into two parts based on the classification problem addressed by the studies. In Table 2A, we have gathered studies that reported at least one of the two main classification problems in AD literature (HC versus MCI and HC versus AD). Alternatively, in Table 2B, we have included works that studied the classification of other AD cohorts (indicated in brackets under *Performance* column), and works that approached the discrimination of HC, MCI, and AD as a multiclass classification problem.

With respect to the protocol followed, electrophysiology techniques are more flexible than medical imaging techniques, since the latter require the patient to remain completely still. For instance, different authors have recorded MEG [28] and EEG [40, 77] while the participants completed diverse cognitive tests. Likewise, in [40], the authors studied the differences in audio ERP of healthy aging people and MCI subjects. However, the majority of MEG and EEG studies in Table 2 reported data acquisition during resting state protocol. Through this protocol acquisitions become simpler and less stressing for the participant. For an extensive review about resting state EEG for AD detection, refer to [47].

In the case of electrophysiology studies, electrical setup is an additional important aspect. While most of MEG studies reported in Table 2 used more than 300 channels, all EEG studies except [76] used 32 channels or less. Indeed, the number of channels was reduced below 10 in the case of [35, 40–42, 64, 66]. In this respect, the selection of a particular reference montage in EEG approaches strongly influences the performance of a classifier. In [77], the authors assessed the performance of five different

Table 2
Summary of some of the main AD automated detection approaches over the past decade. In Table 2A, we included works that addressed at least one of the two main AD classification problems in literature (HC versus MCI and HC versus AD). We included two *Performance* columns, one for each of these two problems. In Table 2B, we gathered the works that analyzed a different classification task (in those cases only a *Performance* column is reported, and the specific task is indicated in brackets in that column). The studies that analyzed the HC versus MCI versus AD multiclass problem are also included in Table 2B. A, R, S, and AUC, stand for accuracy, sensitivity, specificity, and area under the receiver operating curve, respectively.

Table 2A
Studies that addressed the HC versus MCI and the HC versus AD classification tasks

Study	Source	Cohorts	Protocol	Features (feature selection)	Model	Validation	Performance (HC versus MCI)	Performance (HC versus AD)
López et al. [23] (2011)	PET	HC: 52 MCI: 114 AD: 53	-	Voxel data (LDA and PCA)	SVM, ANN	LOO CV	A = 79.52 R = 93.86 S = 48.08	A = 89.52 R = 86.68 S = 85.72
Górriz et al. [90] (2011)	SPECT	NOR: 43 AD: 30	-	Gaussian Mixture Model	SVM	k-fold CV	-	A = 84.51 R = 76.67 S = 90.24
Trambaiolli et al. [31] (2011)	EEG (19)	HC: 19 AD: 16	Resting state	Coherence and spectral peaks (Weka tool)	SVM	Non-cross validation	-	A = 79.9 R = 83.2 S = 76.4
Padilla et al. [91] (2012)	SPECT	NOR: 41 AD: 56	-	Voxel data (Non-Negative Matrix Factorization)	SVM	LOO CV	-	A = 91.42 R = 90.56 S = 92.30
Segovia et al. [92] (2013)	SPECT	HC: 41 AD: 56	-	Partial Least Squares (Out-Of-Bag Error)	SVM	LOO CV	-	A = 91.75 R = 92.68 S = 91.07
McBride et al. [93] (2013)	EEG(32)	Not reported	Resting state	EEG reconstruction scores (LOO CV)	SVM	LOO CV	A = 90.3 R = 87.5 S = 93.3	A = 90.6 R = 88.2 S = 93.3
Aghajani et al. [76] (2013)	EEG (128)	HC: 17 AD: 17	Resting state	PSD (Singular Value Decomposition)	SVM	LOO CV	-	A = 84.4 R = 75 S = 93.7
Liu et al. [83] (2014)	MRI, PET	HC: 77 MCI: 169 AD: 65	-	MRI volumes and PET patterns (alteration of the number of neurons)	DNN	k-fold CV	A = 76.92 R = 74.29 S = 78.13	A = 91.4
Fiscon et al. [59] (2014)	EEG (19)	HC: 14 MCI: 37 AD: 49	Resting state	FFT	Decision tree	LOO CV	A = 90 R = 90 S = 87	A = 87.76 R = 88.57 S = 87.22
McBride et al. [65] (2014)	EEG (32)	HC: 15 MCI: 16 AD: 17	Resting state	Spectral and complexity parameters (LOO CV)	SVM	LOO CV	A = 96.8 R = 93.8 S = 100	A = 96.9 R = 100 S = 93.3
Munteanu et al. [67] (2015)	MRI	HC: 99 MCI: 94 AD: 67	-	Voxel volumes (Filtering)	ANN, Forest	k-fold CV	AUC = 0.81	AUC = 0.89
Khedher et al. [24] (2015)[a]	MRI	HC: 229 MCI: 401 AD: 188	-	Voxel gray and white matter (Voxel selection)	SVM	k-fold CV	A = 81.89 R = 82.16 S = 81.62	A = 88.49 R = 91.27 S = 85.11

Moradi et al. [73] (2015)	MRI	HC: 231 AD: 200	-	Voxel data (ElasticNet)	SVM, LDS	k-fold CV	-	A = 81.7 R = 86.7 S = 73.6
Wang et al. [30] (2015)	EEG (16)	HC: 14AD: 14	Resting state	PSD and coherence (PCA)	Cluster analysis	None	-	A = 91.4 R = 100 S = 82.9
Maestú et al. [29] (2015)	MEG (306)	NC: 82 MCI: 102	Resting state	Connectivity via Mutual Information (Clinical Data Partitioning)	Multiple classifiers	Bootstrap	A = 83 R = 100 S = 69	-
Morabito et al. [68] (2016)	EEG (19)	HC: 23 MCI: 56 AD: 63	Resting state	Skewness, mean and std in three frequency bands	CNN	k-fold CV	A = 85 R = 84 S = 81	A = 85 R = 85 S = 82
Amezquita et al. [28] (2016)	MEG (148)	HC: 19 MCI: 18	Sternberg test	Permutation entropy (One-way ANOVA)	EPNN	CV	A = 98.4	-
Cassani et al. [42] (2017)	EEG (7)	HC: 24 AD: 35	Resting state	Spectral power, coherence, amplitude modulation (L1 norm)	SVM	LOSO CV	-	A = 69.5 R = 71.4 S = 66.6
Trambaiolli et al. [85] (2017)	EEG (19)	HC: 12 AD: 22	Resting state	Spectral peaks in the main EEG spectral bands (Filtered Subset Evaluator)	SVM	LOSO CV	-	A = 91.18 R = 90.91 S = 91.67
Kulkarni et al. [61] (2017)	EEG (16)	HC: 50 AD: 50	Resting state	Relative Power, WT and complexity	SVM	LOSO CV	-	A = 96
Tong et al. [72] (2017)	MRI	HC: 229 AD: 191	-	Voxel intensities (ElasticNet)	SVM, RF	k-fold CV	A = 80.7 R = 86.7 S = 72.6	A = 73 R = 73 S = 46
Dimitriadis et al. [80] (2018)	MEG (306)	HC: 30 MCI: 24	Resting state	Functional connectivity (MRMR)	SVM	k-fold CV	A = 98	-
Ruiz-Gómez et al. [45] (2018)	EEG (19)	HC: 37 MCI: 37 AD: 37	Resting state	Spectral and nonlinear features (Fast Correlation Based Filter)	MLP, QDA, LDA	LOSO CV	A = 78.43 R = 82.35 S = 70.59	A = 98.05 R = 97.99 S = 98.21
Fiscon et al. [60] (2018)	EEG (19)	HC: 23 MCI: 37 AD: 49	Resting state	Fourier transform and WT	Decision Trees	LOO CV	A = 91.7 R = 91.7 S = 91.5	A = 83.3 R = 83.3 S = 78.0
Mazaheri et al. [75] (2018)	EEG (19–32)	HC: 11 MCI: 25	Language task	Oscillatory changes	SVM	LOO CV	R = 0.80 S = 0.95	-
Khatun et al. [40] (2019)	EEG (1)	HC: 15 MCI: 8	Audio ERP	Temporal and amplitude of the ERP (Random Forest)	SVM	LOO CV	A = 87.9 R = 84.8 S = 95	-
Durongbhan et al. [64] (2019)	EEG (1)	HC: 20 AD: 20	Resting state	FT and WT	KNN	k-fold CV	-	A = 99.2
Ieracitano et al. [35] (2020)	EEG (10)	HC: 63 MCI: 63 AD: 63	Resting state	Continuous WT and BiSpectrum	MLP	k-fold CV	A = 96.24 R = 95.86	A = 96.95 R = 94.91

Table 2B
Studies that addressed the classification of other AD cohorts or considered a 3-label multiclass problem

Study	Source	Cohorts	Protocol	Features (feature selection)	Model	Validation	Performance
Chapman et al. [41] (2011)	EEG (1)	sMCI: 28 pMCI: 15	Number letter test	ERP components (PCA)	Discriminant analysis	LOO CV	(sMCI versus pMCI) A = 79 R = 80 S = 79
Podgorelec et al. [66] (2012)	EEG (2)	No AD: 12% AD: 88%	Not reported	Time and frequency domain parameters (tree-based method)	Evolutionaryalgorithm	k-fold CV	(No AD versus AD) A = 86.05 R = 88.89 S = 71.43
Poil et al. [86] (2013)	EEG (21)	sMCI: 39 pMCI: 25	Resting state	Neurophysiological Biomarker Toolbox (Student's t test and GA)	Logistic regression and GA	Half split CV	(sMCI versus pMCI) R = 88 S = 82
Li et al. [84] (2015)	MRI, PET, CSF	HC: 52 MCI: 99 AD: 51	-	Multi-domain features (PCA and Lasso)	DNN with dropout	k-fold CV	(HC versus MCI versus AD) A = 77.4
Buscema et al. [94] (2015)	EEG (19)	HC: 99 MCI: 46 AD: 127	Resting state	Spatial invariants via MS-ROM (TWIST algorithm)	Multiple classifiers	TWIST algorithm	(HC versus MCI versus AD) A = 98.27 R = 98.29 S = 98.21
Farooq et al. [26] (2017)[a]	MRI	HC>1000 MCI>1000 AD>1000	-	Voxel gray matter (None)	DNN	Not reported	(HC versus MCI versus AD) A = 98 R = 94–99 S = 94–99
Nanni et al. [69] (2018)[b]	MRI	HC: 100 MCI: 200 AD: 100	-	Physical measurements (Fischer score)	SVM	k-fold CV	(HC versus MCI versus AD) A = 0.57
Houmani et al. [71] (2018)	EEG (30)	SCI: 22 pAD: 49	Resting state	Epoch based entropy and bump models (Orthogonal Forward Regression)	SVM	LOSO CV	(SCI versus possible AD) A = 91.6 R = 87.8 S = 100
Lu et al. [95] (2018)	PET	sMCI: 409 pMCI: 112	-	Metabolism features in regions of interest (None)	DNN	k-fold CV	(sMCI versus pMCI) A = 81.55 R = 73.33 S = 83.83
Pusil et al. [79] (2019)	MEG (306)	sMCI: 27 pMCI: 27	Resting state	ROI connectivity (centroid selection)	SVM	k-fold CV	(sMCI versus pMCI) A = 100 R = 100 S = 100

Pusil et al. [78] (2019)	MEG (306)	sMCI: 27 pMCI: 27 HC: 27	Resting state	Connectivity, temporal lobe volume and test scores (None)	Logistic regression	LOO CV	(sMCI versus pMCI versus HC) A = 96.2 R = 92.6 S = 100
Amezquita et al. [70] (2019)	EEG (19)	MCI: 37 AD: 37	Resting state	Fractal dimension and Hurst exponent (one-way ANOVA)	EPNN	Random subject selection	(MCI versus AD) A = 90.3 R = 92.1 S = 87.9

[a]These studies analyzed images from an image database, thus the figures reported in the table refer to images in each cohort. [b]This work utilized a database that stored data from four classes (HC, non-converters MCI, converters MCI and AD) thus, for the sake of clarity, the two MCI categories have been collapsed in the table. AD, Alzheimer's disease; ANN, artificial neural networks; AUC, area under receiver operating curve; CNN, convolutional neural networks; CSF, cerebrospinal fluid; CV, cross validation; DNN, deep neural networks; EEG, electroencephalography; EPNN, enhanced probabilistic neural network; ERP, event-related potentials; FFT, fast Fourier transform; FT, Fourier transform; GA, genetic algorithm; HC, healthy controls; k-fold CV, k-fold cross-validation; KNN, K-nearest neighbors; LDA, linear discriminant analysis; LDS, low density separation; LOO CV, leave-one-out cross-validation; LOSO CV, leave-one-subject-out cross-validation; MCI, mild cognitive impairment; MEG, magnetoencephalography; MLP, multi-layer perceptron; MRI, magnetic resonance imaging; MRMR, minimum redundancy maximum relevance; MS-ROM, multi scale ranked organizing maps; NC, normal control; NOR, normal; pAD, possible Alzheimer's disease; PCA, principal component analysis; PET, positron emission tomography; pMCI, progressive mild cognitive impairment; PSD, power spectral density; QDA, quadratic discriminant analysis; RF, random forest; ROI, region of interest; SCI, subjective cognitive impairment; sMCI, stable mild cognitive impairment; SPECT, single photon emission computed tomography; SVM, support vector machine; WT, wavelet transform.

EEG montages in the discrimination of HC versus AD patients from spectral features. The results yielded a better classification performance for the Counterpart Bipolar montage, what evidences the importance of electrode montage selection.

Regarding feature extraction, in MEG and EEG works, the most recurrent features include spectral power, coherence [30, 31, 42, 45, 65, 76], and connectivity [29, 78–80], as it has been proved that neural networks in AD patients tend to be less complex and efficient [81, 82]. Conversely, in medical imaging studies, investigators tend to extract information from image voxels. Alternatively, other works in this field have combined multiple techniques to obtain multi-domain features [67, 83, 84]. In this context, feature selection is appropriate to avoid overfitting, what becomes especially relevant in medical imaging studies, where authors typically extract a high number of features through image processing. Likewise, as evidenced by Trambaiolli et al. in [85], feature selection plays an important role in EEG-based studies. In this work, the authors demonstrated that the right choice of the feature selection method removed up to 82% of the EEG spectral features and increased the accuracy of the classifier more than 17%.

In relation to model selection, SVM was the most recurrent classifier among those studies in Table 2 that addressed a binary discrimination of AD cohorts. In the case of multiclass classification studies, more complex classifiers like ensemble methods and deep networks have been tested with diverse results [26, 35, 69].

Regarding model validation, the studies gathered in this section used mainly three validation approaches: leave-one-subject-out cross-validation (LOSO CV), k-fold cross-validation (k-fold CV), and leave-one-out cross-validation (LOO CV). In this respect, it is mandatory to prevent the models from using highly correlated data for development and evaluation, as this would introduce a positive bias in the predictions. LOSO CV (covered in [42, 45, 61, 71, 85]) overcomes this issue by ensuring that the information from one subject is utilized only in the training or the test set. This is not feasible in LOO CV, as the data from a subject is included in both sets. With regard to k-fold CV, a proper experimental design is required to prevent data leakage. Considering this, we deem LOSO CV as the most straightforward and clear model validation approach for AD classification.

The last aspect that we considered in Table 2 is performance. Most of the works collected disclosed accuracy, sensitivity, and specificity. Other works

only reported accuracy [28, 69, 80, 84]. However, accuracy does not assess the rates of false positives and false negatives, that are particularly important in clinical-related classification problems. In all, performance report is consistent over the works that we collected, as only [28, 35, 61, 67, 69, 75, 80, 84, 86] did not provide accuracy, sensitivity, and specificity jointly. Moreover, it is important to acknowledge the dependency of metrics like accuracy and AUC with group balance [87], an issue that can be confronted via additional metrics like precision-recall curves, sensitivity, and specificity. With regard to performance results, the heterogeneity of the studies gathered in Table 2 hinder comparisons; however, accuracy, sensitivity, and specificity are generally much higher than random choice (in most cases above 80% for binary classification problems). The fact that many different classifiers achieved similar performance demonstrates the widespread knowledge that classifiers are generally not as important as the quality of the features. Hence, developing discriminative features that enable the detection of AD in its early stages acquires paramount importance.

In terms of data availability, many of the medical imaging studies gathered in Table 2 reported the use of a public database to obtain brain data. The use of public medical imaging databases like ADNI or OASIS [88] is a common practice in AD literature (see [89] for a detailed report about querying and organization of AD data). On the other hand, in EEG studies, due to the high accessibility of this technique, researchers generally acquire their own data.

To sum up, in general the proposals compiled in this section yielded positive results in terms of AD cohort discrimination. The studies achieved similar performance using different medical techniques, namely MRI, SPECT, PET, MEG, and EEG. In MEG and EEG studies, some cognitive tasks were monitored, but resting state was the most recurrent protocol during data acquisition. Regarding feature extraction, multiple approaches were conducted based on the source of the brain data. With respect to classification, SVM was the most extended classifier for binary classification, and we concluded that LOSO CV is the most suitable validation alternative based on its intrinsic capability to avoid data leakage.

Lastly, after discussing the works in Table 2, it is notable that the performance of AD classifiers based on EEG data can equal or even outperform the performance of approaches based on medical imaging. Moreover, imaging-based studies rely on image processing techniques for feature extraction, that are computationally demandant compared to EEG signal processing techniques. In addition, EEG time resolution is higher relative to medical imaging, what enables investigators to study dynamical changes in brain activity. EEG is also non-invasive and far more accessible and inexpensive than medical imaging and MEG. These aspects are crucial, since as stated in the introduction of this work, AD prevalence increases every year, especially in developing countries that lack awareness and technological means. Therefore, a reliable, inexpensive, and non-invasive AD diagnosis technique is required. In this context, EEG represents an appropriate technique to support clinicians in AD detection.

CONCLUSION

In this survey, we discussed state-of-the-art approaches to assist the diagnosis of AD. The works compiled in this paper used diverse medical techniques to acquire brain activity, and feature extraction to derive features from it. In these works, authors trained automated models to discriminate between AD cohorts. The three main cohorts considered in the studies that we reviewed were HC, MCI, and AD subjects. With regard to the classifiers, even though all the approaches that were discussed could discriminate between AD groups with reliable performance, SVM was the most extended alternative. However, the heterogeneity of the disease, along with the discrepancies in the validation approach among the studies, make classification results difficult to compare. In respect to model validation, we consider that LOSO CV is the most suitable approach, since it does not require a particular experimental design to avoid data leakage. Regarding the suitability for assisting the early diagnosis of AD, we believe EEG is the most appropriate technique, since it is unexpensive, highly available, and non-invasive. Its accessibility facilitates the performance of longitudinal studies to monitor the evolution of AD, and it also allows the acquisition of brain data during the performance of cognitive tasks. Regarding electrode setup, authors should consider comparing different EEG montages, since the right choice of the electrode configuration could enhance the discrimination performance of the classifiers [77]. Despite resting state was the most frequent protocol for EEG recording, different cognitive tasks should be studied, as they may provide insights on how AD affects certain cognitive areas. Since AD is expected to affect a large part of the

population in the following years, especially in low-income countries that lack medical resources, EEG represents a suitable technique to assist clinical professionals on early diagnosis. For this purpose, we believe that future studies should prioritize the study of new features that support the early detection of AD.

ACKNOWLEDGMENTS

This work was supported by project PGC2018-098813- B-C31 (Spanish "Ministerio de Ciencia, Innovación y Universidades"), by European Regional Development Funds (ERDF) and by the Nicolo Association for the R&D in Neurotechnologies for disability.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-1455r1).

REFERENCES

[1] Cummings JL, Cole G (2002) Alzheimer disease. *JAMA* **287**, 2335-2338.

[2] Castellani RJ, Rolston RK, Smith MA (2010) Alzheimer disease. *Dis Mon* **56**, 484-546.

[3] Patterson C (2018) *World Alzheimer Report 2018. The state of the art of dementia research: New frontiers*. Alzheimer's Disease International, London.

[4] Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M (2016) *World Alzheimer Report 2016. Improving healthcare for people living with dementia: Coverage, quality and costs now and in the future*. Alzheimer's Disease International, London.

[5] Wimo A, Jönsson L, Bond J, Prince M, Winblad B (2013) The worldwide economic impact of dementia 2010. *Alzheimers Dementia* **9**, 1-11.e3.

[6] Riemenschneider M, Lautenschlager N, Wagenpfeil S, Diehl J, Drzezga A, Kurz A (2002) Cerebrospinal fluid tau and beta-amyloid 42 proteins identify Alzheimer disease in subjects with mild cognitive impairment. *Arch Neurol* **59**, 1729-1734.

[7] Rodrigues PM, Freitas D, Teixeira JP, Bispo B, Alves D, Garrett C (2018) Electroencephalogram hybrid method for Alzheimer early detection. *Procedia Comput Sci* **138**, 209-214.

[8] Kim D, Kim K (2018) Detection of early stage Alzheimer's disease using EEG relative power with deep neural network. In *2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 352-355.

[9] Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 280-292.

[10] Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L (2001) Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol* **58**, 397-405.

[11] Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med* **1**, a006189.

[12] Perl DP (2010) Neuropathology of Alzheimer's disease. *Mt Sinai J Med* **77**, 32-42.

[13] Minati L, Edginton T, Grazia Bruzzone M, Giaccone G (2009) Reviews: Current concepts in Alzheimer's disease: A multidisciplinary review. *Am J Alzheimers Dis Other Demen* **24**, 95-121.

[14] Freitas S, Simões MR, Alves L, Santana I (2013) Montreal Cognitive Assessment: Validation study for mild cognitive impairment and Alzheimer disease. *Alzheimer Dis Assoc Disord* **27**, 37-43.

[15] Kuslansky G, Katz M, Verghese J, Hall CB, Lapuerta P, LaRuffa G, Lipton RB (2004) Detecting dementia with the Hopkins Verbal Learning Test and the Mini-Mental State Examination. *Arch Clin Neuropsychol* **19**, 89-104.

[16] Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA (2000) Modelling Mini Mental State Examination changes in Alzheimer's disease. *Stat Med* **19**, 1607-1616.

[17] Perrin RJ, Fagan AM, Holtzman DM (2009) Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature* **461**, 916-922.

[18] Virhammar J, Cesarini KG, Laurell K (2012) The CSF tap test in normal pressure hydrocephalus: Evaluation time, reliability and the influence of pain. *Eur J Neurol* **19**, 271-276.

[19] Lovestone S, Francis P, Kloszewska I, Mecocci P, Simmons A, Soininen H, Spenger C, Tsolaki M, Vellas B, Wahlund L-O, Ward M, AddNeuroMed Consortium (2009) AddNeuroMed–the European collaboration for the discovery of novel biomarkers for Alzheimer's disease. *Ann N Y Acad Sci* **1180**, 36-46.

[20] Berger H (1929) Über das Elektrenkephalogramm des Menschen. *Arch Psychiatr* **87**, 527-570.

[21] Kirschstein T, Köhling R (2009) What is the source of the EEG? *Clin EEG Neurosci* **40**, 146-149.

[22] Sutherling WW (2012) Magnetoencephalography. In *Aminoff's Electrodiagnosis in Clinical Neurology*. Elsevier, pp. 219-229.

[23] López M, Ramírez J, Górriz JM, Álvarez I, Salas-Gonzalez D, Segovia F, Chaves R, Padilla P, Gómez-Río M (2011) Principal component analysis-based techniques and supervised classification schemes for the early detection of Alzheimer's disease. *Neurocomputing* **74**, 1260-1271.

[24] Khedher L, Ramírez J, Górriz JM, Brahim A, Segovia F (2015) Early diagnosis of Alzheimer's disease based on partial least squares, principal component analysis and support vector machine using segmented MRI images. *Neurocomputing* **151**, 139-150.

[25] Sørensen L, Igel C, Pai A, Balas I, Anker C, Lillholm M, Nielsen M (2016) Differential diagnosis of mild cognitive impairment and Alzheimer's disease using structural MRI cortical thickness, hippocampal shape, hippocampal texture, and volumetry. *Neuroimage Clin* **13**, 470-482.

[26] Farooq A, Anwar S, Awais M, Alnowami M (2017) Artificial intelligence based smart diagnosis of Alzheimer's disease and mild cognitive impairment. In *2017 International Smart Cities Conference (ISC2)*, pp. 1-4.

[27] Illán IA, Górriz JM, López MM, Ramírez J, Salas-Gonzalez D, Segovia F, Chaves R, Puntonet CG (2011) Computer aided diagnosis of Alzheimer's disease using component based SVM. *Applied Soft Comput* **11**, 2376-2382.

[28] Amezquita-Sanchez JP, Adeli A, Adeli H (2016) A new methodology for automated diagnosis of mild cognitive impairment (MCI) using magnetoencephalography (MEG). *Behav Brain Res* **305**, 174-180.

[29] Maestú F, Peña J-M, Garcés P, González S, Bajo R, Bagic A, Cuesta P, Funke M, Mäkelä JP, Menasalvas E, Nakamura A, Parkkonen L, López ME, del Pozo F, Sudre G, Zamrini E, Pekkonen E, Henson RN, Becker JT (2015) A multicenter study of the early detection of synaptic dysfunction in mild cognitive impairment using Magnetoencephalography-derived functional connectivity. *Neuroimage Clin* **9**, 103-109.

[30] Wang R, Wang J, Yu H, Wei X, Yang C, Deng B (2015) Power spectral density and coherence analysis of Alzheimer's EEG. *Cogn Neurodyn* **9**, 291-304.

[31] Trambaiolli LR, Lorena AC, Fraga FJ, Kanda PAM, Anghinah R, Nitrini R (2011) Improving Alzheimer's disease diagnosis with machine learning techniques. *Clin EEG Neurosci* **42**, 160-165.

[32] Cecchi M, Moore DK, Sadowsky CH, Solomon PR, Doraiswamy PM, Smith CD, Jicha GA, Budson AE, Arnold SE, Fadem KC (2015) A clinical trial to validate event-related potential markers of Alzheimer's disease in outpatient settings. *Alzheimers Dement (Amst)* **1**, 387-394.

[33] Lehmann C, Koenig T, Jelic V, Prichep L, John RE, Wahlund L-O, Dodge Y, Dierks T (2007) Application and comparison of classification algorithms for recognition of Alzheimer's disease in electrical brain activity (EEG). *J Neurosci Methods* **161**, 342-350.

[34] Jeong J (2004) EEG dynamics in patients with Alzheimer's disease. *Clin Neurophysiol* **115**, 1490-1505.

[35] Ieracitano C, Mammone N, Hussain A, Morabito FC (2020) A novel multi-modal machine learning based approach for automatic classification of EEG recordings in dementia. *Neural Networks* **123**, 176-190.

[36] Cassani R, Falk TH, Fraga FJ, Kanda PAM, Anghinah R (2014) The effects of automated artifact removal algorithms on electroencephalography-based Alzheimer's disease diagnosis. *Front Aging Neurosci* **6**, 55.

[37] Dauwels J, Vialatte F, Cichocki A (2010) Diagnosis of Alzheimer's disease from EEG signals: Where are we standing? *Curr Alzheimer Res* **7**, 487-505.

[38] Fraga FJ, Mamani GQ, Johns E, Tavares G, Falk TH, Phillips NA (2018) Early diagnosis of mild cognitive impairment and Alzheimer's with event-related potentials and event-related desynchronization in N-back working memory tasks. *Comput Methods Programs Biomed* **164**, 1-13.

[39] Missonnier P, Gold G, Fazio-Costa L, Michel J-P, Mulligan R, Michon A, Ibáñez V, Giannakopoulos P (2005) Early event-related potential changes during working memory activation predict rapid decline in mild cognitive impairment. *J Gerontol A Biol Sci Med Sci* **60**, 660-666.

[40] Khatun S, Morshed BI, Bidelman GM (2019) A single-channel EEG-based approach to detect mild cognitive impairment via speech-evoked brain responses. *IEEE Trans Neural Syst Rehabil Eng* **27**, 1063-1070.

[41] Chapman RM, McCrary JW, Gardner MN, Sandoval TC, Guillily MD, Reilly LA, DeGrush E (2011) Brain ERP components predict which individuals progress to Alzheimer's disease and which do not. *Neurobiol Aging* **32**, 1742-1755.

[42] Cassani R, Falk TH, Fraga FJ, Cecchi M, Moore DK, Anghinah R (2017) Towards automated electroencephalography-based Alzheimer's disease diagnosis using portable low-density devices. *Biomed Signal Process Control* **33**, 261-271.

[43] Fan M, Yang AC, Fuh J-L, Chou C-A (2018) Topological pattern recognition of severe Alzheimer's disease via regularized supervised learning of EEG complexity. *Front Neurosci* **12**, 685.

[44] Yang S, Bornot JMS, Wong-Lin K, Prasad G (2019) M/EEG-based bio-markers to predict the MCI and Alzheimer's disease: A review from the ML perspective. *IEEE Trans Biomed Eng* **66**, 2924-2935.

[45] Ruiz-Gómez SJ, Gómez C, Poza J, Gutiérrez-Tobal GC, Tola-Arribas MA, Cano M, Hornero R (2018) Automated multiclass classification of spontaneous EEG activity in Alzheimer's disease and mild cognitive impairment. *Entropy* **20**, 35.

[46] Al-Nuaimi AHH, Jammeh E, Sun L, Ifeachor E (2018) Complexity measures for quantifying changes in electroencephalogram in Alzheimer's disease. *Complexity* **2018**, 1-12.

[47] Cassani R, Estarellas M, San-Martin R, Fraga FJ, Falk TH (2018) Systematic review on resting-state EEG for Alzheimer's disease diagnosis and progression assessment. *Dis Markers* **2018**, 5174815.

[48] Maestú F, Cuesta P, Hasan O, Fernandéz A, Funke M, Schulz PE (2019) The importance of the validation of M/EEG with current biomarkers in Alzheimer's disease. *Front Hum Neurosci* **13**, 17.

[49] Dauwels J, Vialatte F, Musha T, Cichocki A (2010) A comparative study of synchrony measures for the early diagnosis of Alzheimer's disease based on EEG. *Neuroimage* **49**, 668-693.

[50] Woltering S, Jung J, Liu Z, Tannock R (2012) Resting state EEG oscillatory power differences in ADHD college students and their peers. *Behav Brain Funct* **8**, 60.

[51] Benz N, Hatz F, Bousleiman H, Ehrensperger MM, Gschwandtner U, Hardmeier M, Ruegg S, Schindler C, Zimmermann R, Monsch AU, Fuhr P (2014) Slowing of EEG background activity in Parkinson's and Alzheimer's disease with early cognitive dysfunction. *Front Aging Neurosci* **6**, 314.

[52] Fernández A, Gil Gregorio P, Maestú F (2012) Actividad espontánea electroencefalográfica y magnetoencefalográfica como marcador de la enfermedad de Alzheimer y el deterioro cognitivo leve. *Rev Esp Geriatr Gerontol* **47**, 27-32.

[53] Moretti DV (2015) Theta and alpha EEG frequency interplay in subjects with mild cognitive impairment: Evidence from EEG, MRI, and SPECT brain modifications. *Front Aging Neurosci* **7**, 31.

[54] Kanda PAM, Oliveira EF, Fraga FJ (2017) EEG epochs with less alpha rhythm improve discrimination of mild Alzheimer's. *Comput Methods Programs Biomed* **138**, 13-22.

[55] Minguillon J, Lopez-Gordo MA, Pelayo F (2016) Stress assessment by prefrontal relative gamma. *Front Comput Neurosci* **10**, 101.

[56] Lotfan S, Shahyad S, Khosrowabadi R, Mohammadi A, Hatef B (2019) Support vector machine classification of brain states exposed to social stress test using EEG-based brain network measures. *Biocybern Biomed Eng* **39**, 199-213.

[57] Tan H, Wade C, Brown P (2016) Post-movement beta activity in sensorimotor cortex indexes confidence in the estimations from internal models. *J Neurosci* **36**, 1516-1528.

[58] Bohbot VD, Copara MS, Gotman J, Ekstrom AD (2017) Low-frequency theta oscillations in the human

hippocampus during real-world and virtual navigation. *Nat Commun* **8**, 14415.

[59] Fiscon G, Weitschek E, Felici G, Bertolazzi P, De Salvo S, Bramanti P, De Cola MC (2014) Alzheimer's disease patients classification through EEG signals processing. In *2014 IEEE Symposium on Computational Intelligence and Data Mining (CIDM)*, pp. 105-112.

[60] Fiscon G, Weitschek E, Cialini A, Felici G, Bertolazzi P, De Salvo S, Bramanti A, Bramanti P, De Cola MC (2018) Combining EEG signal processing with supervised methods for Alzheimer's patients classification. *BMC Med Inform Decis Mak* **18**, 35.

[61] Kulkarni NN, Bairagi VK (2017) Extracting salient features for EEG-based diagnosis of Alzheimer's disease using support vector machine classifier. *IETE J Res* **63**, 11-22.

[62] Fraga FJ, Falk TH, Kanda PAM, Anghinah R (2013) Characterizing Alzheimer's disease severity via resting-awake EEG amplitude modulation analysis. *PLoS One* **8**, e72240.

[63] Trambaiolli LR, Falk TH, Fraga FJ, Anghinah R, Lorena AC (2011) EEG spectro-temporal modulation energy: A new feature for automated diagnosis of Alzheimer's disease. In *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pp. 3828-3831.

[64] Durongbhan P, Zhao Y, Chen L, Zis P, De Marco M, Unwin ZC, Venneri A, He X, Li S, Zhao Y, Blackburn DJ, Sarrigiannis PG (2019) A dementia classification framework using frequency and time-frequency features based on EEG signals. *IEEE Trans Neural Syst Rehabil Eng* **27**, 826-835.

[65] McBride JC, Zhao X, Munro NB, Smith CD, Jicha GA, Hively L, Broster LS, Schmitt FA, Kryscio RJ, Jiang Y (2014) Spectral and complexity analysis of scalp EEG characteristics for mild cognitive impairment and early Alzheimer's disease. *Comput Methods Programs Biomed* **114**, 153-163.

[66] Podgorelec V (2012) Analyzing EEG signals with machine learning for diagnosing Alzheimer's disease. *Elektron Elektrotech* **18**, 61-64.

[67] Munteanu CR, Fernandez-Lozano C, Mato Abad V, Pita Fernández S, Álvarez-Linera J, Hernández-Tamames JA, Pazos A (2015) Classification of mild cognitive impairment and Alzheimer's disease with machine-learning techniques using 1H magnetic resonance spectroscopy data. *Expert Syst Appl* **42**, 6205-6214.

[68] Morabito FC, Campolo M, Ieracitano C, Ebadi JM, Bonanno L, Bramanti A, Desalvo S, Mammone N, Bramanti P (2016) Deep convolutional neural networks for classification of mild cognitive impaired and Alzheimer's disease patients from scalp EEG recordings. In *2016 IEEE 2nd International Forum on Research and Technologies for Society and Industry Leveraging a better tomorrow (RTSI)*, pp. 1-6.

[69] Nanni L, Lumini A, Zaffonato N (2018) Ensemble based on static classifier selection for automated diagnosis of mild cognitive impairment. *J Neurosci Methods* **302**, 42-46.

[70] Amezquita-Sanchez JP, Mammone N, Morabito FC, Marino S, Adeli H (2019) A novel methodology for automated differential diagnosis of mild cognitive impairment and the Alzheimer's disease using EEG signals. *J Neurosci Methods* **322**, 88-95.

[71] Houmani N, Vialatte F, Gallego-Jutglà E, Dreyfus G, Nguyen-Michel V-H, Mariani J, Kinugawa K (2018) Diagnosis of Alzheimer's disease with electroencephalography in a differential framework. *PLoS One* **13**, e0193607.

[72] Tong T, Gao Q, Guerrero R, Ledig C, Chen L, Rueckert D, Alzheimer's Disease Neuroimaging Initiative (2017) A novel grading biomarker for the prediction of conversion from mild cognitive impairment to Alzheimer's disease. *IEEE Trans Biomed Eng* **64**, 155-165.

[73] Moradi E, Pepe A, Gaser C, Huttunen H, Tohka J (2015) Machine learning framework for early MRI-based Alzheimer's conversion prediction in MCI subjects. *Neuroimage* **104**, 398-412.

[74] Cheng B, Liu M, Zhang D, Munsell BC, Shen D (2015) Domain transfer learning for MCI conversion prediction. *IEEE Trans Biomed Eng* **62**, 1805-1817.

[75] Mazaheri A, Segaert K, Olichney J, Yang J-C, Niu Y-Q, Shapiro K, Bowman H (2018) EEG oscillations during word processing predict MCI conversion to Alzheimer's disease. *Neuroimage Clin* **17**, 188-197.

[76] Aghajani H, Zahedi E, Jalili M, Keikhosravi A, Vahdat BV (2013) Diagnosis of early Alzheimer's disease based on EEG source localization and a standardized realistic head model. *IEEE J Biomed Health Inform* **17**, 1039-1045.

[77] Trambaiolli LR, Lorena AC, Fraga FJ, Kanda PA, Nitrini R, Anghinah R (2011) Does EEG montage influence Alzheimer's disease electroclinic diagnosis? *Int J Alzheimers Dis* **2011**, 761891.

[78] Pusil S, López ME, Cuesta P, Bruña R, Pereda E, Maestú F (2019) Hypersynchronization in mild cognitive impairment: The 'X' model. *Brain* **142**, 3936-3950.

[79] Pusil S, Dimitriadis SI, López ME, Pereda E, Maestú F (2019) Aberrant MEG multi-frequency phase temporal synchronization predicts conversion from mild cognitive impairment-to-Alzheimer's disease. *Neuroimage Clin* **24**, 101972.

[80] Dimitriadis SI, López ME, Bruña R, Cuesta P, Marcos A, Maestú F, Pereda E (2018) How to build a functional connectomic biomarker for mild cognitive impairment from source reconstructed MEG resting-state activity: The combination of ROI representation and connectivity estimator matters. *Front Neurosci* **12**, 306.

[81] Vecchio F, Miraglia F, Marra C, Quaranta D, Vita MG, Bramanti P, Rossini PM (2014) Human brain networks in cognitive decline: A graph theoretical analysis of cortical connectivity from EEG data. *J Alzheimers Dis* **41**, 113-127.

[82] Yu M, Gouw AA, Hillebrand A, Tijms BM, Stam CJ, van Straaten ECW, Pijnenburg YAL (2016) Different functional connectivity and network topology in behavioral variant of frontotemporal dementia and Alzheimer's disease: An EEG study. *Neurobiol Aging* **42**, 150-162.

[83] Liu S, Liu S, Cai W, Pujol S, Kikinis R, Feng D (2014) Early diagnosis of Alzheimer's disease with deep learning. In *2014 IEEE 11th International Symposium on Biomedical Imaging (ISBI)*, pp. 1015-1018.

[84] Li F, Tran L, Thung K-H, Ji S, Shen D, Li J (2015) A robust deep model for improved classification of AD/MCI patients. *IEEE J Biomed Health Inform* **19**, 1610-1616.

[85] Trambaiolli LR, Spolaôr N, Lorena AC, Anghinah R, Sato JR (2017) Feature selection before EEG classification supports the diagnosis of Alzheimer's disease. *Clin Neurophysiol* **128**, 2058-2067.

[86] Poil S-S, de Haan W, van der Flier WM, Mansvelder HD, Scheltens P, Linkenkaer-Hansen K (2013) Integrative EEG biomarkers predict progression to Alzheimer's disease at the MCI stage. *Front Aging Neurosci* **5**, 58.

[87] Saito T, Rehmsmeier M (2015) The precision-recall plot is more informative than the ROC plot when evaluating binary classifiers on imbalanced datasets. *PLoS One* **10**, e0118432.

[88] LaMontagne PJ, Benzinger TLS, Morris JC, Keefe S, Hornbeck R, Xiong C, Grant E, Hassenstab J, Moulder K, Vlassenko A, Raichle ME, Cruchaga C, Marcus

D (2019) OASIS-3: Longitudinal neuroimaging, clinical, and cognitive dataset for normal aging and Alzheimer disease. *medRxiv* doi: https://doi.org/10.1101/2019.12.13.19014902.

[89] Arisi I, Bertolazzi P, Cappelli E, Conte F, Cumbo F, Fiscon G, Sonnessa M, Taglino F (2018) An ontology-based approach to improve data querying and organization of Alzheimer's Disease data. In *2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pp. 2732-2734.

[90] Górriz JM, Segovia F, Ramírez J, Lassl A, Salas-Gonzalez D (2011) GMM based SPECT image classification for the diagnosis of Alzheimer's disease. *Applied Soft Comput* **11**, 2313-2325.

[91] Padilla P, Lopez M, Gorriz JM, Ramirez J, Salas-Gonzalez D, Alvarez I (2012) NMF-SVM based CAD tool applied to functional brain images for the diagnosis of Alzheimer's disease. *IEEE Trans Med Imaging* **31**, 207-216.

[92] Segovia F, Górriz JM, Ramírez J, Salas-González D, Álvarez I (2013) Early diagnosis of Alzheimer's disease based on partial least squares and support vector machine. *Expert Syst Appl* **40**, 677-683.

[93] McBride J, Zhao X, Munro N, Jiang Y, Smith C, Jicha G (2013) Scalp EEG signal reconstruction for detection of mild cognitive impairment and early Alzheimer's disease. In *2013 Biomedical Sciences and Engineering Conference (BSEC)*, pp. 1-4.

[94] Buscema M, Vernieri F, Massini G, Scrascia F, Breda M, Rossini PM, Grossi E (2015) An improved I-FAST system for the diagnosis of Alzheimer's disease from unprocessed electroencephalograms by using robust invariant features. *Artif Intell Med* **64**, 59-74.

[95] Lu D, Popuri K, Ding GW, Balachandar R, Beg MF (2018) Multiscale deep neural network based analysis of FDG-PET images for the early diagnosis of Alzheimer's disease. *Med Image Anal* **46**, 26-34.