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Machine Learning Algorithms and Statistical Approaches for Alzheimer's Disease Analysis Based on Resting-State EEG Recordings: A Systematic Review

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Alzheimer's Disease (AD) is a neurodegenerative disorder and the most common type of dementia with a great prevalence in western countries. The diagnosis of AD and its progression is performed through a variety of clinical procedures including neuropsychological and physical examination, Electroencephalographic (EEG) recording, brain imaging and blood analysis. During the last decades, analysis of the electrophysiological dynamics in AD patients has gained great research interest, as an alternative and cost-effective approach. This paper summarizes recent publications focusing on (a) AD detection and (b) the correlation of quantitative EEG features with AD progression, as it is estimated by Mini Mental State Examination (MMSE) score. A total of 49 experimental studies published from 2009 until 2020, which apply machine learning algorithms on resting state EEG recordings from AD patients, are reviewed.

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Results of each experimental study are presented and compared. The majority of the studies focus on AD detection incorporating Support Vector Machines, while deep learning techniques have not yet been applied on large EEG datasets. Promising conclusions for future studies are presented.

Keywords: Alzheimer's disease; dementia; EEG; EEG analysis; machine learning; electroencephalogram.

1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease, both devastating for the patient and the caregiver with 50% of the carers claiming that their health has been negatively affected as a result of their responsibilities to AD patients.[1] According to a 2015 report,[2] the worldwide prevalence of AD is over 46 million, rendering AD the most common type of dementia. People with AD, experience difficulty in remembering simple things, have trouble recognizing familiar faces, can be easily frustrated and confused and finally, tend to not realize nor accept their condition. The diagnosis is performed by experienced neurologists based on patient's clinical symptoms and a series of diagnostic procedures.

The diagnosis is based on a series of evaluation procedures, including physical and neurological examination, biochemical tests and brain imaging techniques, such as Magnetic Resonance Imaging (MRI), functional Magnetic Resonance Imaging (fMRI) or Computed Tomography (CT).[3] The evaluation of cognitive state is assessed with screening tests, such as the Mini Mental State Examination (MMSE) score,[4] and the Montreal Cognitive Assessment (MoCA) test.[5] MMSE is a 30-scale questionnaire and the most commonly used screening method. A low score in MMSE indicates a more severe state of AD. On the other hand, MoCA is a newer method proposed as an alternative to MMSE, showing more accurate results in the diagnosis of Mild Cognitive Impairment (MCI).[6]

The pathophysiology of the disorder is multifactorial and heterogeneous.[7,8] The clinical symptoms of the disease are varied and occur with varying intensity at different stages of the disease. Early stages of AD are hard to diagnose and often the treatment starts after symptoms have occurred for a long time. Clinical symptoms may lead to misdiagnosis of other disorders or dementia such as frontotemporal dementia; thus, differential diagnosis of other types of dementia and AD is imperative.[9] The National Institute on Ageing and the Alzheimer's Association (NIA-AA) recently proposed a framework[10] to diagnose AD solely from biomarkers and not from clinical symptoms.

Recently, it has been concluded that the presence of amyloid-β plaques and tau tangles is evident in the brain of an AD patient. Even though AD can only be detected with safety in a brain tissue postmortem examination, imaging biomarkers and biofluids are able to detect amyloid-β plaques and tau tangles in AD patients. Positron Emission Tomography (PET) biomarkers[11] and biomarkers *in vivo*[10,12] can diagnose AD and differentiate it from other dementia types. *In vivo* biomarkers include cerebrospinal fluid amyloid-β and tau tangles. However, amyloid-β depositions and tau tangles may not be associated with cognitive decline[13] nor be the primary cause of AD.[10]

Brain lesions evident in brain biopsies or autopsies of AD patients (initially labeled as "senile dementia") have been recorded since the middle of the previous century.[14] Clinically, dementia was impossible to differentiate and its diagnosis was based on autopsy findings that did not have any diagnostic benefit.

Since Electroencephalogram (EEG) is a cost-effective and reliable diagnostic method found not only in hospital equipment but also in commercial wearable devices, EEG researchers have set their sights on correlating the quantitative EEG features with detection and progression of AD. Alterations in EEG features found in patients with dementia either in resting-state[15] or during a working memory task[16,17] and their association with cognitive functions have been the research subject in recent decades. The first proper clinical research performed on electroencephalographs, observed abnormal EEG activity in all subject cases with AD and concluded that the delta (δ) wave activity was shown in patients' EEG, mainly in the temporal, occipital and parietal areas of one hemisphere.[18,19] These

findings were confirmed in studies performed on a 10-channel electroencephalograph.[20] Hughes *et al.*[20] studied EEGs from patients with AD and observed dispersed slow waves in patients with dementia in resting state, particularly in those with increased severity. The study by Rae-Grant *et al.*[21] showed severe brain lesions. In EEG recordings from AD patients, there was a slowing in background activity and the and the enhancement of δ wave by increase of δ wave frequency band power.[21] In addition, numerous focal abnormalities, peaks, sharp waves, asymmetric and triphasic waves were observed. A correlation between neuronal loss and disease's severity was seen during autopsy in a portion of patients with AD. Furthermore, there has been a correlation between decreased Corticotropin Releasing Factor (CRF) and reduced oxygen in the brain with the appearance of slow EEG waves and cognitive decline.[22]

Nowadays, EEG studies are carried out with more sophisticated instruments and are able to manage more spatial information.[23] In the last two decades, significant research has been conducted on AD-related EEG analysis. Researchers have studied the resting state EEG with statistical features,[24,25] spectral features extracted from Fourier Transform[26,27] time-frequency analysis features extracted from Wavelet Analysis,[28,29] nonlinear features and chaos theory,[30–33] aiming to examine the complexity, the slowing and the synchronization of EEG in AD.[26,27,34] Therefore, signal processing methodologies and techniques are constantly evolving in order to better study EEG abnormalities occurring in AD.

This paper reports experimental studies that aim to automatically detect AD from resting-state EEG data or to correlate the quantitative characteristics of EEG recordings from patients with AD, with MMSE score. This systematic review focuses on a comprehensive and objective presentation of the most recent experimental studies. The methodological approach used to find relevant studies follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[35]an established protocol for identification, selection and analysis of research records. The PRISMA statement is an established and widely accepted methodology for reporting systematic reviews and it was selected with purpose to validate and enhance the credibility of the literature review and limit its objective. A structured summary of the proposed research methodology is presented in Fig. 2, according to the PRISMA guidelines.[36]

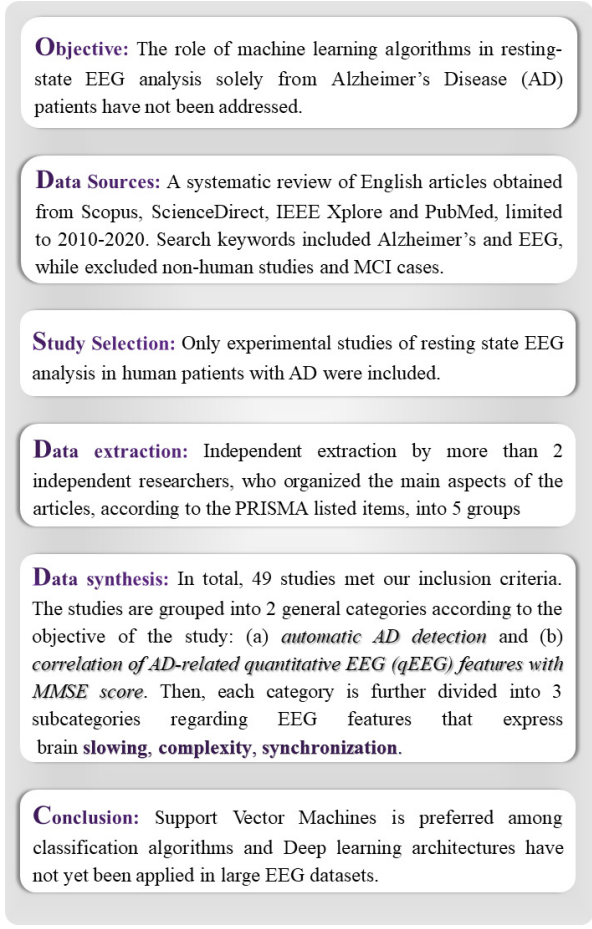

Fig. 1. Structured summary of the proposed systematic review.

2. Research Methodology

The literature search was performed on June 2020 using the most popular and comprehensive search engines for scientific articles: Elsevier's Scopus, IEEE Xplore, Elsevier's ScienceDirect and MEDLINE PubMed. The search was limited to explore recent studies (until 10 years ago) that focus exclusively on EEG analysis in AD and its stages while excluding cases of MCI. Therefore, only studies containing the keywords "Alzheimer's" and "EEG" in the title or abstract of the paper were included. On the other hand, studies containing the keywords "mouse", "mice" or "MCI" in the paper's title or abstract were excluded.

After the first search results, during the screening phase, theoretical studies such as systematic Reviews, Books and Book Chapters of nonexperimental studies were excluded. Articles written in a language other than English, corrections to published articles (Erratum/Corrigendum), articles presented at scientific Conferences as well as Abstract papers and Poster presentations were also removed.

In the final stage, eligibility criteria are applied. More than two eminent independent researchers skimmed the papers for eligibility. Initially the paper's title and abstract were read by the researchers and then specific sections of the paper (i.e. Methodology and Discussion), wherever needed to clarify the objective and the methodology of the paper. Then, each researcher reported the main aspects of the experimental papers in a data extraction sheet. For each experimental study all the 27 items listed in Ref. 36 are extracted and organized into 5 groups, namely:

- *Study rationale*, wherein the objective of the paper is described
- *Study population*, which incorporates the number of subjects, their MMSE score, their demographic characteristics and the name of the EEG database (if reported)
- *Experimental protocol*, where the electrodes, the brain ROIs, the participants' state during recording are reported
- *Methodology*, including the preprocessing step, the feature extraction, the classification/statistical analysis and
- *Results*, wherein the findings from the systematic literature review are reported

Afterwards, the data sheets were examined. In case of disagreement between the researchers, the papers were marked and discussed thoroughly at the end of the process to decide whether the paper met the inclusion criteria or not.

Thus, studies that fell in one or more of the following categories were excluded:

(1) Inaccessibility (i.e. invalid Digital Object Identity document (DOI), inability to find and/or obtain the study)
(2) Application of EEG analysis methodology to animals (e.g. rats, mammals).
(3) Studies exploring the effect of medication on patients' EEG recordings
(4) Non EEG-based study (e.g. Functional Magnetic Resonance Image analysis, Magnetoencephalography (MEG), Transcranial Magnetic Stimulation with EEG)
(5) Nonresting state EEG studies (e.g. Sleep studies,Event Related Potentials)
(6) Application of EEG analysis methodology to patients with other dementias (e.g. frontotemporal dementia, Lewy body dementia) and/or comorbidities (e.g. epilepsy, depression, schizophrenia, Autism Spectrum Disorder, diabetes, stroke, Creutzfeldt-Jakob disease, migraine).
(7) Application of EEG analysis methodology to nonage-matched subjects
(8) Neurofeedback studies
(9) Studies presenting and evaluating EEG recording devices
(10) Studies applying invasive methods (e.g. Deep Brain Stimulation)

3. Survey of EEG Analysis Methods for AD

The database search found 1494 papers in total from all 4 search engines. Then, using the Mendeley tool, 872 duplicate records were detected and removed from a total of 1492 records, proceeding to the first evaluation phase.

From the 620 records that have been extracted, theoretical studies, such as Systematic Reviews (36), Books and Book Chapters of nonexperimental studies (41), articles written in a language other than English (5), corrections to published articles (Erratum/Corrigendum) (5), papers presented at scientific conferences (118) as well as abstract papers and poster presentations (64) were removed.

Finally, eligibility criteria were applied to the remaining 350 articles with purpose to extract the final studies for the analysis. The eligibility criteria described in Sec. 2 limited the number of studies to 49. The flowchart in Fig. 2 follows the PRISMA statement where at the chart's top, the research query is presented. Then, the various stages of the systematic literature review are displayed, showing the number of records detected, evaluated and excluded as well as the reasons why the records were restricted.

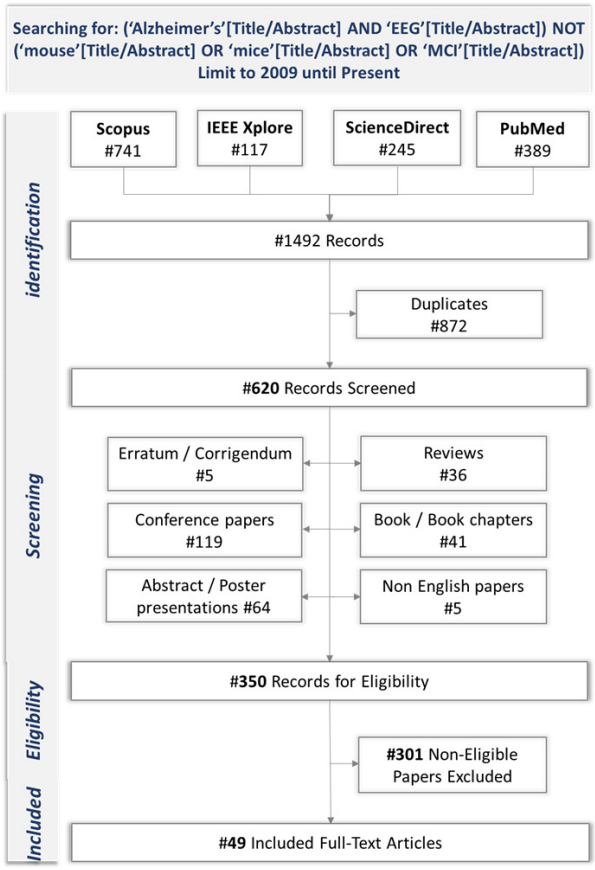

Fig. 2. Literature review flowchart according to PRISMA statement (from the last 10 years).

The 49 papers included in the literature review are grouped into 2 general categories according to the objective of the study. The first category incorporates studies that focus on automatic detection of AD and the second category includes studies that estimate the progression of AD, using as reference the MMSE score, from quantitative features extracted from EEG recordings. Studies that cover both research subjects are analyzed separately in each category.

Further separation of the research studies is based on the features calculated from the EEG recordings to detect changes in the EEG status of patients with AD. There are three sub-categories that describe the EEG state of each measure. The first category analyzes EEG measures that characterize brain slowing, while the second category mainly focuses on measures that characterize the complexity of brain activity, while third category describes EEG measures that characterize brain synchronization Fig. 3.

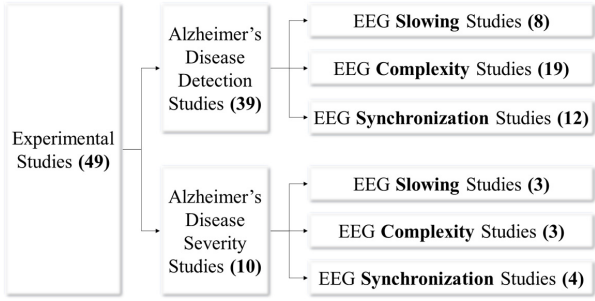

Fig. 3. Grouping the selected papers according to the objective of the study into 2 main categories. The first category contains articles focusing on Alzheimer's disease detection while the second category on estimating the progression of Alzheimer's disease through the MMSE score.

3.1. *Alzheimer's disease detection*

Research interest is mainly focused on the detection of Alzheimer's disease by the extraction of EEG measures. In recent years, researchers have proposed a variety of signal processing features and techniques to study the slowing, complexity and synchronization of EEG in patients with AD. In several cases, modifications to existing measures are recorded with purpose to improve detection results. The features are calculated either in electrode pairs or in formed Regions of Interest (ROIs).

3.1.1. *Brain slowing*

The prevalence of slow brain waves (δ and θ) instead of dominant α and β rhythms is the first finding observed in EEG analysis of patients with AD.[33] The relative band power of the EEG rhythms $\delta, \theta, \alpha, \beta$ and γ as well as the ratio of some EEG rhythms have been used to distinguish between patients with AD and healthy subjects. The θ to α ratio appears to be significantly higher in patients with AD compared with healthy subjects. In specific tasks, the $\frac{\theta}{\alpha}$ ratio distinguishes the two groups better than the ratios α and θ separately.[37]

3.1.1.1. *Band power and EEG rhythms ratio*

Results of experimental studies focused on EEG analysis in AD patients have indicated an increase of the relative band power of low-frequency bands (δ and θ rhythm) along with a decrease in the power of high-frequency bands (α, β), suggesting that patients with AD exhibit a slower brain activity compared to

healthy people. Tylova *et al.*[38] calculated the relative band power using Fourier Transform for each EEG rhythm from 16 AD patients and 16 healthy participants.

Using a two-sample t-test and a 3-layer Multi-Layer Perceptron (MLP) network, the authors verified that the relative band power is significantly lower in AD patients and the power of α, β showed better classification performance at the occipito-parietal region. Fahimi *et al.*[37] studied the change in brain rhythms in 50 AD patients versus 50 healthy subjects. In more detail, they calculated the power of α and θ rhythms, as well as the ratio of θ to α rhythm using the Fast Fourier Transform (FFT) from 10 min EEG recordings. Statistical analysis with the t-test showed that the ratio of θ rhythm to α rhythm was significantly higher in patients with AD compared to healthy subjects and that the index of $\frac{\theta}{\alpha}$ ration can be a useful tool for identifying the disease at an early stage.

In a similar direction, Schmidt *et al.*[39] proposed a methodology based on the calculation of the α to θ ratio. This study utilized 40 s EEG recordings from 57 healthy subjects and 50 patients with AD, were the $\frac{\alpha}{\theta}$ ratio of the mean potential of the C3 and O1 channels was calculated. The discrimination of EEG signals of AD patients from the ones of healthy controls showed 76.4% sensitivity, 84.6% specificity and an area under the ROC curve of 0.92.

A study focused on the reactivity of θ and α rhythm in EEG recordings from AD patients was presented in Ref. 40. Fonseca *et al.* used EEG recordings from 34 AD patients and 30 healthy subjects from the Neurology Clinic of the Celso Pierro Hospital in Brazil and recorded 46–66 s of EEG activity. Recordings were performed while participants were in a relaxed, sitting position with their eyes closed and their eyes open. After applying FFT in 2.56 s epochs, absolute band power was calculated for the frequency bands δ, θ, α and β for all electrodes, as long as for the left hemisphere, the right hemisphere, the occipital and the frontal region. In this work, additional features related to the reactivity of θ and α indices when the person's resting state is switched from eyes-closed to eyes-opened state were studied. Specifically, the change in θ rhythm (θ reactivity index) and the change in α rhythm (α reactivity index) during eye opening were calculated as well as the ratio of the two variations ($\frac{\alpha}{\theta}$ index). The θ reactivity index was calculated as the ratio of the absolute θ power when the individuals had their eyes open during recording, to the corresponding absolute power when the individuals had their eyes closed. The same procedure was used for the calculation of the α reactivity index and the $\frac{\alpha}{\theta}$ index was the combination of α and θ indices. When comparing α reactivity index between the two groups, values were found to be higher, which is interpreted as less activity in patients with AD compared to healthy subjects. Finally, results from the ROC curve showed that the classification accuracy regarding the $\frac{\alpha}{\theta}$ index for the left hemisphere reached 95.3%, with specificity 96.6% and sensitivity 94.1%.

Wang *et al.*,[41] found differences in the γ rhythm of resting state EEG in patients with AD comparing to healthy age-matched subjects. EEG signals were recorded from 8 patients and 12 healthy subjects. Then, wavelet power spectrum and bicoherence of EEG were analyzed in the 5 basic rhythms and a non-parametric permutation method was applied. Compared to the group of healthy subjects, the relative power of δ and γ frequencies was increased while the power of α rhythm in AD group was decreased. In addition, it was found that the increased δ rhythm was mainly located in the central, parietal and occipital regions. The α rhythm was reduced in the entire cerebral cortex and the γ rhythm was increased mainly in the midline frontal, central and occipital regions. Concerning bicoherence, there was an increase in the association between the frequencies of the $\beta - \gamma$ rhythms and between low frequencies in patients with AD in comparison with healthy subjects.

Chen *et al.*[42] studied brain slowing utilizing EEG recordings of 95 patients with AD from Taiwan's Taipei Hospital. The 10 s EEG recordings were analyzed in 4 EEG rhythms (δ, θ, α and β) using FFT. The authors calculated the ratio of band powers and interhemispheric coherence of α rhythm between 8 electrode pairs. Specifically, the $\frac{\theta}{\alpha}$ band power ratio, the θ and δ ratio to the α and β, the θ ratio to the α and β and the θ and δ to α band power for 16 electrodes were calculated. EEG recordings were divided into 4 groups according to the severity of the disease, ranging from mild to severe according to MMSE score. One-way analysis of variance (ANOVA) and Mann-Whitney test showed that the best results were given by the ratio δ and θ to the α

and β band powers and the interhemispheric coherence of the α rhythm at the electrode pairs of the central and parietal regions.

In study,[43] the main objective was the comparison between signal processing techniques and particularly between FFT and Continuous Wavelet Transform (CWT). Durongbhan *et al.* collected EEG data from 20 patients with AD and 20 healthy subjects from Sheffield's Teaching Hospital. The EEG recordings lasted 30 min, from which 12 s artifact-free signals were selected and were split into 4 s epochs. Then, the average magnitude of FFT was calculated taking into consideration all coefficients of each EEG rhythm (δ, θ, α, β, γ), for each of the 23 channels. The average magnitude of CWT was also calculated. Alzheimer's Disease detection results were better when applied CWT than with FFT and their classification accuracy with the k-Nearest Neighbor (KNN) algorithm reached 99% for P3 and O1 channels. Furthermore, researchers observed that features extracted from δ and θ rhythms had the best classification results. Finally, Durongbhan *et al.* studied window lengths of less than 4 s, concluding that the 4 s window (8000 data points at a sampling frequency of 2 KHz) produced the best results for detecting AD.

3.1.1.2. *Amplitude modulation*

Another EEG feature characterizing brain slowing is amplitude modulation. Falk *et al.*,[44] introduced amplitude modulation rate-of-change to study EEG slowing regarding AD. According to the proposed methodology, the EEG recording was analyzed through its envelope. The amplitude modulation was calculated using the Hilbert transform for 4 EEG rhythms (δ, θ, α, β) and the rate at which the amplitude modulations change over short periods of time (approximately 5 s) was extracted.

Afterwards, the percentage modulation energy was calculated for electrode pairs from the frontal, parietal, occipital and temporal region and was compared between 11 healthy subjects (Controls) and 21 patients with different AD severity (11 with mild AD and 10 with moderate to severe AD). Four classification problems were conducted namely Control/AD, Control/mild AD, Control/moderate AD and mild AD/moderate AD and Support Vector Machines (SVM) provided Accuracy rate of 90.6%, 74.1%, 71.4% and 53.8%, respectively. Results of the study[44] showed that the majority of the features selected for classification were derived from modulating the low frequencies δ and θ. This indicates that the major abnormalities occur in slowly-varying amplitude modulations. Table 1 presents the spectral/power features used for AD analysis.

Table 1. Spectral/Power features utilized in experimental studies of EEG analysis in AD patients.

Category	Features	Studies
Power Features	Relative Band Power	24, 25, 45, 46 40, 47, 37, 48
	Power Spectrum Density	49, 50, 41, 51 52, 53, 37
	Ratio of EEG Rhythms	54, 39, 40, 42
	Energy	24, 25
	Signal-to-Noise Ratio	55
Spectral Features	Amplitude Modulation	56

3.1.2. *EEG complexity*

Most EEG analysis studies in patients with AD focus on the complexity of EEG dynamics. The complexity of brain activity is calculated by some nonlinear measures from Information Theory such as Multiscale Entropy, Fuzzy Entropy, Lempel–Ziv complexity, Approximate Entropy, Tsallis Entropy, Sample Entropy and Mutual Information to name just a few. Over the last 10 years, a variety of signal processing techniques and nonlinear features have been proposed expressing complexity, irregularity, variability and predictability, concluding that the complexity of brain activity decreases in patients with AD.

3.1.2.1. *Entropy features*

Recently, Azami *et al.*[57] studied a feature based on dispersion entropy and fluctuation called multi-scale Fluctuation-based Dispersion Entropy (MFDE). EEG recordings from 11 AD patients and 11 healthy subjects were divided into 5 s epochs (1280 data points) and the MFDE,the Multi-scale Sample Entropy (MSE), the Multi-scale Fuzzy Entropy (MFE) and the Multi-scale Dispersion Entropy (MDE) were calculated. Comparison of the mean and standard deviation between the two groups showed

that the features from AD patients had lower values than those of the healthy subjects at short-time scales, while they were higher on long-time scales.

The same group of authors, in a previous study[58] proposed the multivariate Multi-Scale Entropy, which is an extension of variation-based Multiple-Scale Entropy (mvMSE_{σ^2}). Azami *et al.* studied the proposed feature in different frequency bands and compared it with previous studies based of mean-based MSE (MSE_{μ}), multivariate MSE (mvMSE) and variation-based MSE (MSE_{σ^2}). The experiments involved 11 patients with AD and 11 healthy individuals from Alzheimer's Patients' Relatives Association of Valladolid (AFAVA) at the University Hospital of Valladolid in Spain. Each EEG recording of 5 min was performed with 19 electrodes and then was segmented into 5 s epochs. Results of the Mann-Whitney test showed a complexity decrease in individuals with AD, emphasizing the advantage of mvMSE and mvMSE_{σ^2} features in separating AD patients from healthy subjects. In addition, the most important information derived from the O1, O2, F4, P3 and T5 electrodes.

Usually, the degree of regularity in a time series is estimated by the appearance of repeated patterns. According to Pincus,[59] m is a factor for pattern length and it usually takes values 1 or 2 and r is a similarity factor that takes values 0.1, 0.15, 0.20, 0.25 and 0.50. Furthermore, in the original study of MSE, Costa *et al.*[60] proposed a coarse-gaining procedure to estimate the entropy, based on a integer time scale factor τ, which takes values over the interval [2,20]. In 2013, Yang *et al.*[61] proposed an EEG study evaluating the use of MSE across various time scales in AD analysis. EEG signals of 30 s from 15 patients with moderate to severe AD and 15 healthy individuals recorded at the Neurological Institute, Taipei Veterans General Hospital (TVGH) in Taiwan were cut into 10 s epochs and analyzed using Fourier transform in the 5 EEG rhythms. MSE was calculated for $m = 2$ and $r = 0.15$ and for various τ scale values in frontal, frontal-central,temporal and parieto-occipital regions. Results from two-way ANOVA are in agreement with Ref. 57 and showed that MSE decreases in AD for short-time scales (τ from 1 to 6), while it increases for long-time scales (τ from 16 to 20), making MSE a reliable feature to discriminate AD patients from healthy subjects.

MSE was also utilized in a recently published study.[62] In this study, 15 healthy subjects, 69 patients with mild AD, and 15 patients with moderate AD participated and the EEG recordings were performed at the Neurological Institute, TVGH in Taiwan, while participants were with eyes closed, opened and during photic stimulation. Then, the Empirical Mode Decomposition (EMD) was applied and MSE was extracted from each channel. Classification results for separating AD patients from healthy subjects using Linear Discriminant Analysis (LDA), showed that the best performance in terms of F1 score (0.828) was obtained for T5 and P3 electrodes.

In study,[63] Fuzzy entropy was used to characterize the alterations of brain activity in patients with AD. The calculation of Fuzzy entropy is based on the original Sample Entropy algorithm proposed by Richman and Moorman[64] and depends on the values of m, r and n, where n is a factor that shows the gradient of the fuzzy exponential distance function. Simons *et al.* analyzed EEG recordings from 11 patients with AD and 11 healthy individuals from AFAVA in Spain and extracted Fuzzy entropy and Sample entropy from 5 s (1280 data points) epochs. Entropy attributes were calculated for different values of m, r and n for 16 channels. Lilliefors and Kruskal–Wallis tests showed that for all values of m, r and n, fuzzy entropy decreases for individuals with AD at almost all electrodes with statistical significance at T6, P3, P4, O1 and O2 electrodes. In addition, the best classification results are shown for $n = 1, m = 2$ and $r = 0.25$ for the O2 electrode with 86.36% Precision, 90.91% Sensitivity and 81.82% Specificity.

Wang *et al.*[65] proposed a method to detect differences in brain activity of 20 healthy subjects and 14 patients with AD which was applied to clinical 130 s EEG recordings and to surrogate EEG data created using the Fourier transform. Results from clinical data based on Student's t-test showed that Sample entropy in AD patients was significantly reduced at C3, F3, O2 and P4 electrodes, which confirmed that AD can cause loss of brain complexity. However, concerning synthetic data, it was found that there was a significant decrease in Sample entropy in the clinical data over the surrogate data at C3 and O2 electrodes. Also, significant differences between healthy subjects and patients with AD was found.

Another entropy feature, Permutation entropy was studied in Ref. 66. Tylova *et al.* obtained 5 min EEG recordings from 10 patients with AD and 10 healthy subjects and examined the association of sampling frequency and window length with the discrimination between the two groups. The EEG recordings were segmented in 10 s epochs and the Permutation entropy was calculated using the Miller approach, which is an estimate of Permutation Entropy proposed by Miller.[67] Results with two-sample t-test showed that in the AD case, a decrease in Permutation entropy was observed compared to that of healthy subjects for all EEG channels. Furthermore, the best results were obtained for 200 Hz sampling frequency using the 10 s epoch.

A combination of weighted permutation entropy and multiscale multivariate method is proposed in Ref. 68. Deng *et al.* recorded 5 min of EEG activity from 14 AD patients and 14 healthy subjects and segmented them in 5 epochs of 8 s duration. Then, the permutation entropy was extracted based on the multivariate analysis. Validation was performed on both synthetic and original data and the one-way ANOVA test showed an AUC of 0.93. A similar methodology was proposed in Ref. 69. Morabito *et al.* included MCI cases and extracted multiscale multivariate permutation entropy from 3 MCI patients, 3 AD patients and 3 healthy controls for each EEG channel. The discrimination performance of Multi-Scale analysis was higher between CN/AD patients than MCI/AD.

Abasolo *et al.*[70] studied the regularity of brain dynamics through the Approximate entropy, using 11 AD patients from AFAVA and 11 healthy individuals. A total of 30 epochs of 5 s each (1280 data points) were selected on average from the EEG recordings. Abasolo *et al.* tested different values of m and r and they concluded that the best pair was $m = 1$ and $r = 0.25$ times the standard deviation. Student's t-test showed that Approximate entropy was significantly lower in AD patients on P3, P4, O1 and O2 channels. In addition, the classification accuracy of the two groups with the ROC curve ranged from 72.73% to 81.82%, achieving better Accuracy (81.82%), Sensitivity (63.64%) and Specificity (100%) when $m = 2$ and $r = 0.25$.

A combination of entropy features was proposed in Ref. 24. Tzimourta *et al.* utilized 16 min EEG recordings from 14 AD patients and 10 healthy participants and extracted spectral (Energy, Relative band power, Approximate entropy, Permutation entropy, Sample entropy, Tsallis entropy for each EEG rhythm and Shannon entropy, MSE for 0.5–60 Hz) and statistical features (mean, standard deviation, variance, skewness, kurtosis, IQR) from epochs of 12 s. Results with Random Forests indicated high levels of accuracy (ranging from 88.79% to 96.76%) for 6 classification problems (CN/AD,CN/mild AD, CN/moderate AD, CN-mild AD/moderate AD, mild AD/moderate AD, CN/mild AD/moderate AD). In Table 2 the entropy features are presented.

3.1.2.2. *Lempel–Ziv complexity*

In 2018, Al-Nuaimi *et al.*[72] examined the complexity of brain dynamics in AD with three complexity features: Lempel–Ziv complexity, Higuchi's fractal dimension (HFD) and Tsallis entropy in 5 EEG rhythms in patients with AD and healthy subjects having similar and nonsimilar age. For the study of similar-age subjects, they utilized 19 electrodes to record EEG data with duration from 61 to 240 s using 8 healthy subjects and 3 patients with AD. The SVM algorithm was used for classification and the results showed that the Lempel–Ziv complexity presented better discrimination ability than Tsallis entropy and HFD. Specifically, for channel C3, the Lempel–Ziv complexity of θ rhythm yielded 95% Accuracy, 100% Sensitivity and 92.31% Specificity. For all features Student's t-test yielded lower values for patients with AD than healthy subjects. HFD was also used in a recent studies based on Temporal-scale-specific

Table 2. Entropy features utilized in experimental studies of EEG analysis in AD patients.

Category	Features	Studies
Entropy Features	Shannon Entropy	24, 25, 71
	Approximate Entropy	24, 25, 70
	Tsallis Entropy	24, 25, 72, 71, 48
	Permutation Entropy	24, 25, 66
	Multiscale Entropy	62, 24, 25, 73, 71 57, 58, 61
	Sample Entropy	24, 25, 63, 65, 74
	Spectral Entropy	24, 25, 48
	Bispectral Entropy	51
	Fuzzy Entropy	63, 57
	Dispersion Entropy	57

fractal dimension.[75] Nobukawa *et al.* performed fractal analysis and power analysis using FFT in 60 s segments from 16 AD and 18 healthy participants to extract PSD. Results with ANOVA showed that reduced fractality was shown for beta and gamma rhythms of AD group and was associated with cognitive decline. Ahmadlou *et al.*[76] proposed two fractal dimension algorithms, namely Katz Fractal Dimension (KFD) and HFD, and showed that the accuracy for KFD in the beta band was above 99%.

To investigate the complexity of brain activity in AD, Liu *et al.*[50] examined the Lempel–Ziv complexity and Power Spectrum Density (PSD) in 14 patients and 14 healthy individuals. A 3-level Wavelet Decomposition was performed in five 8 s epochs (8096 points) for each frequency of interest (δ, θ, α, β). Burg's method was used to calculate PSD. Classification with SVM with features extracted from α rhythm yielded 91.4% Accuracy, 100% Sensitivity and 82.9% Specificity. One-way ANOVA showed that PSD of θ rhythm increased in patients with AD in contrast to healthy subjects, while the α PSD decreased. Furthermore, the Lempel–Ziv complexity of α rhythm was reduced in patients with AD, which is consistent with the study proposed by Al-Nuaimi *et al.*.[72]

3.1.2.3. *Mutual information*

Complexity features and features from Information Theory have been used in a study proposed by Kim *et al.*[77] with purpose to investigate the information transmission between brain regions. EEG recordings from 10 patients with mild AD and 10 healthy subjects were acquired from the department of psychiatry of Taejon St Mary's hospital. EEG recordings of 33 s duration were analyzed using the Fraser–Swinney algorithm, aiming to extract the time delayed mutual information between two channels. Omega complexity from EEG data was also calculated. Then, a modified form of Karhunen–Loeve decomposition was used, in order to quantify the information transmission in the brain. Statistical analysis with Student's t-test and Bonferroni's correction test showed differences in the way information was transmitted between the two groups, indicating a clear discrimination between the two groups. Furthermore, it was observed that combining mutual information and Omega complexity was more effective in information transmission between parts of the brain than computing only mutual information.

In another study,[78] Vyšata *et al.* used mutual information and wavelet coherence to study the slowing of brain activity and the brain connectivity in AD. For the proposed study, EEG recordings from 110 patients with moderate AD and 110 healthy individuals were obtained. Initially, the EEG recordings were segmented in six epochs lasted between 60–80 s each and a 5-level Wavelet Transform was applied. Then, mutual information and wavelet coherence for 171 electrode pairs were extracted. Statistical analysis with two-sample t-test showed that mutual information calculated from low frequencies decreased in patients with AD in the frontal and temporal region, while increased in the central and parietal regions for all frequencies. Furthermore, wavelet coherence also decreased in the frontal and temporal regions for AD patients, mainly at the right hemisphere and at low frequencies. In the same database, the same group of authors proposed a methodology based on the power law distribution of the EEG power spectrum.[52] Maintaining the same pre-processing part, PSDs and the slope α of the power spectra in the log–log scale were estimated. The two-sample t-test showed significant differences between groups in the frontal area and the discrimination of AD from healthy subjects with area under ROC curve reached over 90% at the temporal area. Table 3 shows Complexity features and features from Information theory that were used to extract EEG information from recordings in AD studies.

3.1.2.4. *Spectral features*

In study,[45] a set of spectral features and the SVM algorithm was used in order to classify EEG data

Table 3. Complexity features and features from Information theory utilized in experimental studies of EEG analysis in AD patients.

Category	Features	Studies
Complexity Features	Lempel–Ziv Compl.	72, 45, 50
	Ω Complexity	77
Information Theory	Mutual Information	71, 79, 77, 48, 78

from patients with AD from the ones from healthy subjects. Kulkarni and Bairagi calculated spectral features, features extracted from Wavelet Analysis and EEG complexity features using EEG data acquired from 50 healthy individuals and 50 AD patients. In more detail, EEG recordings were segmented in epochs lasting from 3 to 5 s and the relative band power, the Lempel–Ziv complexity, the mean value and the variance of each decomposition level were calculated using Wavelet Analysis. Additional spectral features such as Spectral Entropy, Spectral roll-off, Spectral Centroid and Zero Crossing Rate were extracted. The spectral entropy, spectral roll-off, spectral centroid and zero crossing rhythm features were able to separate the groups with SVM achieving the best Accuracy (96%).

Wang *et al.*[51] proposed spectrum and bispectrum analyses to extract features in order to discriminate 14 healthy subjects and 14 AD patients. From each EEG recording, a 40 s segment was isolated and divided into 8 s epochs. Then, the PSD was calculated using Burg's method and also, the Spectral entropy of α and θ rhythms, the ratio of the Spectral entropy of α to θ frequency band and the bispectral entropy. Statistical analysis with one-way ANOVA showed that PSD in AD group was significantly higher for the θ rhythm compared to control group, while it was lower for the α rhythm in the central, parietal and occipital regions. In addition, the ratio of Spectral entropy of α to θ frequency band in both spectrum and bispectrum analysis is reduced, indicating that the electrophysiological activity in the brain of patients with AD is much slower and less chaotic. Finally, SVM classification showed a maximum Accuracy of 90.2%.

In a different study,[80] Ieracitano *et al.* proposed a CNN architecture to extract EEG features and discriminate between 63 controls, 63 AD and 63 MCI patients. The network was fed with gray-scale images that were created from the calculated PSD and results for the binary problem AD/CN in terms of accuracy was 92.95%.

In Table 4, all the spectral features described in this subsection are presented.

Table 4. Spectral Features utilized in experimental studies of EEG analysis in AD patients.

Category	Features	Studies
Spectral Features	Phase Shift	79
	Phase Sync. Index	81, 46
	Phase Coherence	46
	Coherence	79, 46, 82, 83 84, 48, 78, 85
	Partial Coherence	79, 83
	Bispectrum	51
	Bicoherence	41
	Spectral Centroid	45
	Spectral Roll-Off	45
	Spectral Peak	84, 86, 47
	Average Magnitude	43
	Median Frequency	51

3.1.2.5. *Statistical characteristics*

Kanda *et al.*[55] proposed a methodology based on statistical features extracted from EEG data by applying Wavelet Analysis. In this study, 162 EEG recordings of 40 s duration were used from 74 healthy subjects and 88 patients with mild to moderate AD. Wavelet analysis was performed using the Morlet wavelet and the EEG rhythms (δ, θ, α and β) were extracted. Then, 11 statistical features were calculated, including maximum, minimum, average, median, standard deviation, variance, interquartile range, coefficient of variation, variance-to-mean ratio and the signal-to-noise ratio for each rhythm and for each of the 20 EEG channels. The SVM classifier utilized 66% of the dataset for training and 34% for testing which resulted in 92.72% Accuracy. Lately, autoregressive models have been examined on various types of data, enhancing the prediction performance.[87] Tylova *et al.*[88] recorded EEG signals from 139 healthy subjects and 26 patients with AD and proposed a predictive modelling approach for detecting AD. In particular, the authors created 3 linear autoregressive models: one predictive model, one symmetric model and one back-predictive model. Then, from each model they calculated two sets of features (a) the standard deviation (STD), the mean of the absolute differences from the mean value (MAD1) and the mean of the absolute differences from the median value (MAD2) and (b) the median of the absolute differences from the median (MAD3), the interquartile range (IQR) and the first quartile of the absolute mutual differences (MED). The two-sample t-test showed that the symmetric predictive model along with the second group of features

Table 5. Statistical Features utilized in experimental studies of EEG analysis in Alzheimer's Disease patients.

Category	Features	Studies
Statistical Features	Mean	24, 25, 45
	Variance	24, 25, 89, 45, 55, 83
	Skewness	24, 25, 89
	Kurtosis	24, 25, 89
	STD	24, 25, 55, 88
	IQR	24, 25, 55, 88
	Maximum	55
	Minimum	55
	Average	55
	Median	55
	Variance to Mean Ratio	55
	Power Law Distribution	52
	First Quartile of the Absolute Mutual Differences (MED)	88
	Mean of the Absolute Differences from the Mean Value (MAD1)	88
	Mean of the Absolute Differences from the Median Value (MAD2)	88
	Median of the Absolute Differences from the Median Value (MAD3)	88

showed statistically significant differences between the two groups in the frontal lobe.

Another study[89] investigated the interactions between brain regions in three different datasets to examine the switch from one brain state to the other with temporal EEG features. Mora-Sánchez *et al.* acquired EEG recordings lasting 20 s from 21 AD patients and 38 healthy controls and extracted statistical moments (skewness, variance, kurtosis) parameterized by time. The features were used as an input to an LDA classifier to discriminate between healthy and AD participants and the Area Under the Curve (AUC) of a ROC curve measured the classification performance. Results showed that large transitions in brain dynamics are better correlated with AD diagnosis and the area under the ROC curve was 0.71.

A study proposed by Ferreira[90] incorporated 511 subjects, including AD patients (135), MCI patients, Parkinson's Disease and other dementia patients and normal age-matched subjects (141). In this study, statistical pattern recognition (SPR) was used and the SPR-based EEG diagnosis of AD was compared with the diagnosis based on CRF and cognitive analysis and the diagnosis based on biomarkers obtained from neuroimaging analysis. Mann-Whitney U test and one-way Kruskal–Wallis test showed an AUC of 90.50% for the discrimination between AD/CN.

Table 5 shows the statistical features used for EEG analysis in experimental studies with AD patients.

3.1.3. *Synchronization and functional connectivity*

Synchronization refers to the simultaneous appearance of discrete rhythmic patterns in different regions of the brain, either unilateral (in one hemisphere) or bilateral (in both hemispheres). The synchronization of the brain is affected by the degeneration that occurs in dementia. A variety of different synchronization measures have been reported in literature,[91,92] such as Granger causality, phase synchrony, coherence and many more regarding disruption on neural synchrony. Most studies in patients with AD, show a decrease in cerebral synchrony as a result of cognitive decline compared to healthy elders.[79] EEG recording synchronization measures are used by a number of studies in order to build connected brain networks. Using graph theory, nodes corresponding to EEG channels are constructed and the connectivity between two nodes (electrode pairs)

is studied.[93] The communication between different brain nodes that may not be structurally related is called functional connectivity. FMRI studies support that significant changes have been observed in brain networks of patients with AD.[94] In EEG studies, features such as Current Source Density (CSD), Frequency Peak and Lagged Linear Connectivity (LLC) have been used to characterize communication between two regions in terms of amplitude, phase and different frequencies of the EEG signal.[95]

3.1.3.1. *Features from LORETA software*

The sLORETA/eLORETA software is a tool that creates three-dimensional (3D) images of the brain by extracting features from EEG or MEG measurements. The sLORETA method attempts to identify active cortical sources by analyzing features from EEG or MEG measurements obtained from the cerebral cortex. The results from this method are presented in a 3D visualization of the brain. Recently, a number of studies have been proposed to study AD using the LORETA software.[96]

Trigianni *et al.*[49] studied the capability of four EEG features to distinguish patients with AD and healthy individuals. In this study, 5 min EEG recordings from 120 patients with AD and 100 healthy individuals were used which were segmented into 2 s epochs. The eLORETA software was used to calculate the LLC, the PSD and the CSD for δ (2–4 Hz), θ (4–8 Hz), $\alpha 1$ (8–10.5 Hz) and $\alpha 2$ (10.5–13 Hz) and for 6 ROIs. The highest Accuracy (77%) with Artificial Neural Network (ANN) classifier was achieved using (a) the ratio between θ activity of parietal sources and $\alpha 1$ rhythm, (b) the ratio between θ activity of frontal sources and $\alpha 1$, (c) the ratio between the θ activity of occipital sources and $\alpha 1$ and (d) the ratio between the δ activity of occipital sources and $\alpha 1$. Good classification results were also obtained in terms of Sensitivity (79.3%) and Specificity (74.3%).

Similar to Ref. 49, Lizio *et al.*[54] utilized the same database with Trigianni *et al.*[49] and used a single EEG metric to study functional connectivity of the brain. This metric, is the ratio between the activity of δ rhythm in parietal-occipital region (2–4 Hz) and the activity of low frequencies of α rhythm, namely $\alpha 1$. The study was performed on 127 patients with AD and 121 healthy subjects using the LORETA software. The 5 min EEG recordings were segmented into 2 s epochs and the individual alpha frequency (IAF) peak was calculated for the 6–14 Hz frequency band. The classification Accuracy between healthy subjects and patients with AD according to ROC curve reached 71.2%. The group of AD patients, showed a significant decrease in the activity of $\alpha 1$ rhythm in the occipital region, along with an increase in δ rhythm.

Babiloni *et al.*[53] used the sLORETA software to check if cortical EEG sources are changing in AD and whether they are indicators of disease progression. For this study, 5 min of EEG activity with 19 channels from 88 patients with mild AD and 35 healthy subjects were recorded and the recording was repeated one year later. In a later similar study[97] the PSD of the cortical sources was calculated through eLORETA from EEG recordings from 100 healthy subjects and 120 AD patients. ANOVA and the Area Under the Receiver Operating Characteristic Curve (AUROC) showed a discrimination accuracy of above 0.7. In a more recent study,[54] data was segmented into 2 s epochs and the spectral power density for δ (2–4 Hz), θ (4–8 Hz), $\alpha 1$ (8–10.5 Hz), $\alpha 2$ (10.5–13 Hz), $\beta 1$ (13–20 Hz), $\beta 2$ (20–30 Hz) and γ (30–40 Hz) was calculated. Finally, the IAF peak was extracted. Results of ANOVA showed that the δ power increased in patients with AD while the α power decreases in all areas of interest. Moreover, one-year follow-up, showed a decrease in β activity in parietal, occipital and temporal areas in AD patients. Regarding the localization of cortical sources, it has been observed that AD patients have increased δ power in general and reduced the α power in occipital sources compared to healthy individuals.

3.1.3.2. *Coherence*

Coherence (also called magnitude squared coherence) has been used in conjunction with mutual information in order to study brain complexity as seen in the study of Vyšata *et al.*[78] and cortical connectivity of the brain as seen in the study of Sankari *et al.*.[85] In particular, Sankari *et al.* used EEG recordings from 7 healthy subjects and 20 patients with AD with purpose to test their methodology. The methodology is based on the Continuous Wavelet Transform (CWT) and the calculation of wavelet coherence for the 5 EEG rhythms in 19 channels.

Results of one-way ANOVA are in agreement with the results of study[78] and showed that wavelet coherence of δ rhythm decreases in the temporal and central regions. Furthermore, the connectivity decreases in the parietal and central regions mainly for θ and α frequencies. The same group of authors proposed a series of different techniques[98,99] resulting in the same conclusion. In their research the coherence in AD patients decreased, indicating a decline in cortical connectivity.

Trambaiolli *et al.* proposed two studies examining the electrode montage sensitivity in AD analysis[86] and the slowing of brain activity and the functional connectivity between electrode pairs using spectral peak and coherence.[84] In their first study[86] 12 healthy subjects and 22 probable AD patients were recruited. The 20 min EEG recordings were obtained and 40 epochs of 8 s were selected for the analysis. Using the Fourier transform, the spectral peak from each EEG band was calculated, which is the point in the PSD where the energy is maximized. Five electrode montages were examined (Biauricular reference, Longitudinal Bipolar, Crossed Bipolar, bipolar inter-hemispheric and Cz reference) and Logistic Regression showed that the bipolar inter-hemispheric montage outperformed and the classification accuracy was over 90%. In their second study,[84] 19 healthy elderly and 16 patients with AD were recruited and the pre-processing part was the same as Ref. 86. In this particular study,[84] the Spectral peak and coherence between electrode pairs were calculated for frequency bands which correspond to EEG rhythms that are analyzed in more depth. These rhythms are $\delta 1$ (0.1–2 Hz), $\delta 2$ (2.5–4 Hz), $\theta 1$ (4.5–6 Hz), $\theta 2$ (6.5–7.5 Hz), $\alpha 1$ (8–10 Hz), $\alpha 2$ (10.5–12 Hz), $\beta 1$ (12.5–15 Hz), $\beta 2$ (15.5–21 Hz), β_3 (>21 Hz). This method used 68% of the data for SVM training and 32% for testing, reaching a 79.9% classification Accuracy.

In another EEG synchronization study,[46] the main objective was the investigation of artifact removal algorithms. Cassani *et al.* tested 3 artifact removal methods on EEG recordings and specifically the Statistical artifact rejection, the Blind Source Separation and the Independent Component Analysis which was based on Wavelet Analysis. The proposed study, utilized EEG recordings acquired from 24 healthy subjects and 35 patients with AD (20 with mild AD and 15 with moderate AD). Afterwards, spectral power, amplitude modulation rate-of-change, coherence and phase coherence/synchrony for each EEG rhythms were calculated. SVM classification was performed and accuracy reached 78.9%, 90.8% and 96.3% for Control/mild AD/moderate AD, Control/mild AD and mild AD/moderate AD, respectively. Regarding the calculated features, features extracted from δ, θ and β rhythms correspond to 80% of the selected features for each of the 3 classification problems while features extracted from γ rhythm were not selected at all.

In another study,[100] investigating the topological reorganization of functional brain networks in AD, 108 AD patients and 15 healthy controls from the TVGH in Taiwan were recruited as described in Ref. 61. Chen *et al.* selected 3 epochs of 9 s duration for each participant and then filtered the signals into the 5 EEG rhythms. The phase coherence from EEG bands was used to construct functional brain networks and then the average clustering coefficient and the global efficiency were extracted to quantify brain synchronization. Statistical Analysis using ANOVA revealed significant topology alterations in α rhythm in patients with AD.

Dubovik *et al.*[82] examined whether modifications in functional connectivity are related to the cognitive function of patients with AD. In the proposed study, 5 min EEG signals were recorded from 15 patients with AD and 15 healthy subjects from University Hospital of Geneva and imaginary coherence between brain ROIs was calculated. Coherence Φ is the imaginary part of coherence when it is expressed as a complex number for a given time window. Statistical analysis with t-test showed a disruption of functional connectivity between the parietal and temporal regions in AD patients compared to the rest of the brain, mainly for α rhythm. Also, a shift in functional connectivity from α frequencies to θ frequencies and from Broca region to the right hemisphere was observed in a network involved in episodic verbal memory. Frequency shift was associated with good verbal memory performance in patients with AD which demonstrates an adaptive restructuring of brain networks in early stages of AD. Therefore, these findings could be used for automated detection of AD.

3.1.3.3. *Phase synchronization index*

Phase synchronization index is a feature that has been used in recent studies analyzing the synchronization and functional connectivity of AD patients. In Ref. 81 a methodology for identification of AD from EEG data, based on a Takagi–Sugeno–Kang (N-TSK) fuzzy classification model is described. Recordings were obtained from 30 AD patients and 30 healthy individuals while subjects were in a relaxed, sitting position with eyes open and eyes closed. Yu *et al.* created networks based on the phase synchronization index, calculated from 15 8 s epochs, aiming to extract network topology properties. The calculation of phase synchronization index creates a value of connectivity strength for each pair of electrodes which indicates the connectivity between all possible electrodes. The proposed model utilized 5-fold cross-validation and obtained 97.3% classification Accuracy when recordings were performed while patients were with their eyes-closed.

In a recent study,[101] a research on how neural networks change in the brain and especially in areas of high connectivity was conducted. For the proposed study Engels *et al.* used 318 patients with different stages of AD (mild, moderate, severe) and 133 healthy subjects. Phase synchronization index and a measure to quantify the importance of an electrode (node) within the neural network, betweenness centrality, were calculated from 4 s (4096 points) epochs. Diagrams were created and the center of mass was calculated, using the values of centrality. Results from x2-test and one-way ANOVA showed that functional connectivity decreases with increased disease severity for α rhythm. All regions, except the posterior region, showed that centrality values increased when the severity of the disease was increased. The center of the mass was shifted from the posterior region to the anterior region for high frequencies, as the severity of the disease increased, indicating a loss of functional connectivity of the posterior regions of the brain.

A different use of MSE was proposed in Ref. 73. Song *et al.* created a functional brain network by calculating MSE. According to this methodology, MSE is calculated from 16-channel EEG recording obtained by 15 healthy and 15 AD patients and represents the dynamic of each channel (node). It is then displayed on a hyperplane with purpose to calculate the distance between the nodes and determine the network connectivity.

The SVM algorithm achieved 96.24% classification accuracy for the detection of AD patients from healthy subjects. Regarding connectivity, the Mann-Whitney test showed that AD patients had reduced connectivity for whole brain, especially for connections between remote channels compared to healthy subjects. In addition, reduced connections between the frontal region and other regions, revealed that signal transmission related to frontal lobe is damaged in patients with AD. All the Loreta features are presented in summary in Table 6.

3.2. *Disease severity estimation through MMSE score by quantitative EEG features*

Numerous studies have studied quantitative EEG features in patients with AD; however, little information is available on the correlation of quantitative EEG with disease progression, using as reference the MMSE score. In the same context of AD detection, researchers proposed quantitative EEG measures that characterize slowing, complexity and synchronization of brain activity, aiming to investigate predictor variables that show high correlation with MMSE score variation.

3.2.1. *Correlation of EEG slowing features with MMSE score*

The relationship between EEG measures and the progression of cognitive decline has undoubtedly

Table 6. Features from LORETA software utilized in experimental studies of EEG analysis in AD patients.

Category	Features	Studies
LORETA Features	Phase Locking Factor	47, 101
	Degree Node	47
	Mean Degree of Network	47
	Small Worldness of a Network	47
	Closeness Centrality of a Node	47
	Absolute Average Deviation	47
	Betweenness Centrality	101
	Center of Mass	101
	Lagged Linear Connectivity	49, 102
	Current Source Density	49, 102

gained the research interest. Slowing of background activity and the dominance of low frequencies δ and θ is a fact in AD. A number of researchers have studied the relative power of EEG rhythms in AD and the ratio of power of EEG rhythms, particularly of α and θ. Results of these studies show a high positive correlation between the power of δ and θ rhythms with the severity of the disease. Studies have shown that the $\frac{\alpha}{\theta}$ ratio is also positively correlated with the MMSE variation, meaning that it decreases as the disease severity increases.

3.2.1.1. *Relative band power*

In a large study[48] of 118 patients with mild to severe AD acquired from the prospective longitudinal studies of the Austrian Alzheimer Society (PRODEM) database, it was investigated which quantitative EEG measure or combination of measures was best correlated with the severity of AD, as estimated by the MMSE score. Garn *et al.*[48] studied various complexity, slowing and synchronization features in EEG recordings of people sitting with their eyes closed (158 s) and during a cognitive test (86 s). The EEG recordings were segmented into 4 s epochs with 2 s overlap. Then, the relative power of the 5 EEG rhythms, the coherence, the Canonical correlation, the Granger causality, the Shannon entropy, the Tsallis entropy and the Mutual Information were extracted. Researchers used Quadratic Least-Squares Regression and observed that the increased relative power of θ rhythm is correlated with cognitive decline. The best regression results were the relative power of θ rhythm in the left temporal region ($R^2 = 0.28$), the mutual information on the left hemisphere ($R^2 = 0.31$) and the model created by the total of the features extracted while the patients performed the cognitive test.

In another EEG slowing study,[56] Fraga *et al.* used EEG recordings lasting approximately 5 min from 27 healthy subjects and 49 patients with AD (27 with mild AD and 22 with moderate AD). The amplitude modulation for the 5 EEG rhythms ($\delta, \theta, \alpha, \beta$ and γ) is calculated using Hilbert transformation and the energy is extracted using amplitude modulation between frequency bands. One-way ANOVA showed statistically significant differences in amplitude modulation between the 3 groups. In addition, δ modulation decreased dramatically at β rhythm and appeared at θ rhythm when the disease severity was increased, making the methodology an important tool for correlating EEG activity with disease progression.

3.2.1.2. *Ratio of EEG-rhythm power*

Fonseca *et al.*[40] that described in Sec. 3.1.1 studied α and θ EEG rhythms in patients with AD and healthy subjects aiming to calculate the power of EEG rhythms while participants opened their eyes. Thus they calculated the absolute power of $\delta, \theta, \alpha, \beta$ from EEG recordings while participants were with their eyes-closed and eyes-opened. Then they utilized these metrics to calculate the θ reactivity index (absolute θ power of eyes-opened divided by the absolute θ power of eyes-closed), α reactivity index and the α index to the θ index ($\frac{\alpha}{\theta}$ index). Results from Logistic Regression showed that the $\frac{\alpha}{\theta}$ index from left hemisphere was the highest correlated with the MMSE feature, compared to the other calculated features.

3.2.2. *Correlation of EEG complexity features with MMSE score*

Taking into consideration the experimental studies that mainly explore Information Theory features, we can conclude that complexity features are moderately to highly correlated with MMSE score variation. In addition, there is a decline in their value as the disease progresses. The decrease is particularly noticed at the Central region and at the cortical areas of the Left hemisphere.[25]

3.2.2.1. *Sample entropy*

Tsai *et al.*[74] studied Sample Entropy in 27 patients with AD from the neurological clinic at National Yang Ming University Hospital in order to find the correlation between quantitative EEG and MMSE score. A 30 s epoch of each EEG recording was selected for analysis and Sample Entropy ($m = 2, r = 0.15$) was calculated using EMD. Stepwise regression results showed a moderate correlation ($0.361 - 0.523, p < 0.05$) between MMSE score and Sample Entropy in Fp1, Fp2, F4 and T3 channels. In addition, Spearman's correlation coefficient showed a high correlation (0.975) between MMSE variation

and the variation of Sample Entropy at F7 in 5 patients who received a follow-up examination 6 months later.

In another complexity study,[25] entropy features showed promising results. Tzimourta *et al.* examined the ability of some statistical and spectral features proposed in their previous work[24] to predict MMSE score variation. EEG recordings were extracted from 14 AD patients and 10 healthy controls and segmented into epochs of 10 s. Results of Multiple Regression Analysis indicated high correlation of MMSE with Sample Entropy of θ rhythm, Relative θ power and Permutation Entropy of δ rhythm and the best R^2 was obtained for O2 (0.542) and F4 (0.513) electrodes.

3.2.2.2. *Mutual information*

Coronel *et al.*[71] studied features from Information Theory with purpose to describe alterations in brain complexity of people with AD and their correlation with MMSE score. Specifically, they recorded 168 s of EEG activity on average from 79 probable patients with AD, utilizing the PRODEM database. From the EEG recordings, epochs of 4 s with 2 s overlap were chosen and the Mutual Information,the Shannon entropy, the Tsallis entropy, the MSE and the Spectral entropy were calculated. In the multiple regression models, the Multiple Correlation Coefficient R^2 showed high values for Mutual Information in C3 (0.46), Cz (0.43) and F3 (0.43) channels, as well as in the Central region (0.43) and the left hemisphere (0.42). Also, MSE showed high R^2 values at channel C3 ($R^2 > 0.4$). The regression models with main predictors the Shannon entropy and the Tsallis entropy showed $R^2 > 0.3$. Finally, results showed a decrease in complexity features as MMSE decreased and consequently as the disease's severity increased.

3.2.3. *Correlation of EEG synchronization and functional connectivity features with the MMSE score*

Experimental studies that examine the relationship between quantitative EEG features with AD progression using as reference the MMSE score, indicate that connectivity and synchronization features are positively correlated with MMSE score variation. In particular, connectivity features exported with LORETA software as well as synchronization measures, such as Granger causality, coherence and phase shift which are calculated mainly from the δ rhythm, are reduced as MMSE score decreases mainly at Anterior, Central, Left temporal and Posterior regions.

3.2.3.1. *LORETA features*

LORETA has been used to calculate synchronization and functional connectivity features of cortical signals. Recently, Tait *et al.*[47] recorded EEG signals from 47 participants (21 patients with AD and 26 healthy subjects) while subjects were in a relaxed, sitting position with their eyes open. Fourier transform was applied in 20 s epochs in order to calculate the relative power of the 5 EEG rhythms, the peak frequency from each frequency band and the phase locking factor, calculated between electrode pairs from 40 ROIs. Regarding each rhythm's functional network structure, graph theory measures were calculated: the degree of node, the mean degree of the network, the small-worldness of a network and the closeness centrality of a node. Results from the Mann-Whitney test showed that the changes found in the power spectrum between brain regions were not indicative of the level of cognitive decline in patients with AD. However, the small-worldness of the networks was positively correlated with MMSE. In addition, the small-worldness of networks and the closeness centrality of each node appeared to decrease in the temporal lobe of patients, while the mean degree of the network increased in patients with AD. These findings confirm the synaptic connectivity loss in patients with AD, particularly located in temporal lobe.

Hata *et al.*[102] used EEG data from 28 patients with AD and 30 healthy subjects in order to correlate EEG functional connectivity features with MMSE score variation. The CSD and Lagged Phase Synchronization (LPS) extracted with eLORETA from EEG recordings was segmented into 2 s epochs. Results from the statistical analysis, showed reduced LPS at δ and θ rhythm in patients with AD compared to healthy individuals for most of the ROIs. In addition, δ rhythm connectivity was positively correlated with MMSE, whereas patients with AD did not show statistically significant difference in Current

source density in any of the frequency bands in comparison with healthy controls.

3.2.3.2. *Synchronization features*

Waser *et al.*[79] used 79 patients from the PRODEM database in order to correlate EEG synchronization features with AD severity. During EEG recording, the subjects were in a relaxed, sitting position with their eyes closed and their eyes open while a cognitive test (active phase) was taking place. The recordings were segmented into 4 s epochs with a 2 s overlap, from which coherence, partial coherence, phase shift and dynamic canonical correlation were calculated for δ, θ, α and low frequency β (13–15 Hz). In addition, Granger causality, conditional Granger causality, canonical correlation and cross-mutual information were calculated in time domain. Synchronization features were analyzed among electrode clusters, namely Anterior (FP1, FP2, F3, F4), Left Temporal (F7, T7, P7), Central (FZ, C3, CZ, C4, PZ), Right Temporal (F8, T8, P8) and Posterior (P3, P4, O1, O2). Quadratic Least Squares Regression results confirmed that synchrony is reduced in EEG recordings from AD patients with correlation coefficient $R^2 = 0.353$ for the Anterior and Left Temporal regions when recordings performed while participants had their eyes were closed. In addition, coherence, partial coherence, Granger causality and phase-shift of δ rhythm showed the strongest correlation with MMSE score and were positively correlated with MMSE mainly in the Central-Left Temporal ($R^2 = 0.332$) and Posterior-Left Temporal regions ($R^2 = 0.271$). Also, Waser *et al.* observed that the correlation with MMSE was even higher for the active phase, reaching R^2 values equal to 0.462.

Similarly,[83] the same group of authors studied EEG from the PRODEM database, using 83 AD patients having their eyes closed. In this study, Waser *et al.* calculated fewer features (i.e. coherences, partial coherences, bivariate and conditional Granger causality, dynamic canonic correlations, variance) following the same methodology as Ref. 79. They observed that Granger causality decreases as MMSE score decreases, which is interpreted as increased disease severity. Furthermore, correlation coefficient R^2 reached a maximum value equal to 0.392 for all features.

4. Discussion and Conclusions

4.1. *Summary of literature review findings*

In this systematic review, 39 experimental studies aiming to detect AD from EEG features and 10 experimental studies with purpose to associate MMSE score with quantitative EEG are presented.

Even though different methodological approaches are proposed, the literature review results in a common methodological approach adopted in most of the papers: signal pre-processing, time-frequency/nonlinear analysis, feature extraction and classification/regression as seen in Fig. 4.

In many cases, artifact-free epochs are visually selected from EEG recordings lasting a few minutes or even a few seconds. During the pre-processing stage, bandwidth is limited and high frequencies are removed from the EEG recordings. These high frequencies represent subjects' muscular movements during the recording and they are of no scientific interest, as EEG changes occur in the [0.5–60] Hz band. This procedure is done by applying bandpass filters. At the same time, specific frequencies that cause artifacts on the signal (i.e. 0 Hz and 50 Hz) are removed with bandstop filters. Then, in most

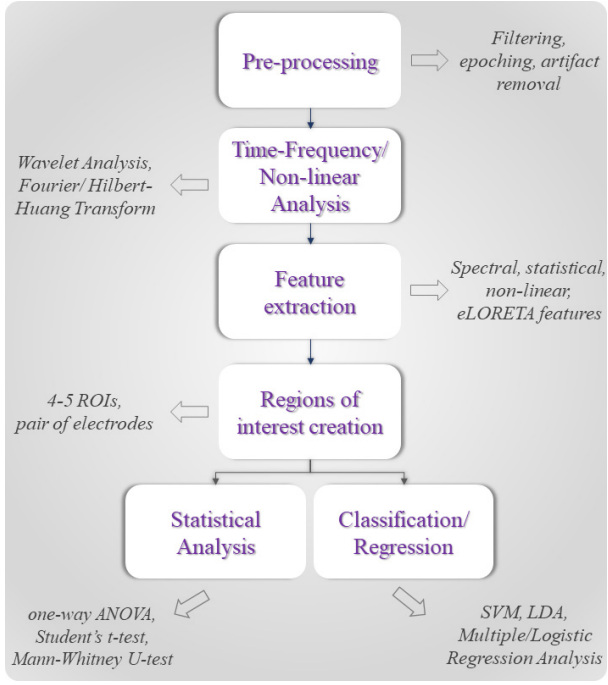

Fig. 4. Methodological stages of experimental studies focused on AD analysis.

methodologies, the recordings are segmented into specific-length epochs either after a short study of epoch length or arbitrarily.

In the signal processing phase, different methodologies are applied on EEG recordings in order to reveal the frequencies of the 5 EEG rhythms. The most commonly Time-Frequency methods used are Fourier transform and Wavelet Analysis. However, in many studies simple filtering is applied. Furthermore, in some studies[49,53,54,84] the frequencies are analyzed in more depth, dividing each rhythm into 2 or even 3 sub-bands. For example, α rhythm that is shown in 8–13 Hz, is divided into 2 frequencies, $\alpha 1$ at 8–10,5 Hz and $\alpha 2$ at 10, 5–13 Hz. Then, EEG features are calculated in order to analyze the complexity and/or slowing and/or synchronization of brain dynamics.

Another stage is the formation of ROIs. AD is a progressive disease that is initially triggered in specific brain structures (i.e. hippocampus); thus, an EEG analysis in regions seems mandatory in order to study how different sites affect brain dynamics.[103] In the experimental studies[24,25,40–42,47–49,51–54,58,61,63,65,70–73,78,79,82,83,85,101,102] the ROIs are created from either electrode pairs or from groups of electrodes. Frequently, recordings are performed on an EEG recording device of 16 or 19 scalp electrodes. ROIs are most often 4 or 5 and include electrodes covering

- the Anterior or Frontal area (FP1, FP2, F3, F4),
- the Posterior or Occipito-Parietal area (P3, P4, O1, O2)
- the Central area (FZ, C3, CZ, C4, PZ),
- the Temporal area of the left hemisphere (F7, T7, P7),
- the Temporal area of the right hemisphere (F8, T8, P8).

At the final stage, some AD detection studies apply statistical analysis tests in order to examine whether there are changes in brain dynamics in patients with AD compared to healthy subjects. These changes in some EEG measures may be an indication to identify AD patients from healthy individuals. Statistical analysis is usually performed with Student's t-test, nonparametric Mann-Whitney test, or ANOVA. The rest of the studies, which may or may not apply statistical analysis tests, utilize machine learning algorithms and especially the SVM classifier.[44–46,50,51,55,72,73,84] According to the algorithm, instances that need to be classified are mapped to a high-dimensional feature space, wherein they are separated by a very clear gap, named hyperplane. The vectors of the margin are called support vectors and the objective of the algorithm is to find an optimal hyperplane that maximizes the distance between the margin and the support vectors, while minimizes the classification error.[104] SVM is a good classifier for a binary classification problem and compared to other algorithms (e.g. Random Forests), SVM is trying to find the distance between the support vectors and the margin instead of the probability of an instance to belong to class. The rest of the studies utilize LDA,[62,89] KNN,[43] Random Forests,[24] ANN[49] and fuzzy classifier.[81]

The statistical techniques and the machine learning algorithms that are used in the literature are depicted in Fig. 5.

The selected data along with the training and testing of the classifier are crucial for the performance of the model. Data obtained from a small number of participants in combination with a chaotic

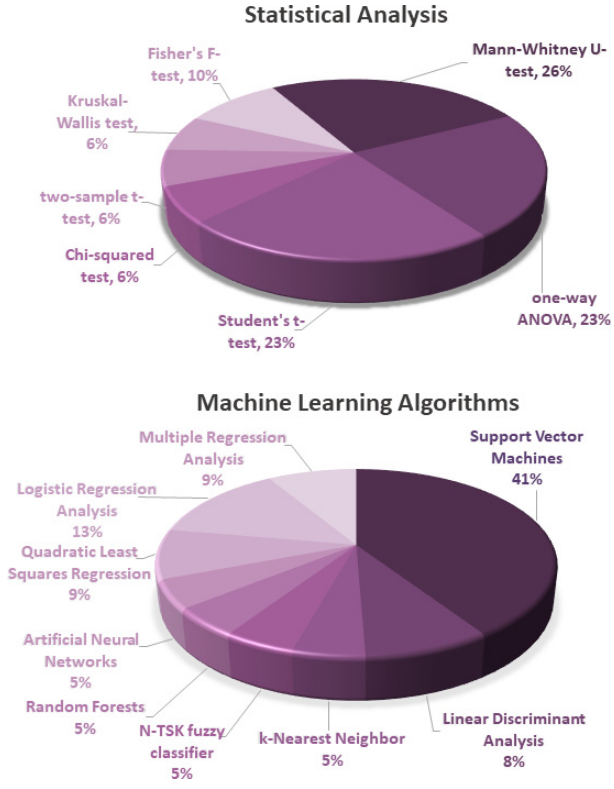

Fig. 5. Methodological stages of experimental studies focused on AD analysis.

feature vector may limit the discrimination ability of the classifier, leading to a high risk of overfitting. In that case, the classifier would be trained very well on a part of the dataset, showing very good performance on the training data but at the same time extremely poor prediction ability on new data, deteriorating the ability to generalize.

Cross-validation is a widely-used learning method successfully addressing the risk of overfitting. However, different validation methods have been applied on EEG-based AD datasets, mainly cross-validation and leave-one-subject-out, with different the training and testing datasets in each methodology; thus, the comparison of the findings between studies is not straightforward.

Results from the systematic literature review show that in the majority of the studies the methodological approach is focused on EEG feature extraction and less on signal processing or on the application of more complex machine learning algorithms.[105] Research interest is mainly focused on discovering the complexity and the synchronization of the brain activity by finding appropriate EEG biomarkers and the most relevant areas in the brain, so to adjust the therapeutic intervention; thus, more complex machine learning techniques have not been used extensively as much in EEG research in AD as in imaging. Deep learning architectures and Convolutional Neural Networks have not yet been applied on a large AD database using EEG data[106]; however, deep learning methodologies have been presented on MRI scans[107–109] and EEG recordings from MCI patients.[80]

The classification problem that is most commonly studied is the discrimination between AD patients and healthy elderly, which are referred as "control" group (CN/AD). Most methods focus on separating AD group from the control group, without examining the stage of the disease (mild, moderate or severe) in which AD patients are. Only few methods test more classification problems, such as

- CN/mild AD,[24,44,46]
- CN/moderate AD,[24,44]
- CN-mild AD/moderate AD,[24]
- mild AD/moderate AD,[24,44,46]
- CN/mild AD/ moderate AD.[24,46]

Concerning the classification problem, MMSE score range does not match in many studies that deal with the discrimination of AD patients from healthy controls. Some studies may refer to AD patients including subjects at mild and moderate stage, while other studies may include only mild or moderate AD patients, without reporting the stage of the disease.[49–51,53,62,66,78,81] This fact causes confusion in the comparison of the results especially when the classification problem deals with stages of AD (e.g. CN/mild AD or CN/moderate AD). Furthermore, in many studies the MMSE score range was not even reported.[37,41,43,45,65,72,85,88,89]

On the other hand, in the final step of regression analysis, the relationship between EEG features and MMSE score and in particular, how EEG characteristics change with MMSE variation is examined. In some studies,[56,74] the behavior of only one feature is analyzed regarding the MMSE score variation. However, in most Regression studies[25,40,48,71,79,83,102] the behavior of many EEG features is analyzed. These features take the role of predictor and are able to form regression models. Regression models are created with either Logistic regression analysis[39,40,86] or Multiple Regression Analysis[25,71] or Quadratic Least Squares Regression[79,83] and are evaluated with the correlation coefficient R^2. The coefficient R^2 ranges from 0 to 1, with higher values indicating greater correlation of EEG characteristics with the variation of MMSE score. Tables 7 and 8 present in brief the studies that have been proposed the last 10 years that focus on detecting AD from quantitative EEG feature (Table 7) and on correlating MMSE score with quantitative EEG features (Table 8).

It can be observed that the small number of participants in many studies as long as the heterogeneity in MMSE score range constrain the comparison between experimental studies. Studies that have recruited a small number of participants[63,70,72] have the risk of overfitting, limiting the classifier's performance and thus, ruining the machine learning model. These studies lack generalizability of the outcome compared to the ones that have recruited a larger sample size.[49,52,54]

Multicenter research studies evaluated on large publicly available databases have not yet been proposed. Therefore, the effectiveness of algorithms cannot be verified and the superiority of one algorithm over another lies solely in the data in which it is trained. Thus, evaluation of the proposed machine-learning methodologies on different EEG datasets is

Table 7. A comparison of performance of experimental studies proposed in the literature for the detection Alzheimer's Disease. The majority of the studies addresses the classification problem AD/CN. Studies noted with *, ** and *** in the Results deal with more than one classification problem. EMD:Empirical Mode Decomposition, Multiscale Entropy: MSE, Linear Discriminant Analysis: LDA, STD: Standard Deviation, IQR: Interquartile Range, FFT: Fast Fourier Transform, CWT: Continuous Wavelet Transform, KNN: k-Nearest Neighbor, SVM: Support Vector Machines, Lempel–Ziv Complexity (LZC), ANOVA:Analysis of Variance.

Authors	AD/CN (MMSE)	EEG Duration (seconds)	Methodology	Results
Hsu *et al.*[62]	15/84	30	EMD, MSE, LDA	F1 score: 0.828
Tzimourta *et al.*[24]	14 (14–22)/10 (30)	780	12 s epochs, moments, STD, IQR, Energy, Relative Band Power, Shannon Entropy, Approximate Entropy, Tsallis Entropy, Permutation Entropy, MSE, Sample Entropy, 10-fold cross-validation, Random Forests	*(a) Accuracy: 91.80% (b) Accuracy: 91.77% (c) Accuracy: 96.76% (d) Accuracy: 91.71% (e) Accuracy: 94.99% (f) Accuracy: 88.79%
Yu *et al.*[81]	30 (12–15)/30 (28–30)	120	8 s epochs, Phase Synchronization Index, 5-Fold Cross Validation, N-TSK	Accuracy: 97.3% Sensitivity: 95.48% Specialty: 96.87%
Mora-Sanchez *et al.*[89]	21/38	20	2.5 sec. epochs, Variance, Skewness, Kurtosis, 10-fold cross-validation, LDA	Accuracy: 71%
Durongbhan *et al.*[43]	20/20	12	4 s epochs (8000), FFT, CWT, FFT and CWT Average Measure, 10-Fold Cross Validation, KNN	Accuracy: 83.41% Sensitivity: 73,80% Specificity: 86,89% Accuracy: 99% (P3-O1)
Al-nuaimi *et al.*[72]	3/8	61–240	Tsallis Entropy, Higuchi Fractal Dimension, LZC, 60% Training, 40% Testing, SVM	Accuracy: 90% (LZC of θ in C3)
Simons *et al.*[63]	11 (13.1 ± 5.9)/11 (30 ± 0)	300	5 s epochs (1280), Fuzzy Entropy, Sample Entropy, Lilliefors Test, t and Kruskal–Wallis	Accuracy: 86.36% Sensitivity: 90.91% Specificity: 81.82% (O2)
Song *et al.*[73]	15 (21.3 ± 5.8)/15 (27.1 ± 1.3)	60	8 s (8192), MSE, SVM, Mann-Whitney Test	Accuracy: 96.24%
Kulkarni and Bairagi[45]	50/50	—	3–5 s epochs (3072–5120), Relative Band Power, LZC, Mean and Variance of each Wavelet Decomposition Level, Spectral Entropy, Spectral Centroid, Spectral Roll-Of, Zero Crossing Rate, 50% training, 50% testing, SVM	Accuracy: 96%
Triggianni *et al.*[49]	120 (19.0 ± 0.3)/ 100 (28.8 ± 0.1)	300	2 s epochs (256), Lagged Linear Connectivity, Spectral Power Density, Source Current Density, $\theta/\alpha 1$ Torsional, Temporal and Inanimate ratios, $\delta/\alpha 1$ ratio of Inanimate Sources, 60% training,20% testing, 20% validation, Artificial Neural Networks	Accuracy: 77% Sensitivity: 79.3% Specificity: 74.3%

Table 7. (*Continued*)

Authors	AD/CN (MMSE)	EEG Duration (seconds)	Methodology	Results
Lizio *et al.*[54]	127 (20.4 ± 4)/123 (28.3 ± 1.3)	300	2 s epochs (512), FFT, $\delta/\alpha 1$ of the Bregmotonic sources, α rate Peak Frequency, ROC Curve	Accuracy: 71.2% Sensitivity: 77.2% Specificity: 65%
Liu *et al.*[50]	14 (11.5–14.2)/14 (27.2–29.7)	40	8 s epochs (8096), Wavelet Analysis, Burg Method, Power Spectral Density, LZC, One-factor ANOVA	Accuracy: 91.4% Sensitivity: 100% Specificity: 82.9%
Vysata *et al.*[52]	110 (15.8 ± 1.7)/110	300–480	Power Law Distribution, α Slope, ROC Curve	Accuracy: 94.00% (temporal area)
Wang *et al.*[51]	14 (11.7–14.9)/14 (28.1–30)	40	8 s epochs (8096), Spectral Power Density, α and θ Spectral Entropy, α/θ Spectral Entropy Rate, Double Spectral Entropy, One-factor ANOVA,5-Fold Cross Validation, SVM	Accuracy: 90.2%
Cassani *et al.*[46]	35 (16.8 ± 8.3)/24 (28.5 ± 1.7)	480	Independent Component Analysis Based on Wavelet Analysis, $\delta, \theta, \alpha, \beta, \gamma$ Relative Power, Width Modulation Rate, Consistency, Phase Synchronization, 10-Fold Cross Validation, SVM	**Accuracy: 78.9% Sensitivity: 90.8% Specificity: 96.3%
Kanda *et al.*[55]	88 (17.7 ± 3.8)/74 (28.4 ± 1.49)	40	Wavelet Analysis, Maximum Value, Minimum Value, Average, Median, Standard Deviation, Variance, Interquartile Range, Coefficient of Variation, Variance to Mean Ratio, Signal to Noise Ratio, 66% Training, 33% Testing, SVM	Accuracy: 92.72%
Schmidt *et al.*[39]	50 (12–25)/ 57 (≥ 26)	40	α/θ Ratio, Regression Analysis	Accuracy: 76.4% Specificity: 84.6% AUC: 0.92

Table 7. (*Continued*)

Authors	AD/CN (MMSE)	EEG Duration (seconds)	Methodology	Results
Tylova *et al.*[88]	26/139	—	Self-Regression Symmetric Model, Interquartile Range, the Median of the Absolute Differences from the Median, First Quartile of the Absolute Mutual Differences, Two-Sample t Test	Accuracy: 63.64% Sensitivity: 84.62% Specificity: 59.71%
Falk *et al.*[44]	21 (17.05 ± 6.15)/ 11 (26.6 ± 2.7)	48	Hilbert–Huang Transform, 5 s epochs, $\delta, \theta, \alpha, \beta, \gamma$ Width Modulation Energy, Leave-one-out cross-validation, SVM	***(α) Accuracy: 90.6% Sensitivity: 90.5% Specificity: 90.9% (β) Accuracy: 74.1% (γ) Accuracy: 71.4% (δ) Accuracy: 53.8%
Trambaiolli *et al.*[84]	22/12	320	2.56-secepochs (512) with 90% overlap, FFT, Spectral Peak, Leave-One-Patient-Out, Logistic Regression	Accuracy: 91.18% Sensitivity: 95.45% Specificity: 83.33%
Trambaiolli *et al.*[86]	16 (< 26)/ 19 (> 26)	320	2.56 s epochs (512) with 90% overlap, FFT, Consistency, Spectral Peak, 68.06% Training, 31.94% Testing, SVM	Accuracy: 79.9%
Fonseca *et al.*[40]	34 (17.18 ± 4.54)/ 30 (26.8 ± 2.09)	46–66	2.56-secepochs (512), FFT, $\delta, \theta, \alpha, \beta, \gamma$ Power, Change Index θ, Change Index α, Change Index α/θ, ROC Curve	Accuracy: 95.3% Sensitivity: 96.6% Specificity: 94.1%
Abasolo *et al.*[70]	11 (13.1 ± 5.9)/11 (30 ± 0)	87.5–212.5	5 s epochs (1280), Approximate Entropy, t Test, ROC Curve	Accuracy: 81.82% Sensitivity: 100% Specificity: 63.64%

Note: (a) CN/AD, (b) CN/mild AD, (c) CN/moderate AD, (d) CN-mild AD/moderate AD, (e) mild AD/moderate AD, (f) CN/mild AD/moderate AD **(a) CN/mild AD/moderate AD, (b) CN/mild AD, (c) mild AD/ moderate AD ***(a) CN/AD, (b) CN/mild AD, (c) CN/moderate, (d) mild AD/moderate AD

Table 8. A comparison of performance of experimental studies proposed in the literature regarding disease severity estimation through MMSE score by quantitative EEG features. MSE: Multiscale Entropy, STD: Standard Deviation, IQR: Interquartile Range, EMD: Empirical Mode Decomposition.

Authors	AD/CN (MMSE)	EEG Duration (seconds)	Methodology	Results
Tzimourta *et al.*[25]	14 (14–22)/10 (30)	780	12 s epochs, moments, STD, IQR, Energy, Relative Band Power, Shannon Entropy, Approximate entropy, Tsallis entropy, Permutation entropy, MSE, Sample Entropy, Multiple Regression Analysis	$R^2 = 0.202 - 0.542$, higher at O2 and F4 R^2=0.365 (posterior)
Coronel *et al.*[71]	79 (15–26)/ 0	≈ 168	4 s epochs with 2 s overlap, Auto Mutual Information (AMI), Shannon Entropy, Tsallis Entropy, MSE, Spectral Entropy	$R^2 = 0.46$ for C3, $R^2 = 0.43$ for Cz, F3 and central region and $R^2 = 0.42$ for left hemisphere and AMI, SpecEn and MSE decreases while MMSE decreases
Waser *et al.*[79]	79 (15–26)/ 0	162	4 s epochs (1024) with 2 s overlap, Coherence, Partial Coherence, Phase Shift, Grager Causality, Conditional Granger Causality, Canonical Correlation, Dynamic Canonical Correlation, Cross-Mutual Information	$R^2 = 0.462$, Granger Causality is reduced as MMSE increases in Frontal and Left Temporal Region, the Inter-Mutual Information of b reduces for the Rear and Right Temporal Region.
Waser *et al.*[83]	83 (15–26)/ 0	180	4 s (1024) epochs with 2 s overlap, Cohesion, Partial Cohesion, Granger Causality, Dynamic Normalized Correlation, Variance	R^2=0.392, Granger Causality decreases as MMSE decreases
Tsai *et al.*[74]	27 (19.3 ± 0.7)/ 0	30	EMD, Sample Entropy	$R^2 = 0.361 - 0.523$ for Fp1, Fp2, F4 and T3.

highly recommended to further demonstrate the generality of the methods.

Another characteristic that should be taken into consideration when comparing between studies is the age of the participants. Participants should differentiate statistically significant in age, since dementia is a disease shown with aging. Thus, comparing with young population does not show any clinical interest in identifying AD from EEG recordings. In this systematic review, only studies applied on age-matched subjects are reported. One exception is the study proposed by Al-nuaimi *et al.*[72] wherein participants having similar and nonsimilar age were recruited. In this case, the reported results are the ones from the age-matched subjects.

Research evidence shows that the last two decades more than 200 unsuccessful clinical trials have been conducted for pharmacological therapeutic strategies.[110] On the other hand, a wide range of nonpharmacological AD treatments may eliminate the disease symptoms. Positive impact on the disease symptoms is reported after motor rehabilitation[111]

and cognitive training through Virtual Reality systems,[112,113] nutritional support, Snoezelen therapy, to name just few.[114] Neurofeedback intervention strategies, previously applied on some ADHD and epilepsy cases indicating great results,[115] show the potential to be applied as an alternative therapeutic approach to AD. Recently, Luijmes *et al.*[116] proposed an EEG-based neurofeedback treatment on 10 AD patients and managed to stabilize cognitive functions and even improve memory skills. Computer-aided Diagnosis in constantly gaining ground[117] and ongoing clinical trial[118] examine the possibility Brain Computer Interface along with neurofeedback intervention programs be able to reverse brain slowing, eliminate AD symptoms and increase memory and attention performance. NonInvansive Brain Stimulation (NIBS) techniques, such as Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have presented prominent effects in alleviating cognitive symptoms and enhancing cognitive performance in dementia patients.[119] Recent studies report improvement of patient's behavior and emotions after applying High frequency repetitive TMS[120,121] or tDCS[122–124] in certain ROIs for both AD and MCI patients. All things considered, it is imperative to find reliable quantitative EEG biomarkers evaluated on large publicly-available AD datasets to assist clinical practice.

4.2. *Comparative study*

A wide variety of comprehensive review papers have been presented in the literature, exploring AD markers and recent advances in the field.[125–131] Table 9 summarizes the main parts of these recent review papers dealing with EEG-related diagnosis of AD.

The authors of some of these papers have followed a PRISMA-based methodology to systematically search and collect EEG-based studies for dementia types discrimination,[125] AD diagnosis, progression and differential diagnosis[126] and AD diagnosis based solely on complexity methods,[127] whereas others[128–131] did not apply a research methodology.

Cassani *et al.* limited their research between January 2010–February 2018, Sun *et al.* expanded the limit to 2000–2019 and Nardone *et al.* applied two different date ranges, specifically 1966–Feb 2018 for PubMed search and 1980–Feb 2018 for EMBASE search. Smailovic *et al.*[128] did not follow a research methodology to systematically search, collect and analyze studies that correlate qEEG with biological AD markers and those that distinguish AD from other dementia types. Same with study,[128] in Ref. 129 a search protocol is not presented. Horvath *et al.*[129] incorporated sleep-based EEG, ERP and mismatch-negativity studies to present a review for AD diagnosis based on EEG and ERP findings. In a recent review of 2020 Jafari *et al.*[130] includes resting-state EEG and brain stimulations studies for both human and nonhuman subjects dealing with AD. Another recent review of 2020,[131] focuses on AD diagnosis and provides an overview of AD markers, including EEG (ERP and working memory-related EEG features), genetic, neuropsychologic, neuroimaging and fluid markers. The reader is encouraged to refer to these review papers to expand their knowledge in AD analysis.

The proposed review paper summarizes exclusively experimental studies that have acquired EEG recordings from patients with AD and analyzed them compared to the ones obtained from healthy controls. MCI is an early stage of cognitive decline not severe enough to be characterized as dementia. MCI patients are at increased risk of developing dementia and may or may not evolve into AD.[132]

According to NIA-AA criteria MCI,[10] is deemed a distinct cognitive stage characterized by cognitive impairment, not always presented as amnestic, disguising MCI into amnestic (aMCI) and non-amnestic (naMCI) MCI.[133] aMCI often progresses to the first stage on AD and aMCI biomarkers indicate a high possibility of people with aMCI to develop AD in the next 5 years.[134] Therefore, pharmaceutical interventions is currently one of the most important and prominent research fields for treatment of MCI due to AD.[134] Many studies have been conducted on MCI patients utilizing either MRI data[135,136] or EEG recordings[137–139] or even MEG recordings[140,141] in order to investigate MCI and to predict the onset of AD. EEG-based methodologies extract either entropy features[68,69,142] or spectral features,[80,97,100,106,128,143–145] or eLORETA features[146,147] in order to find differences among healthy controls, AD patients and MCI patients. On the other hand, naMCI affects parts of the brain that are associated to attention, language, executive functions, visuospatial skills, rather than memory and naMCI patients are often more probable to

Table 9. A comparison of recent review papers exploring AD markers and recent advances in the field. These review papers are also able to deal with EEG-related diagnosis of AD.

Authors	Year	Search methodology	Years of coverage	Inclusion criteria
Horvath *et al.*[129]	2018	Not reported	Not reported	sleep-based EEG, ERP, Mismatch-negativity studies, MCI studies
Nardone *et al.*[125]	2018	PRISMA	PubMed (1966–Feb 2018), EMBASE (1980–Feb 2018)	Frontotemporal dementia, Frontotemporal lobar degeneration, AD, Dementia with Lewy bodies, Lewy body dementia, Parkinson's disease dementia, Electroencephalography, Spectral analysis and Connectivity
Cassani *et al.*[126]	2018	PRISMA	Jan 2010–Feb 2018	(1) EEG* (2) Electroencephalogr* (3) Alzheimer* (4) Diagnos*
Smailovic and Jelic[128]	2019	Not reported	Not reported	EEG-based and biological AD markers studies, MCI studies
Rossini *et al.*[131]	2020	Not reported	Not reported	EEG, genetic, neuroimaging, neuropsychological, Cerebrospinal fluid (CSF) based studies
Sun *et al.*[127]	2020	PRISMA	2000–2019	Complexity analysis OR Nonlinear dynamical analysis OR Lempel–Ziv complexity OR fractal dimension OR Hurst exponent OR entropy OR correlation dimension) AND (AD OR Mild Cognitive Impairment OR Subjective Cognitive Impairment
Jafari *et al.*[130]	2020	Not reported	Not reported	EEG and MCI studies
This study	2020	PRISMA	Jan 2010–Mar 2020	EEG, Alzheimer's, NOT MCI, AND NOT mouse, AND NOT mice

develop other dementia types such as Lewy Body Dementia.[133,148,149]

Since MCI is a vague and sometimes but not always a pre-dementia stage of AD, research studies dealing with MCI patients aiming to predict AD must state the subtype of MCI patients they incorporate. This aspect is usually not clarified in the experimental studies and unfortunately, only a few studies report the MCI type when dealing with AD diagnosis[150–152]

To maintain the focus only to AD, research studies incorporating patients with MCI were not included in this review. This narrow focus solely on AD studies is a significant advantage of the proposed review paper that it has not been addressed previously to none of the above reviews. Including studies in the research protocol that deal with naMCI patients is a significant drawback of the methodology, that can result to misleading research findings. Our review has followed PRISMA methodology to systematically search, review and collect only experimental EEG studies. Furthermore, in the proposed review only resting-state EEG studies are incorporated, as well as in Refs. 130 and 126. Also, in contrast with previously published review papers[127,128,130,131] our systematic review focuses

on machine learning algorithms and discuss late advances.

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