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A systematic review and methodological analysis of EEG-based biomarkers of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders in the world. Although there is no known cure for it at the present, preventive drug trials and therapeutic control have been recently developed. Hence, the development of clinical algorithms for early detection or biomarker identification has received a great deal of interest. Electroencephalogram (EEG) signal as a noninvasive and cost-effective clinical tool with a high temporal resolution has drawn considerable attention to the development of automatic AD detection, monitoring, or prediction algorithms. However, EEG recording protocols, demographic and clinical features of subjects, non-stationary nature, and individual differences in EEG data affect the generalization of state-of-the-art methods.

This paper has provided an overview of EEG-based studies that tried to develop electrophysiological biomarkers or propose an automatic system associated with AD detection or classification. It promises to exhaustively investigate the complete process of AD diagnosis from row EEG signals recording to decision making that contains different data collection protocols, pre-processing, feature extraction, post-processing, and decision-making strategies. The advantages, drawbacks, and contributions of each step to the field have been discussed. Finally, insights into the future investigations of automatic AD detection systems have been provided.

1. Introduction

Alzheimer's disease (AD), as a widespread type of neurological chronic condition, especially in elderlies, is the most common cause of dementia among the eleven different ones [1–5]. It is a neurodegenerative and progressive illness, which means brain nerve cells are damaged or destroyed gradually over a long time [5]. Three stages can be considered for Alzheimer's progression, including preclinical stage, Mild Cognitive Impairment (MCI), and dementia caused by AD [6,7]. In the preclinical stage, pathological symptoms only can be tracked thanks to cutting-edge neuroimaging systems. In spite of the fact that no clinical symptoms are observed in the long-term preclinical stage [8], patients' objective cognitive functions slightly decline in the MCI stage [9]. This reduction may be noticeable for family and close friends but not for other strangers [10]. MCI is divided into amnestic mild cognitive impairment (aMCI) and non-amnestic mild cognitive impairment (naMCI) according to memory impairment [11]. A significant reduction of cognitive function is noticeable in the Alzheimer's stage [4]. In addition to memory impairment, some fundamental functions, such as speaking, swallowing, and walking, are impaired in this stage [10,12]. The degrees of dementia due to AD can advance from mild to moderate and moderate to severe when patients become bed-bound and require around-the-clock care [13,14]. From the pathological point of view, β-amyloid plaques, abnormal complex masses of proteins that float in Cerebral Blood Flow (CBF), block the synaptic connections among neurons [15,16], and Tau tangles, intracellular protein, interfere with intracellular molecules which are responsible for nourishing neurons [17–19]. Gradual accumulation of these two toxic substances causes the loss of neurons and AD [6,7]. There are some prominent risk factors that trigger that of substances contain aging, unhealthy cardiovascular system, low educational level, and genetic and family history. A jump from 5.6 million patients in 2019 to 13.8 million in 2060 has been estimated as the result of increasing that of factors [10,20]. It is equivalent to a fourfold rise from $355 billion in 2023 to $1.1 trillion for caregiving, medicine, and other clinical services in 2060 [10]. Although some drugs such as rivastigmine, aducanumab, and galantamine could be able to

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slow the progression of the disease, no cure has been found for it yet [21,22]. It makes automated AD diagnosis tools and biomarkers prominent in each stage [16]. There are different tools for AD detection, monitoring, or prediction, such as different neuroimaging techniques, CBF test or blood biomarkers, cognitive questionnaires, and EEG signal analysis [23–27]. To date, several functional and structural neuroimaging systems, such as functional near-infrared spectroscopy (fNIRS), functional magnetic resonance imaging (FMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) and computed tomography (CT), are adopted to find brain biomarkers of AD [28–33]. In addition, there are some pathological tests such as blood based or CBF tests try to measure the level of β-amyloid plaques, especially in the pre-clinical AD diagnosis [5,34]. Moreover, paper-and-pencil cognitive tests for AD diagnosing. Minimal-Mental state examination (MMSE) and Montréal Cognitive Assessment (MoCA) are two common paper-and-pencil tests for cognitive functions measurement [35].

Although these techniques are clinically accepted, they may have several limitations such as expensive procedure, low temporal resolution, difficulty to access, radiation exposure, or limited to the cortical region. In addition, they can be invasive, expensive, and not available everywhere [39–42]. Consequently, some of these neuroimaging tools are rarely used in clinical applications. Furthermore, not all individuals whose biomarkers indicate the pre-clinical stage will develop MCI or dementia [43]. The questionnaires also may have some limitations. Firstly, they may be affected by biases, intentional conduct, or experience of the neurologists and secondly, they may not be perfectly adequate for the early stages. Consequently, in the recent decade, there has been an increasing interest in conducting AD detection, monitoring, or prediction through EEG signal processing methods that promise to overcome the limitations of AD diagnosis tools [44–48]. EEG is a cost-effective, non-invasive, easy to access, and compact electrophysiological computational tool, which represents the electrical activities of neurons with a high temporal resolution [49–51]. This signal solely or with another functional or structural brain signal\image has been utilized in many studies for AD assessments in unimodal or multimodal strategies to benefit from more neural information [27,52–57]. These considerations motivate this study, where give an overview of these EEG-based methods to detect, monitor, and predict AD and interpret the results with regard to the essential steps of signal processing in the form of a systematic review paper.

The main contributions of this systematic review can be summarized as follows:

- Describing the process of AD classification from a row database to the decision-making in detail and step by step.
- Categorizing the aim of AD-related studies into detection, monitoring, and prediction.
- Introducing various EEG databases for AD assessments and outlines different types of recording protocols, and EEG acquisition systems.
- Comparing various demographic information of participants and technical aspects of EEG databases, such as sampling rate, number of electrodes, and recording duration.
- Discussing the vulnerabilities of the databases and suggesting the conditions of a suitable and comprehensive database.
- Describing the target group for AD-related articles
- Outlining the different types of preprocessing and post-processing techniques in detail.
- Detecting the challenges and gaps in an automatic AD assessments system.

This review paper is organized as follows: Section 2 represents research methodology explaining the process of data gathering for this paper. Thematic review in Section 3 reports database, pre-processing, main processing, post-processing, and decision-making techniques. Section 4 discusses the limitation and challenges of the existing studies. Finally, the paper is concluded in Section 5.

2. Research methodology

The combination of EEG signal processing methods and different techniques of artificial intelligence (AI) have been proposed to automatic AD detection, monitoring, and prediction. They are largely studied according to their impact on improving the quality of the patient's life and the positive impact on the financial system [10]. The proposed review has provided insights on the EEG analysis for computer-aided AD dementia detection/prediction/monitoring with a focus on electrophysiological aspects of the patient's responses, giving space to the discussion about EEG signal recording methodologies and data analysis techniques. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was applied for the identification of studies [62]. In this work, the literature review is based on the search of articles using digital libraries (Scopus, and IEEE Xplore) and the following keywords: "EEG AND Alzheimer AND detection OR classification OR diagnosis OR prediction AND NOT mice AND NOT mouse." Non-human studies and comparing articles have been excluded. The time span has also been limited to the last five years from 2018 up to 2022. By searching the digital libraries, 1390 records have been found based on the title and abstract of the articles. After duplicating the removing procedure, 578 records remained and were screened. Since 506 records was not within the scope of this review, they have been excluded. Finally, 72 original full-text articles have been assessed as shown in Fig. 1.

3. Thematic review

As mentioned, EEG signals can be used for the detection, monitoring, or prediction of AD. In the past decade, most studies have been focused on AD detection, in which EEG-based biomarkers have been used for discriminating between healthy controls (HC) and patients with AD or different kinds of AD-related disorders [55]. The monitoring algorithms have been developed by investigating biomarkers correlated with AD severities to measure dementia progression. They have been designed to describe the change of EEG features during AD progression. The AD prediction is, furthermore, a new step toward the development of AD biomarkers by means of EEG signal processing. It explores the possibility of using EEG features to predict the progression of AD from preclinical stage to dementia due to AD, or to discriminate MCI patients whose disease will be converted to AD from stable MCI in a follow-up study [63]. In this study, the eligible studies whose goals were AD detection, monitoring, or prediction through EEG signal processing have been reviewed. For practical purposes, these studies can be considered in two forms of unimodal and multimodal. In the unimodal studies, EEG signals have been acquired solely [64–68]. However, the EEG signals and other neuroimaging data are simultaneously fed into signal analysis approaches in the multimodal studies [27,52–54,69–73]. In the following, the structure of these studies has been reviewed. Included studies have been characterized by the acquired EEG database and four following steps including pre-processing, main processing, post-processing, and decision-making. The main structure of these studies is depicted in Fig. 2 and described in detail in its corresponding subsections below.

3.1. Database

Many datasets for EEG signals have been acquired in the last five years in the field of AD assessment. In this regard, some settings and requirements, such as participant number and demographic features, recording protocol, and acquisition system, have been defined to design experimental protocol in literature. Table 1 reports detail of existing datasets highlighting the aim of study, target group, recording protocol, demographic information of participants, recording system, and the recording duration. It should be noted that the target column in Table 1, are compared to the HC group if just a single target is written. Moreover,

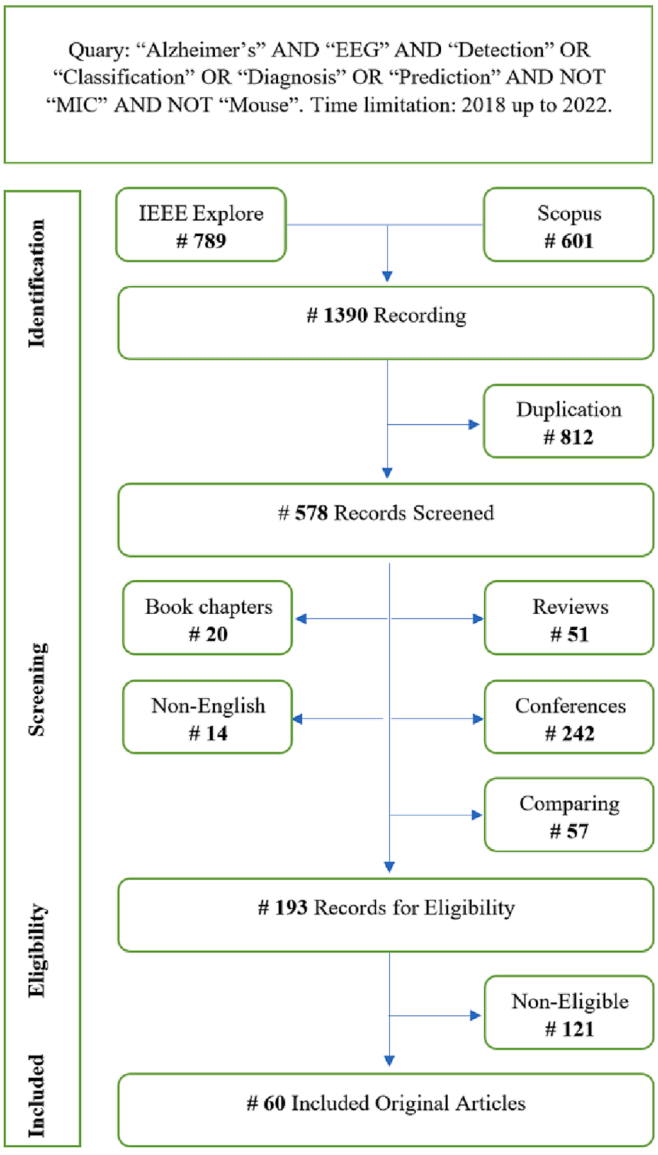

Fig. 1. PRISMA diagram for selecting original articles, including four stages: identification, screening, Eligibility, and inclusion. This process led from 1390 initial studies to 72 final studies.

10–20 montage system is considered if the montage system is not reported. Regarding participants, there are several factors affecting obtained results and complicating the comparison of EEG dataset for AD assessment, such as the number, age, gender, and education of the subjects as well as the target group [15,70]. All four mentioned factors should be balanced in the database to obtain an unbiased result [70]. As can be seen in Table 1, the number of subjects varies across different studies, from 11 to 336. Only 13 out of 72 studies consist of more than 100 participants, therefore most of these studies have a relatively small number of participants which could limit their generalizations. Comparison of the average or the range of the participants' age has demonstrated that the subjects' age for all the studies are more than 65 years and fourteen studies are not statistically age-matched. Gender and educational match are also other prominent factors that are not statistically match between target groups in 7 and 2 studies respectively. Statistical information for comparing the participants' gender and educational level is not reported in 9 and 27 studies, respectively. In addition, according to Table 1, most studies have aimed at detection, while fewer studies have evaluated monitoring or prediction performances.

The recording protocol is another important rule of EEG database acquisition. It follows a standard procedure for getting the electrophysiological information from participants. Each protocol specifically activates some neurological properties whose response effects in EEG signals. It can be performed in a resting state, task-based, or stimulated recording forms. A resting state with eyes-closed (EC) or eyes-open (EO) is the most common types of EEG recording protocol, known as resting EEG (rs-EEG). In this kind of recording, there is no task to do and individuals should sit relax, and do not think about anything. A silent room with minimum lighting system should be provided to reduce environmental interference [74]. The task-based protocol can be classified into memory, mental and physical tasks that participants have to do them in a certain time or scenario. The stimulated recording protocols are also based on a repetitive vocal, visual, olfactory, or physical stimulation during the EEG recording [55,75]. According to Table 1, most of the studies, containing 37 articles, just adopt rs-EEG and 4 of them applied rs-EEG with another protocol, and the rest of them adopted a type of memory task, physical task, evoked protocol, or a combination of them [76].

Previous studies used various types of EEG acquisition systems according to their requirements, category, and targets. From the EEG montage point of view, there is a tradeoff between the optimized number of channels and the performance of the designed system. According to Table 1, seven articles introduced a computationally efficient detection procedure that adopted less than 16 channels of EEG [55,63,64,68,77–79]; while, eleven studies used a dense montage system to increase the algorithm's performance with the aid of 30 channels or more [48,69,72,75,80–86]. In five studies, non-EEG montage channels, such as ECG were simultaneously recorded for artifact reduction [71,74,87,88]. The sampling rate is also another prominent factor in recording systems because it affects both frequency resolution and computational cost. Furthermore, stimulation-based recordings require a high sampling rate due to the immediate response of the evoked neurons [55]. According to Table1, sampling frequency varies in different studies, from 128 Hz to 64768 Hz.

3.2. *Pre-processing*

Pre-processing is the first step of EEG signal analysis and plays an important role in computer-aided AD assessment. EEG signals are usually interfered by eye blink, body/electrode movements, environmental noises, heartbeat, power supply, or baseline wanders. Further, noise-free signals may require some initial processing or data preparation before applying the main processing step. Since some parameters such as contaminated signals, insufficient signal length, or variation in signal statistics may affect the accurate assessment of EEG signals, the preprocessing step is useful in diagnostics. Filtering and EEG rhythm calculation, artifact reduction algorithms, expert supervision, data reduction, baseline correction, re-referencing, interpolation, region of interest (ROI) definition, source localization, data augmentation, normalization, and input generating for Deep Neural Network (DNN) are in the realm of pre-processing techniques and have been investigated for AD assessments. Filtering techniques are widely applied and have multiple applications for noise removal and EEG rhythms calculation [73,78] which are summarized in Table 2. These techniques for noise removal can be applied in the acquisition system before digitalization. It can be seen from the Table that almost all the studies have employed band pass filter or discrete wavelet transform (DWT) to remove some artifacts that lie in a limited frequency band or specific artifacts [101,102,107]. Power supply and its harmonics and movements of electrodes and wiring are among the main sources of noise which can be removed from EEG through different frequency filters [70]. Moreover, filtering techniques, or DWT, that act as hierarchical time–frequency filters [101,102,107], are applied for desired frequency band calculation. In this regard, almost all studies have calculated EEG rhythms from one rhythm [97] up to eight EEG rhythms by dividing alpha and beta

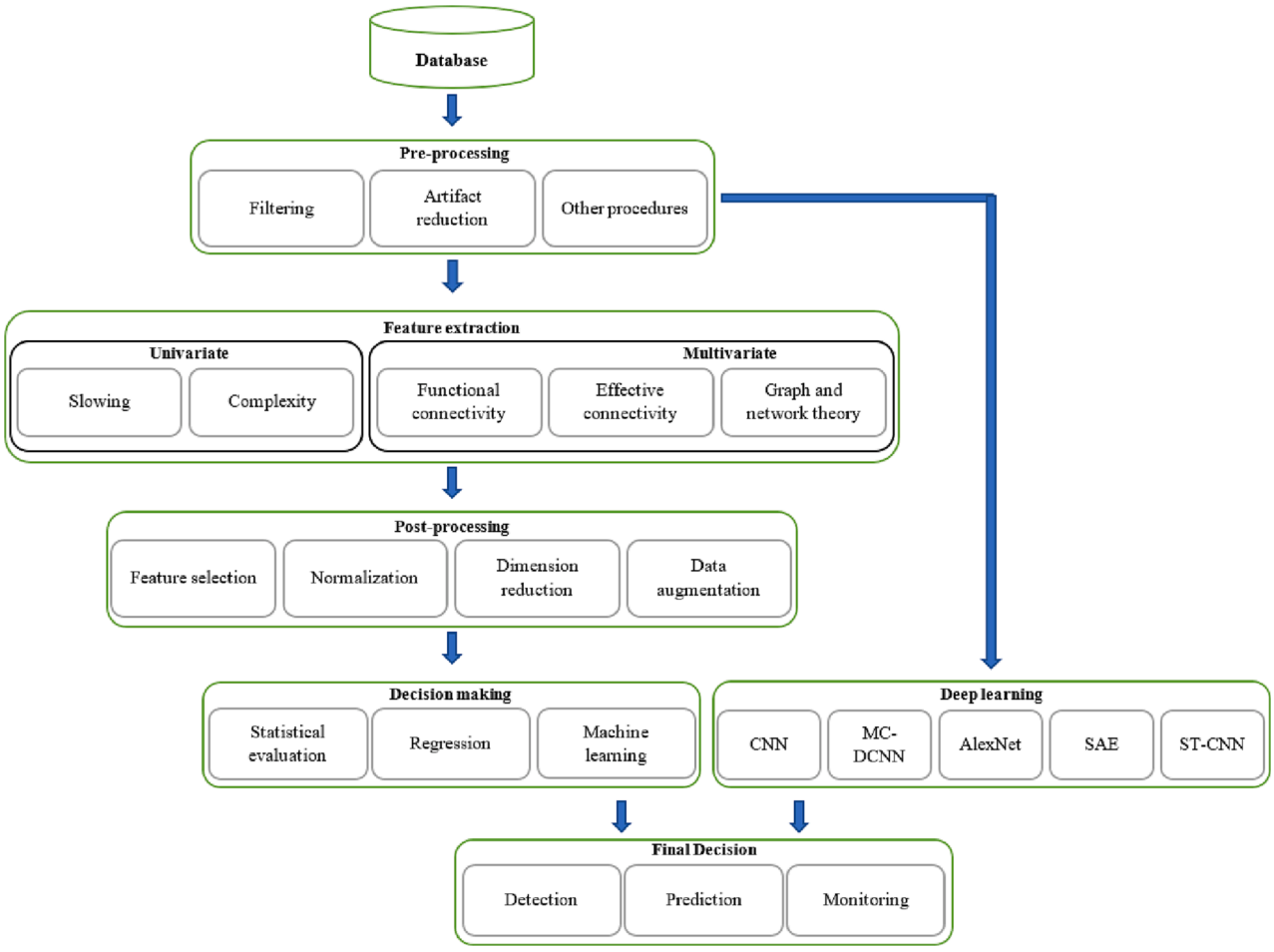

Fig. 2. The structure of AD detection, monitoring, or prediction researches based on EEG signal processing.

into some sub-bands [103]. They illustrate the prominence of EEG rhythms in this area. In this regard, $\frac{\delta}{\alpha}$ power has been known as a classic index widely used for Alzheimer's detection [64,74].

At the data preparation level, artifact reduction, expert supervision, data reduction, baseline correction, re-referencing, interpolation, ROI definition, cortical source localization, data augmentation, normalization, and input generation for deep neural networks can be used to align signals as summarized in Table 3. It can be seen that up to now, multiple artifact reduction techniques have been employed depending on the availability of the source of artifacts. In this regard, a common type of artifact has emerged through electrical activities of cardiovascular and musculoskeletal systems interfering directly in EEG signals. Furthermore, eye blinking and eye movement, have been determined as the other destructive sources of artifacts that can be removed by independent component analysis (ICA) [113]. ICA can be enhanced by DWT and is known as wICA [93,105,114]. ADJUST is also another artifact removal algorithm that is based on ICA [75]. The cut-off thresholding techniques have been also employed to remove electrode or body movement noises on the EEG amplitude [46,55]. Edges in a noisy time series can be smoothed away from the EEG signal through the total variation denoising (TVD) technique [99,115]. The spatial resolution in the high-density electroencephalogram (HD-EEG) can be improved by surface Laplacian declining the effects of volume conduction [80]. Furthermore, several toolbox/ plugin codes have been applied for artifact reduction in some studies, in which authors refused to name the applied algorithms [54,75,82,88,90,97,98,100,108].

In the case of intensive destruction or reformation, signal contents cannot be reconstructed. In this condition, destroyed epochs have been rejected manually by an expert supervision [90,104]. It should be noted that adopting artifact reduction algorithms is not always mandatory. In the EC resting-state condition, interfering is at the minimum level and its effect is lessened [89]. Data reduction in the pre-processing stage is equivalent to down sampling; researchers may use it at the pre-processing stage to optimize the computational cost by down-sampling [93,95]. In regard to evoked potential-based analysis, the onset-lock segment is extracted from stimulated-based protocols [55]. It should be short enough to just project the evoked potential response (ERP) and starts several milliseconds before the onset to correct the baseline of the response [55,85]. Therefore, epoch length is determined around one second. At the onset of the stimulation, the baseline of the ERP changes and it can be corrected by subtracting the ERP from the last steady-state [55]. Re-referencing is also another common preparation procedure. The linked-ear or mastoid is mainly considered as reference electrodes [82,85]. A central electrode like Cz can be considered as another reference to reduce the common noise [64]. In some cases, average of the channels is introduced as a virtual common reference; consequently, EEG signals, are measured independently from the reference electrode [92,103,108]. On the other hand, the montage can be converted from monopolar to bipolar and common noise has been reduced by subtracting pair of channels [53,89]. The next adopted procedure is an interpolation. It can be used when some limited number of channels lost recording for a short period of time. ROIs are defined as a certain group of channels or anatomical areas in cortical source localization. ROIs are calculated via voxels averaging per each area or averaging intra-regional channels [71]. Defining ROIs optimizes the computational process by reducing the number of signals.

In this review paper, cortical source localization is categorized as another pre-processing stage. It is a linear inverse problem that

Table 1
Summary of EEG database used in AD assessment.

Category	Target	Recording protocol	Recording time per subject	EEG recording system			Participants					Reference
				Channel number	Sampling rate	Reference	Total	AD (Age mean / Range)	HC [d] (Age mean / Range)	Sex match	Education match	
			5 mins	16	1024 Hz	A1/A2	28	14 (74 to 78)	14 (70 to 76)	No	-	[103]
Detection	AD	EC [a]	4 mins	19	128 Hz	Average	112	50 (>65)	62 (>65)	Yes	–	[99]
			21 mins	19	500 Hz	A1/A2	18	10 (70.50)	8 (68.50)	Yes	–	[100]
			–	12	–	–	27	15 (67.73)	12 (Age match)	Yes	–	[69]
			20 mins	8	1 KHz	Cz	60	30 (68.83)	30 (64.43)	Yes	–	[75]
			30 mins	16	1024 Hz	A1/A2	60	30 (74 to 78)	30 (70 to 76)	No	–	[101]
			10 mins	16	1024 Hz	A1/A2	40	20 (74 to 78)	20 (70 to 76)	Yes	–	[54]
			64 sec [c]	4 + EOG	64768 Hz	–	75	40 (50 to 80)	35 (65 to 85)	Yes	Yes	[67]
			5 mins	16	1024 Hz	A1/A2	48	24 (78)	24 (75)	No	–	[102]
			10 mins / 20 mins	1	512 Hz	–	23	1 (73)	22 (23–28)	No	–	[73]
			30 mins	19 + EOG + ECG + EMG	500 Hz	–	43	32 (79.3)	11 (73.6)	–	–	[81]
			5–10 mins	16 + EOG	200 Hz	A1/A2	34	16 (57.5)	18 (59.3)	No	–	[53]
			10 mins	16	–	–	40	20 (74 to 78)	20 (70 to 76)	Yes	–	[104]
			5 mins	16	125 Hz	Cz	46	23 (73)	23 (59)	Yes	–	[105]
		EC + EO [b]	4 mins	19	256 Hz	A1/A2	52	20 (77.6)	32 (69.4)	No	–	[106]
			10 mins	19	1024 Hz	–	48	43 (62–88)	5 (-)	Yes	–	[107]
			5 mins	19 + EOG + ECG	1024 Hz	linked earlobes	134	89 (72.5)	45 (70.55)	Yes	Yes	[78]
		Auditory stimulation	–	3	640 Hz	Mastoid	46	25 (-)	21 (-)	–	–	[83]
		EC + Auditory stimulation	5 min (EC) + 8 mins (Auditory stimulation)	2	250 Hz	right earlobe	122	35 (78.1)	87 (68.2)	No	No	[84]
		Memory task	128	–	250 Hz	–	35	17 (67.6)	18 (69.2)	Yes	–	[80]
	Mild AD	EO	3 mins	28 + 3 EOG	512 Hz	–	38	19 (59)	19 (58)	Yes	Yes	[76]
			20 sec	64	1 KHz	–	47	21 (79)	26 (76)	Yes	–	[56]
		EC	5 mins	128	250 Hz	–	35	18 (75.1)	17 (71.4)	Yes	Yes	[40]
		Odur stimulation	20 mins	3 + EOG	2 KHz	A1	24	11 (76.6)	13 (68.2)	Yes	Yes	[85]

(*continued on next page*)

Table 1 (*continued*)

Category	Target	Recording protocol	Recording time per subject	EEG recording system			Participants					Reference
				Channel number	Sampling rate	Reference	Total	AD (Age mean / Range)	HC [d] (Age mean / Range)	Sex match	Education match	
			5 mins	16	1024 Hz	A1/A2	28	14 (74 to 78)	14 (70 to 76)	No	-	[103]
	Mild AD / Moderate AD / HC [d]	EC	516 mins (For all subjects)	20	200 Hz	–	86	**Mild AD** (-)	**Moderate AD** 35 (-)	–	–	[108]
	MCI	EC	5 mins	16	1024 Hz	–	**Total** 49	**MCI** 28 (65.2)	**HC** 21 (67.1)	Yes	Yes	[109]
			30 mins	19	256 Hz	–	27	11 (66.4)	16 (65.3)	–	Yes	[110]
			–	19	128 Hz	–	24	12 (-)	12 (-)	–	–	[111]
		Vocal stimulation	200 times of stimulation	1 (Fpz)	20 KHz	A1/A2	23	8 (74.6)	15 (67.5)	Yes	Yes	[63]
		EO	180 sec	30 + 2 EOGs	500 Hz	A1/A2	51	27 (69.93)	24 (70.96)	Yes	Yes	[90]
		TMS	100 times of stimulation	62	5 KHz	Fcz	43	21 (61.86)	22 (60.77)	Yes	–	[91]
		EC + EO + Mental Arithmetic Eyes closed (MAEC) + Mental Arithmetic Eyes open (MAEO)	5 mins	21	400 Hz	A1/A2	33	13 (67.78)	20 (60.18)	Yes	Yes	[112]
		Eye movement	7 mins	Fp1	500 Hz	A1	336	152 (71.6)	184 (71.7)	Yes	Yes	[71]
		The Visual Short-Term Memory Task (VSTM)	NR	128	512 Hz	–	27	13 (73.08)	14 (67.21)	–	Yes	[92]
		Mental task (N-back)	10 mins	30	500 Hz	A1/A2	41	19 (80.17)	22 (78.98)	Yes	Yes	[93]
	AD / MCI	EC + EO	8 mins	64	5 KHz	NR	**Total** 52	**MCI** 35 (-)	**AD** 17 (-)	–	–	[79]
		Auditory stimulation	500 sec	256	250 Hz	Pz	**Total** 63	**MCI** 21 (72)	**AD** 21 (70) **HC** 21 (67)	No	No	[94]
	HC / MCI / AD	EC	7 mins	19 + 1 ECG	200 Hz	–	35	16 (75.44)	8 (70.5) 11 (69.18)	Yes	–	[97]
			10 mins	21	200 Hz	–	141	37 (78.4)	52 (82.3) 52 (79.6)	Yes	–	[113]
		EC + EO	8 mins	19	200 Hz	Pz	41	9 (67.20)	15 (70) 17 (63.03)	–	–	[114]
		Visual stimulation	Task time	30 + 2 EOG	500 Hz	A1/A2	131	46 (74.50)	37 (75.62) 48 (74.04)	Yes	Yes	[95]
		EC + EO + Auditory stimulation	8 mins	19	200 Hz	–	54	14 (61.21)	20 (67.15) 20 (67.45)	–	–	[115]
	B-amyloid	EC	3 mins	19	200/250 Hz	A linked ear	**Total** 243	**β+** 63 (~73)	**β-** 180 (71.5)	Yes	–	[116]
			–	19	–	–	86	51 (72.30)	35 (71.45)	No	Yes	[60]

(*continued on next page*)

Table 1 (*continued*)

Category	Target	Recording protocol	Recording time per subject	EEG recording system			Participants						Reference
				Channel number	Sampling rate	Reference	Total	AD (Age mean / Range)		HC [d] (Age mean / Range)	Sex match	Education match	
			5 mins	16	1024 Hz	A1/A2	28	14 (74 to 78)		14 (70 to 76)	No	-	[103]
	1- AD 2- MCI	EC	15 mins	21	256 Hz	–	**Total** 186	**AD** 59 (70.5)	**MCI** 7 (67)	**HC** 120 (72.2)	Yes	–	[117]
			2 mins	256	250 Hz	–	40	9 (-)	21 (-)	10 (-)	–	–	[88]
		EC + EO	5 mins	20 + ECG	256 Hz	Mastoids	322	26 (73.5)	53 (71.2)	243 (<70)	Yes	Yes	[98]
	1- Mild AD2- HC / Mild AD / Moderate AD	EC + EO + Memory task + Auditory stimulation	10 min (All tasks)	3 + EOG	1 KHz	–	**Total** 40	**Mild AD** 10 (-)	**Moderate AD** 11 (-)	**HC** 19 (-)	–	–	[86]
	1- AD 2- MCI3-MCI / AD	DTMS	90 sec, 2 times	30 + EOG	500 Hz	A1 / A2	**Total** 74	**AD** 23 (71.65)	**MCI** 24 (70.96)	**HC** 27 (69.93)	Yes	Yes	[82]
		EC + EO + Physical task	5 mins for resting state – 10 mins for task	30 + 2 EOG	500 Hz	–	48	17 (76.7)	16 (74.6)	15 (75.7)	Yes	–	[68]
		EC + EO	4 mins	20 + 2 EOG	500 Hz	A1 / A2	189	60 (71.20)	64 (71.31)	65 (70.06)	Yes	Yes	[62]
	1-SCI [e] / MCI2-SCI / AD3-AD / MCI	EC	20 mins	30	256 Hz	–	**Total** 78	**AD** 28 (80.8)	**MCI** 28 (75.46)	**SCI** 22 (68.9)	Yes	–	[96]
	1-AD 2-MCI3-HC / AD + MCI4-MCI / AD	EC	300 sec	19	256 Hz	Right earlobe	**Total** 109	**AD** 49 (78.4)	**MCI** 37 (74.1)	**HC** 23 (65.6)	Yes	–	[72]
	1- AD 2-MCI3-MCI / AD4-HC / MCI / AD	EC	4 mins	19	256 Hz	A1 / A2	135	45 (76.13)	45 (72.55)	45 (72.82)	Yes	–	[52]
	1- Mild AD2- Mild AD + Moderate AD3- Mild AD / Moderate AD4- HC / Mild AD / Moderate AD	EC	8 mins	20	200 Hz	–	Total 54	Mild AD 15 (75)	Moderate AD 19 (74.1)	HC 20(68)	Yes	No	[118]
	1- HC / AD2- HC / Mild AD3- HC / Moderate AD4- HC + Mild AD / Moderate AD5- Mild AD / Moderate AD6- HC / Mild AD / Moderate AD	EC	NR	19	500 Hz	A1 / A2	24	8 (73.5)	6 (62.5)	10 (67)	Yes	Yes	[119]
	1- MCI2- AD3- Severe AD4- HC / Mild AD + Moderate AD5- MCI / Mild AD + Moderate AD6- MCI / Severe AD7- MCI / AD8- HC / MCI / AD	EC	NR	19	256 Hz	–	Total 38	MCI 8 (80)	Mild /Moderate /Severe AD 19 (79)	HC 11 (74)	–	–	[120]
Monitoring	AD / HC	EC	–	21	–	–	**Total** 27	**AD** 15 (67.73)		**HC** 12 (Age match)	Yes	–	[69]
	aMCI (stable) / aMCI (converted)	Memory task	Scenario time (NR)	59 + EOG	–	Mastoids	**Total**	**aMCI** (Stable)		aMCI (Converted)	Yes	Yes	[55]

(*continued on next page*)

Table 1 (*continued*)

Category	Target	Recording protocol	Recording time per subject	EEG recording system			Participants						Reference
				Channel number	Sampling rate	Reference	Total	AD (Age mean / Range)		HC [d] (Age mean / Range)		Sex match	Education match	
			5 mins	16	1024 Hz	A1/A2	28	14 (74 to 78)		14 (70 to 76)		No	-	[103]
							34	18 (68.4)		16 (69.7)				
	1-Participants / MMSE 2- Participants / MoCA	EC	5 mins	57 + ECG + EOG	500 Hz	Mastoids	**Total** 41	**aMCI** 17 (68.6)		**Mild-AD** 24 (72.3)		No	–	[70]
	1- HC / Mold AD 2- HC / Moderate AD 3-Mild AD / Moderate AD	EC	–	19	200 Hz	A1 / A2	Total 76	Moderate AD 22 (73.9)	Mild AD 27 (73.9)	HC 27 (69.8)		Yes	No	[121]
Prediction	aMCI to AD	EC	–	256	250 Hz	Cz	**Total** 11	**aMCI** (Stabel) 7 (-)		**aMCI (Convertible)** 4 (-)		No	–	[87]
		EO	20 sec	64	1 KHz	–	11	7 (-)		4 (-)		No	–	[56]
		Memory task	Scenario time (NR)	59 + EOG	–	Mastoids	34	18 (68.4)		16 (69.7)		Yes	Yes	[55]
			18 mins	64 + 2 EOG	500 Hz	midline electrode	Total 19	Incident MCI 7 (76.9)		HC 14 (76.4)		Yes	Yes	[122]
	Pre-clinical / HC	Memory task (Encoding)	5 mins	64 channels 10-10 Montage	1 KHz	Average	Total 30	Pre-clinical 15 (-)		HC 15 (-)		Yes	Yes	[67]
	1-β-amyloid 2- ND [f]	EC	1 min	256	250 Hz	Vertex	**Total** 304	**ND +** 72 (76.50)	**ND -** 232 (75.92)	**β+** 85 (76.81)	**β-** 219 (75.76)	Yes	Yes	[77]

Abbreviations: [a] EC: eye-closed, [b] EO: eye-opened, [c] Sec: second, [d] HC: healthy control, and [e] SCI: subjective cognitive impairment.

Table 2
Methods of EEG filtering as a preprocessing step of AD assessment.

Category	Software or Hardware	Filter type			Category	Rhythm calculation	
		High pass	Low pass	Band stop		Main rhythms	Sub-bands
Frequency filter	**Analog**	1 Hz [92],	70 Hz [119], 100 Hz [67,92]	55–65 Hz [84]	**Frequency filter**	δ, θ, α, β, γ [68,76,78,80,85–87,90,93,97,99,100,106,112,116,121,124]	Low α, Main α, High α [61,82,86]
		Band pass				δ, θ, α, β [54,69,71,75,84,96,102,103,125]	Low α, High α [60,62,73,78,112,116]
		0.5–60 Hz [100], 0.3–70 Hz [62,123], 0.5–50 Hz [82], 0.5–45 Hz [118], 3–45 Hz [84], 0.1–100 Hz [98], 0.5–100 [90], 0.01–250 [95], 0.8–300 Hz [54,101], 0.1–200 Hz [67]				δ, θ, α [98]	Low β, Main β,High β [60,116]
						θ, α, β [40]	Low β, High β [78,82,97,126]
	Digital	**High pass**	**Low pass**	**Band stop**	**Discrete Wavelet Transform (DWT)**	θ [109]	Low δ, High δ [114,115]
		0 Hz [109], 0.5 Hz [105,119], 1 Hz [70,93], 1.6 Hz [107]	40 Hz [109], 50 Hz [54,101], 57 Hz [93], 60 Hz [119,121], 200 Hz [68,74,124]	30 Hz [107], 48–52 Hz [91], 50 Hz [40,62,75,77,80,107,109,115,117,119,123,126,127], 60 Hz [68,74,90,105,115,124], 100 Hz [77]		δ, θ, α, γ [78,114,115,120]	
						δ, θ, α, β [52,96,102,104,107,110,119]	
		Band pass					
		0.5–48 Hz [100], 0.5–32 Hz [52,123], 0.5–30 Hz [114,115], 0.5–50 Hz [82], 0.5–60 Hz [76,108], 0.53–35 Hz [69], 0.5–40 Hz [85,122], 0.5–45 Hz [61,75,77], 0.1–45.5 Hz [78,116], 1–80 Hz [80,91], 1–70 Hz [126,127], 1–49 Hz [98], 1–40 Hz [88,120], 1–60 Hz [40,84,113], 0.1–70 Hz [17], 0.5–70 Hz [125], 0–30 Hz [63,94], 1–30 Hz [67], 0.5–30 Hz [71,92,102]					

estimates electrical activities on the cortex surface [116]. It maps the estimated sources into a pre-defined anatomical model based on the averaged MRI [117]. Source localization is mostly applied when the anatomical location of the signals is essential. It is noteworthy, dementia due to AD depends on the cortical areas like Broca's area and Gyrus [70]. In addition, it is proven that some cortical areas, like the occipital lobe, have prominent information about the onset of dementia and its progression [46]. Since further studies have also demonstrated that inter-lobe connectivity is affected from dementia [92,99], therefore, applying cortical source localization is a justifiable pre-processing step in the realm of EEG signal processing for Alzheimer's analysis. In this regard, low resolution electromagnetic tomographic analysis (LORETA) is known as an efficient method for estimating the cortical source [52,71]. In the exact LORETA (eLORETA), theoretical expected variance is unity and zero error localization is achieved through weighted equation while the current density is estimated via a linear equation with a penalty term [118]. LORETA family try to develop approaches localizing the active sources with minimum localization error [116,118].

Data augmentation is looking to increase the observations when more samples are required. Overlapping the consecutive segments is a common data augmentation technique in the pre-processing stage [64,88]. Moreover, normalization as another pre-processing step can eliminate interpersonal differences in the EEG amplitude that was applied in two studies [70]. Input generation for a deep neural network (DNN) is another pre-processing step generating a two-dimensional matrix or image as the input of a DNN [119]. For this purpose, EEG signals have to be converted to a trajectory matrix or an image in a certain procedure summarized in Table 3. These techniques mostly convert time-domain EEG signals to frequency [80] or time–frequency information [100].

Defining the length of the processing window is the last procedure in the pre-processing stage. Long-time signals have to be segmented into the fix time epochs for applying in the main processing stage. This time length directly depends on the recording protocol and main processing technique. The determining of the window size is essential. It should be long enough to be informative about the dynamic of the system and fulfill the processing method. Long processing windows, on the other hand, can violate some assumptions such as stationarity and also increase the computational cost. Therefore, finding a fit window size is an art. The length of the processing window is discussed more in section 4.3.

3.3. EEG-based biomarkers

EEG-based biomarkers are computed in the main processing part of investigations. In recent years, many efforts have been made in developing feature extraction algorithms for revealing AD-related EEG changes. Two major strategies can be considered for, univariate and multivariate. In the first strategy, it is assumed that EEG channels are independent of each other and each of EEG time series is processed separately [55,83,90]. Despite independent attitude to EEG channels in univariate strategy, inter-channel interactions are investigated in multivariable one [97]. Each of these two strategies contains several feature extraction methodologies introduced in this section.

3.3.1. Univariate strategy

Previous studies have demonstrated that EEG dynamics become slower and less complex because of the neural destruction due to dementia [6,7]. Consequently, numerous researchers rely on this statement to propose their EEG processing methods that measure the slowing and the complexity of procedures. Table 4 summarizes the univariate EEG-based biomarkers method in terms of slowing and complexity.

3.3.1.1. Slowing. Dynamic of the EEG signal becomes slow in AD

Table 3
Other procedures in pre-processing stages in AD assessment.

Category	Type	Reference
Artifact reduction	ICA	[75,78,83,88,92,97,100,101,110,111]
	wICA	[53,93,105]
	ADJUST	[75,82]
	Linear model	[109]
	Cut off Thresholding	[46,55,70,78,111]
	TVD	[99]
	Surface Laplacian	[80]
	Toolbox / plugin	[54,75,82,88,90,97,98,100,108]
Expert supervision	Manually rejection	[44,46,64,68,77,78,80,81,86,88,90,91,93,101,102,104,110]
Data reduction	Down sampling	[48,71,72,78,89,93,95,103,104]
Baseline correction	Subtraction	[55]
Re-referencing	Averaging	[54,70–72,81,89,92,103,108,110]
Interpolation	spherical splines	[70,105]
ROI definition	Averaging	[71,110]
Cortical source localization	LORETA	[71,84]
	sLORETA [a]	[110]
	eLORETA [b]	[52,81]
Data augmentation	Overlapping	[53,75,88,90]
Normalization	Z-score	[70]
Input generation for deep neural network	Log-covariance	[119]
	1 pixel for each of 21 channels and 4 dark blue tildes on the corners	[100]
	modified frequency periodogram	[72,80]
	TFR [c] Averaging	[79]

Abbreviations: [a] sLORETA: standardized LORETA, [b] eLORETA: exact LORETA, [c] TFR: time–frequency representation.

Table 4
Univariate processing methods for feature extraction in AD assessment.

Category		Features	references
Slowing	**Time/Frequency features**	Relative power spectrum	[48,54,55,64,68,74,77,88,89,101,102,106,111]
		Power spectrum density	[64,70,72,75,87,88,103,105]
		Lacsogram and cepstrum	[70]
		Other Spectral and frequency features	[53,70,74,77,79,88,105]
		Absolute power	[54,63,88,111]
		Amplitude change	[89]
		Zero-crossing	[89]
		Statistical	[45,55,74,79,83,87,90,93,96,101,106,112,119]
		Energy of EEG rhythms	[90,106]
		Linear model	[104]
		Amplitude Modulation Rate-of-Change	[53,55]
		Modulation Frequency “Patches”	[86]
		Autoregressive (AR) Model coefficients	[98]
		General Linear Model (GLM)	[27]
		warped infinite Gaussian mixture model (WiGMM)	[120]
	ERP based features	Latency	[83,102]
		Amplitude change	[68,83,102]
		Mean ERP	[108]
		Statistics of DWT coefficients	[102]
		Evoked activity & Total activity	[85]
		average voltage peak (amplitude), Average response time, Amplitude deviation, Response time deviation, Center to-edge amplitude difference, voltage peak	[77]
		P300	[102]
Complexity	**Entropy**	Tsallis entropy (TsEn)	[89,95,106]
		Permutation entropy	[93,98,101,106,109]
		Shannon entropy	[55,79,96,106]
		Multiscale Entropy Analysis (MSE)	[45,64,106]
		Information entropy	[68]
		Approximate entropy	[79,106]
		Sample entropy	[82,101,106]
		Spectral entropy	[70,94]
		Sure entropy	[96]
		Bispectral entropy	
		Dispersion Entropy Index (DEI)	[44]
	Fractal dimension	Katz’s fractal dimension (KFD)	[82]
		Higuchi Fractal Dimension (HFD)	[89]
		Box counting	[32]
	Other complexities	Lempel-Ziv complexity (LZC)	[48,64,89]
		Omega complexity	[3334]
		Lyapunov exponent	[79]
		Hjorth complexity	[96]
		Lattice complexity	[64]
		Algorithmic complexity	[70]
		Kolmogorov complexity	[94]

patients and scientist introduced and applied different EEG—based biomarkers to quantify this phenomenon. Power spectrum in different forms, bispectrum, Lacsogram and cepstrum, statistical features, energy, linear models, amplitude modulation, zero-crossing, and some basic ERP features, such as latency and amplitude change trying to describe the respond potential, have all been applied in previous studies for slowing quantification [48,54,55,64,68,70,74,77,83,88,89,101,102,106,108,111]. In this regard, researchers have observed that high frequency activities of the brain cells that project in α and β waves have been reduced while low frequency ones like θ and δ have been increased in AD patients [68]. Moreover, $\frac{\delta}{\alpha}$ index is a classic feature that widely applied for AD diagnosis [64,77].

3.3.1.2. Complexity. Less complexity is also experienced in the AD patients' EEG signal associated with loss of local neurons. A variety of methods have also been proposed to measure complexity in the last five years [70,82,101,106]. Adopting entropy-based signal processing methods is very common in the case of complexity measurement and various types of entropies have been applied up to now [64,82,101,106]. Fractality is another way to estimate complexity in the phase space domain [45,82]. It tries to find a similarity in different scales in the phase space. Lyapunov exponent also measures the divergence of the trajectories in the phase space that can project a kind of complexity [79]. Lempel-Ziv complexity and Omega complexity are the other two powerful methods to quantify AD [48,64].

3.3.2. Multivariate strategy

Complex protein components block synaptic connections between neurons due to Alzheimer's disease and directly reduce inter- and intra-brain lobe neural interactions as the result [15,19]. Hence, scientists hypothesize that interactions between EEG channels are affected by this synaptic interference, and they have proposed a variety of EEG biomarkers to represent inter EEG channel interactions [46,54,97]. In multivariate strategy, therefore, a single EEG signal does not make sense by its own. EEG interactions are investigated in pairs or whole [68]. Functional connectivity, effective connectivity, graph and network theory, and deep learning are four multivariable processing approaches that have been investigated in the last five years to introduce suitable EEG-based biomarkers associated with AD [68,91,97,119]. These three processing groups are introduced in the following and summarized in Table 5.

3.3.2.1. Functional connectivity. A specific statistical property between possible pairs of channels is known as functional connectivity [121]. A considerable number of functional connectivity methods have been applied for finding EEG-based biomarkers in the realm of AD [54,68,97]. In this regard, coherence, asymmetry, epoch-based entropy, phase lag index, different forms of mutual information, relative wavelet entropy, phase synchronization, and dynamic functional connectivity, have been applied as method/models for functional connectivity quantification in articles [68,69,77–79,86–89,97].

3.3.2.2. Effective connectivity. A cause-and-effect relational model describing the effect of an EEG channel or a group of EEG channels on a certain EEG channel is known as effective connectivity [97]. It is called causality if the model predicts the condition of a channel in the future by means of the present state of another channel or channels [97]. As a result of the relationship between cause and effect, the flow of information is seen in the effective connectivity. Despite functional connectivity, adopted functions or models are not commutative in effective connectivity. It should be note that causality can be analyzed in the content of in the directional graph or network. In other words, causality is equivalent to an adjacency matrix that represents a weighted bidirectional graph, and features are generated in the graph theory context. Some studies have converted the effective connectivity matrix to a binary bidirectional graph through thresholding on the adjacency matrix's elements [97]. Causality, transient entropy, and Sugihara causality estimation are applied effective connectivity models in the realm of EEG-based Alzheimer's biomarkers as listed in Table 5.

3.3.2.3. Graph and network theory. Graphs contain nodes and edges. EEG channels are considered as the graph nodes and the path that connects the nodes known as the edge [122]. Although most of the articles have generated graphs from the connectivity matrix [88,89], some studies directly have made graphs by means of visibility graph theory [91]. In this type of graph, each time sample of an EEG signal is defined as a node. Consequently, each EEG channel is converted to an independent complex small-world network [91]. In addition, another type of a graph can be defined in a multilayer form that consists of several two-dimensional graphs produced from several consecutive EEG segments [46]. The properties of each node are investigated over consecutive times in a multilayer graph [46]. Node and graph level features used for Alzheimer's disease are listed in Table 5.

Table 5
Multivariate feature extraction processing and deep learning for in AD assessment.

Category	Method / Model	Graph-based features	Reference
Functional connectivity	Coherence	Connection density, Mean clustering coefficient, Mean hub order, Summation	[69,78,79,87–89]
	Asymmetry	–	[77]
	Magnitude square coherence (MSC)	Degree, Clustering Coefficient, Shortest Path Length, Local Efficiency, Betweeness	[86]
	Epoch-based entropy (EpEn)	Degree, Clustering Coefficient, Shortest Path Length, Local Efficiency, Betweeness	[86]
	Phase lag index (PLI)	Degree, Clustering Coefficient, Shortest Path Length, Local Efficiency, Betweeness	[86]
	Weighted phase lag index (WPLI)	Degree, Leaf fraction (Lf), Diameter, Eccentricity (ECC), Betweenness centrality (BC), tree hierarchy (Th)	[54,99]
	Mutual information (MI)	Degree, Clustering Coefficient, Shortest Path Length, Local Efficiency, Betweeness	[86]
	Cross Mutual Information (CMI)		
	Cross Mutual Information distance (dCMI)		
	weighted Symbolic Mutual Information (wSMI)	–	[70]
	Phase synchronization	Clustering coefficient, Average node degree, Global efficiency, effective density	[68,97]
	Instantaneous functional connectivity (dynamic functional connectivity (dFC))	data-driven window (not graph feature)	[68]
Effective connectivity	Causality (directed transfer function (DTF) network)	Clustering coefficient, Average node degree, Global efficiency, Effective density	[97]
Graph and network theory	Weighted visual graph (WVG)	Clustering coefficient, Average weighted degree, Graph Index Complexity, Network Entropy, Local Efficiency, Average Path Length, Degree Distribution Index	[91]
	Multilayer network	Multiplex clustering coefficient (MCC), Multiplex participation coefficient (MPC)	[46]
	Lagged Linear Connectivity (LLC)	Connection Density Index, Randic Index, Nodal strength, Characteristic path length, Local efficiency, Clustering coefficient	[52,81]

3.4. Post-processing methods

Calculated features may follow some extra processing steps to achieve the optimized and reliable result in the decision-making part. Feature selection, dimension reduction, normalization, and feature rebalancing techniques are the post-processing procedures. They have been applied due to the fact that most of the previous feature calculation methods have generated a large number of features in different ranges. These four approaches can significantly reduce computational operations and improve the efficiency of decision-making algorithms. That of approaches in the realm of EEG-based AD biomarkers are collected and introduced in Table 6.

Feature selection techniques can make the decision-making model more optimized by reducing the size of the feature vector and maintaining the most informative ones meanwhile [123]. The high number of features does not always improve the performance of decision-making model because of the curse of dimensionality and overloading in information [123]. It shows the prominence of feature selection techniques in machine learning problems. Feature selection methods for supervised learning are divided into filter, wrapper, and embedded [124]. The selection procedure is independent of machine learning in filter methods and features take the score depending on their inherent separation potential [124,125]. These methods are mainly based on between-class statistical evaluations such as T-test. Wrapper methods, in contrast to filter ones, try to find the best subset of features that enhance the training performance of a certain machine learning as much as possible [124,125]. Embedded methods add a penalty term to enhance the generalization and make the model more reliable [124–127]. It should be noted that, the feature selection problem is changed to channel selection if only one feature is generated from each EEG channel [69,102]. According to Table 6, filter and wrapper feature selection methods are applied in 21 and 9 studies respectively while it is used in 4 ones for embedded. Furthermore, about 66% of the applied feature selection techniques contain filter methods.

Table 6
Applied post-processing methods in AD assessment.

Category		Method	Reference
Feature selection	Filter	T-Test	[70,101,103]
		Welch's T-test	[70,78]
		ANOVA	[64,79,102,109]
		Kruskal-Wallis	[44,107]
		Anderson-Darling test	[102]
		Statistical non-Parametric Mapping (SnPM)	[84]
		nonparametric cluster-based permutation test	[87]
		correlation feature selection (CFS)	[91]
		maximum relevance minimum redundancy (mRMR)	[53,91]
		Feature Selective Validation (FSV)	[91]
		Fisher	[91]
		Dependence Guided Unsupervised Feature Selection (DGUFS)	[91]
	Wrapper	Genetic algorithms (GA)	[103,107]
		Random selection	[27]
		sequential forward selection (SFS)	[75,96]
		Orthogonal Forward Regression (OFR)	[86]
		Random probes	[86]
		Random forest	[55]
		LASSO logistic regression	[4632]
Dimension reduction		PCA	[45,88,96,102]
		t-Distributed Stochastic Neighbor Embedding (t-SNE)	[83]
		Intraclass correlation coefficients (ICC)	[70]
Normalization		Z-score	[107,110]
		Linear normalization [−1 1]	[83]
		each power modulation spectrogram was normalized by its total power	[64]
Rebalancing		SMOTE	[70,93]

Dimension reduction can increase the machine learning performance when a machine faces a large set of data [123]. Principal component analysis (PCA) converts that large dataset to a reduced one by containing the prominent information [128]. PCA has been applied in some articles and the first few components which contain a huge amount of the energy of the original feature set were selected as the features [123]. Normalization is another post-processing step mainly applied in those studies whose datasets contain multiprocessing approaches to remove the effect of the different range on features [83,110]. However, biased results may be achieved when the population of target groups is not balanced [70]. Feature rebalancing can be beneficial in this condition to prevent unreliable classification results.

3.5. Decision-making

Over the past years, many studies have been conducted on the development of decision-making algorithms for EEG-based AD assessment. Decision-making approaches are adopted according to the researcher's attitude. As summarized in Table 7, these methods can be grouped into three main categories: statistical evaluation, machine learning, and regression. While statistical evaluation approaches investigate biomarkers' ability to distinguish target groups using statistical tests [99], machine learning algorithms tend to introduce an automatic system to detect or predict the target cases [72,87,96]. On the other hand, the last group looks for a regression or correlation technique to model the severity of AD or follow a condition such as MMSE score [84]. It should be noted that some researchers applied both statistical evaluation and machine learning approaches. Totally, in 27% and 62% of the research articles statistical evaluation and machine learning techniques have been applied respectively.

3.6. Deep learning

In this review paper, deep learning is assumed as an independent group of methodologies that directly classify the subjects through their inputs. Table 8 summrizes several deep learning architectures, such as different kinds of the convolutional neural network, AlexNet, and stacked autoencoder, which have been applied so far in the category of AD detection [71,72,79,80,100,119]. Automatic feature extraction is the main advantage of the deep learning and just takes an image or a two-dimensional matrix as the input in eligible articles. The converting techniques of EEG signal to that of a matrix were summarized in Table 3 as the pre-processing stage. However, working with deep learning has its challenges such as regulating hyper-parameters of the model [130]. The number of layers and type of activation functions in structural design, as well as initial learning rate, epoch size, iteration number, and the optimization algorithm, are some of the hyper-parameters that have to be chosen by a designer [130]. A considerable number of inputs is needed to obtain a generalized and reliable model [130]. Moreover, training a deep model could be very time-consuming and a require powerful system [100]. It should be noted that DNNs make a decision as a classifier in their last fully connected layer and do not follow the post-processing stage in Fig. 2.

3.7. Modality of studies

Although discovering EEG-based biomarkers for AD detection seems to be successful, studies have not been only limited to EEG machine and applied other neuroimaging devices to discover a combined biomarker. In this regard, this review paper categorized the eligible researches into unimodal and multimodal studies.

3.7.1. Unimodal studies

According to categorization in this paper, unimodal studies are those

Table 7
Applied decision-making methods in AD assessment.

Category	Method	Reference
Statistical evaluation	Wilcoxon	[75,77,81]
	T-test	[27,64,68,77,83,88,97,103]
	ANOVA	[48,52,54,91,111]
	ANCOVA	[99,108]
	TANOVA	[48]
	Kruskal-Wallis	[107,108,110]
	Mann-Whitney *U* test	[46,48,63,77,110]
	Welch's *t*-test	[70]
	Permutation test	[69,85]
Machine learning	Support Vector Machine (SVM) family	[46,48,55,70,75,78,82–84,86,90,92,93,96,98,101,103,105–107,119,129]
	Linear Discriminant Analysis (LDA)	[70,73,75,79,82,88,89,92,93,97,112,119]
	Regularized linear discriminant analysis (RLDA)	[96]
	Naïve Bayse (NB)	[46,90,92,93,97,106]
	K-nearest-neighbor (KNN)	[46,53,82,83,87,90,93,96–98,106,112,119]
	Elman	[79]
	Multilayer perceptron (MLP)	[90,93,97,101,102,106,107,109]
	Random Forest (RF)	[53,70,83,90,93,106,112]
	Decision Tree (DT)	[90,106]
	Surrogate decision trees (SDT)	[107]
	Takagi-Sugeno-Kang (TSK)	[91,92]
	Fuzzy logic interferes	[44]
	Bagged Trees	[87]
	Binary logistic regression	[55,64,93]
	Elastic Net	[54]
	Fisher Discriminant Analysis (FDA)	[46]
	Quadratic Discriminant Analysis (QDA)	[82,112]
	Extreme Learning Machine (ELM)	[98,112]
	Adaboost	[93]
Regression	Logistic Regression (LR)	[45,77]
	Multivariable Linear Regression	[77]
	Artificial Neural Network (ANN)	[102]
	support vector machine regression (SVMR)	[53]
	Correlation	[63]
	Person coefficients	[53,69,77,88,108]
	Spearman Correlation	[53,85,99]

Table 8
Deep learning techniques in AD assessment.

Deep learning	Reference
Convolutional neural network (CNN)	[80,119]
MC-DCNN	[79]
AlexNet	[100]
Stacked autoencoder (SAE)	[71]
Spatial Temporal Convolutional Networks (ST-CNN)	[72]

studies whose investigations are limited to EEG signals for finding biomarkers associated with AD. This type of study can benefit from some advantages such as easy acquisition, and low financial and computational cost. Moreover, EEG machines can be found in most neurological clinics. That is why EEG biomarkers can be adopted easily in clinical applications.

3.7.2. Multimodal studies

In the multimodal studies, researchers applied EEG and another neuroimaging acquisition system for a same AD problem with same participants. They try to find more reliable biomarkers through an unbiased comparison of the EEG-based biomarkers with other neurological biomarkers or enhance the automatic classification performance by generating a set of combined biomarkers [52,70]. Therefore, the EEG processing methods in this group of studies are not different from the unimodal EEG-based studies. Additional neuroimaging systems can be structural and contain information about hippocampus atrophy acquired by MRI in AD patients. Moreover, the neurovascular change of brain tissue is measurable via fMRI whose output for each voxel is known as the blood-oxygen-level-dependent (BOLD) signal. This signal illustrates the volume of oxyhemoglobin per time for each voxel [70]. In other words, fMRI indirectly monitors the neural metabolism, affected by AD and decreased gradually. Cortical oxyhemoglobin, deoxyhemoglobin, and total hemoglobin volume can be track in time by fNIRS machine [131]. Electrical corresponding of those volumes can be simultaneously measured with EEG signal and a combination of them is applied to automatic AD detection [27]. The simultaneity and compactness of fNIRS systems give the researchers a chance of monitoring both neuro-electrical and neurovascular changes for a certain recording protocol at the same time. This option is also true for the MEG system. The multimodal studies in the realm of AD biomarkers are mentioned in the Table 9. It can be seen that there is a combination of the EEG and structural neuroimaging system as well as EEG and functional neuroimaging and three studies are observed for each condition. Only one research adopted EEG simultaneously with structural and functional neuroimaging systems [70].

4. Discussion

This review provides a theoretical and methodological analysis of EEG-based AD detection or classification. For this purpose, dementia

Table 9
Multimodal neuroimaging system and their aim in AD assessment.

Aim	Multimodal set	Reference
prediction of AD severity level	EEG + sMRI	[53]
Detection of AD from aMCI	EEG + sMRI	[54]
Detection of AD	EEG + sMRI	[71]
Detection of aMCI	EEG + fMRI	[52]
Mild AD detection	EEG + fNIRs	[27]
Detection of AD	EEG + fNIRs	[73]
Prediction of β-amyloid occurrence and neurodegenerative disease	EEG + sMRI + fMRI + PET	[70]

due to AD is introduced and EEG-based biomarkers in this realm of study are explained up to now. Critical factors for an ideal database, selecting the more valuable targets, processing window size, designing a practical processing procedure, decision-making techniques and their distribution in studies, results, and innovations, and the trend of the studies are discussed in this section.

4.1. Database

The databases of the eligible articles are analyzed in section 3.1. Critical factors of an AD database are discussed in this section and explain how to set them ideally. Different factors in databases can exert a negative influence on the biomarkers and make the results unreliable or biased. The first one is the age-matching demographic feature between the target groups. Because aging is the most important factor in AD, it should be matched between inter- and intra-groups. In other words, the difference between the average and variance in the age of the healthy control subjects and patients should be minimized as much as possible to reduce dependency of results to the age factor. In some studies, whose target was distinguishing between AD and/or MCI and HC, the average age of the HC was even fourteen years lower than the group of patients [93]. These studies unintentionally ignore the effect of aging in their results. As described in section 3.3, complexity and connectivity of the brain activity are widely calculated as the AD biomarkers, naturally reduced by aging [132]. Classification results, therefore, can be affected by this natural phenomenon, and aging was detected unintentionally instead of the disease associated with AD.

The next factor is clinical criteria; the clinical diagnosis for disorders related to AD should meet the strict criteria. National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria has been meet in the most of studies [133]. Because cognitive assessment tests, such as MMSE and MoCA, are not the gold standard in dementia diagnosis, they should not be applied as the main and single criteria, especially when it comes to cognitive impairment (CI). Researchers are looking for an EEG biomarker to detect dementia, not an MMSE score. Pathological tests through PET scan and CSF tests fulfill AD criteria since β-amyloid or τ tangle is measurable through them and applying them is highly recommended.

Mentioning the details of the patients' disease is another prominent factor. The severity of AD patients did not mention in some studies or they just report the average of the MMSE score. The less severe the disease, the more difficult it is to classify. It is recommended to mention the number of patients for each category of severity instead of just reporting their average MMSE score or the number of AD patients. Mentioning the type of MCI is also important in the realm of EEG-based detection since aMCI affects the hippocampus and is detectable in MRI while it is not easy for naMCI [11]. Therefore, naMCI via an EEG-based biomarker can be more valuable. It is also true for subjective cognitive impairment (SCI) and objective CI.

Balancing the number of subjects in each group is the next important factor while data augmentation techniques can balance the features matrix before the decision-making. Family history, nationality, and demographic information are also effective and should be mentioned in the studies. Finally, the need to provide an open-access and proper EEG database for the problems in the realm of AD disease is clearly observed. Although an open-access MRI and fMRI database exists in the field of AD [134], it is not available for EEG to the best of our knowledge. It makes the studies more comparable since the mentioned factor will be the same. Almost all the researchers applied their own database and it makes the comparison among the performance of studies very challenging.

4.2. Target of the studies

Detection is the most prevalent aim among the different types of studies with single and multi-target aims, as shown in Table 1. It should be noted that although some articles may use the word "prediction" for the diagnosis of MCI or pre-clinical state of AD, they are categorized as the detection in this review paper. It is because all the subjects with pathological symptoms in pre-clinical or CI stages will not be converted to AD [6,7]. Therefore, researchers can only detect those stages directly through the pathological symptoms or estimate them via measuring the subjects' brain functional activity [70]. Diagnosing severe and moderate AD is not a very challenging issue for neurological clinicians, while detection of Mild AD, CI due to AD, and pre-clinical stage of AD can be more problematic. This is due to symptomatic manifestations caused by these stages are not existed or observed difficulty. Moreover, paper-and-pencil methods such as MoCA are vulnerable to detect them [99]. Consequently, introducing an EEG-based biomarker or a combined biomarker consisting of EEG and other neuroimaging techniques is more valuable than the others in the category of the detection and automatic classification of these three stages of AD.

In the monitoring category, relevant studies try to estimate the progression of the disease. They propose a biomarker that may correlate with the MMSE score, the MoCA score, or the AD severity. This type of studies may help the neurologist to prescribe the right medicine for AD patients. Introducing a biomarker to track the AD progression mostly is not the main target of studies. They often generate an EEG-based biomarker and investigate its regression or correlation with the state of participants like MMSE score or the level of AD.

Studies in the realm of AD biomarkers become more prominent when it comes to prediction. As mentioned before, detecting or estimating the existence of β-amyloid in pre-clinical or CI stages does not mean prediction. Scientists only have to follow up their AD-prone subjects for a long-time span. They are hoping to find a reliable biomarker which has the capability to predict the MCI to AD or pre-clinical to CI /AD converting. This is an open field of study that can be time-consuming but very valuable. In 2021, S. Gaubert et al. published an article and introduced neuroimaging biomarkers to predict the appearance of β-amyloid and degenerating progress associated with Alzheimer's disease [70]. They followed up 304 elderlies to understand how they suffered from SCI for 5 years and. The concentration of β-amyloid was frequently measured through ^{18}F-florbetapir radiotracer PET scan. They found the critical level of β-amyloid concentration in 85 subjects after the time span. Metabolic brain activities of four lobes, posterior cingulate cortex, inferior parietal lobule, precuneus, and inferior temporal gyrus, were also measured through ^{18}F-fluorodeoxyglucose PET scan. Meanwhile, rs-EEG and MRI had been acquired 62% and 61% with accuracy obtained respectively for β-amyloid and neurodegeneration prediction. Although the contribution of EEG-based features was only 2% in the selected features for β-amyloid, all five selected features for neurodegenerative disease prediction were EEG-based. This research illustrates that finding EEG-based biomarkers for predicting the β-amyloid production level can be a new challenge [70]. A 4 years follow-up research was also published in 2021 by Tait L. et al. to predict the aMCI to AD development [48]. They used two separate databases, one for training and the other for testing the designed prediction system which makes the result more generalized with 81.30% accuracy.

As mentioned, the studies in the realm of EEG-based AD biomarkers are categorized into detection, monitoring, and prediction in this review paper. As shown in Fig. 3, the share of detection as a substantial portion of all studies is 85%. It should be noted that AD and MCI detection respectively were the most popular targets in the last decade. Although only 9% of studies belong to prediction, they are very valuable since AD prediction through EEG biomarkers can be a challenge. Evidence illustrates that current studies have not introduced an EEG-based biomarker yet for AD prediction [48,70,80,99]. The time-consuming process of data gathering in follow-up studies seems to be the main reason for lack of AD prediction studies in the last decade. Monitoring, in addition, was not the main goal of research in most of the articles and the studies tried to show the correlation between the generated features and the

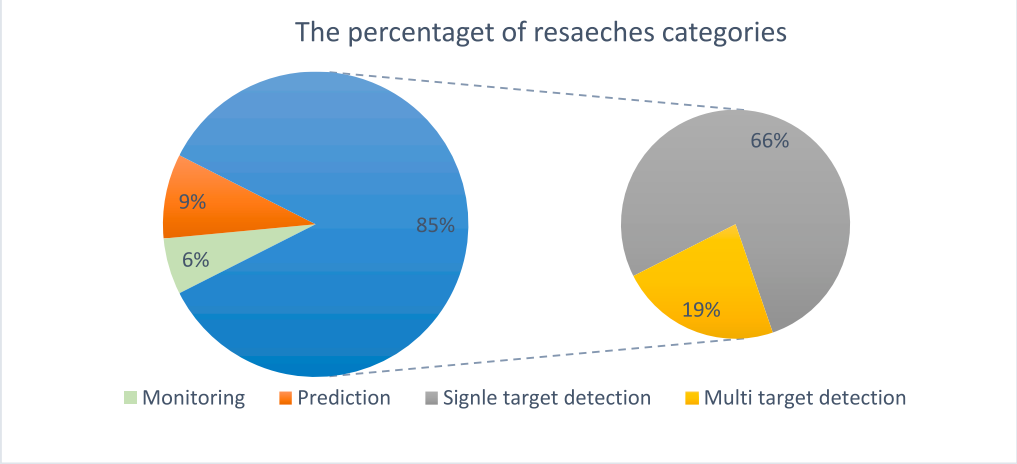

Fig. 3. Portion of research for each category in the past five years in the realm of EEG-based biomarker generation.

participant's state.

As mentioned, clinical AD and CI detection as well as AD prediction can be challenging. This systematic review paper highly recommends researchers to focus on mild AD, and CI detection studies as well as follow-up-based prediction of pre-clinical to AD, and CI to AD, according to data acquisition criteria mentioned in the section 4.2.

4.3. Processing window size

This paper categorizes the applied main processing methods into univariate and multivariate that described in section 3.3. Main processing procedures work on constant-length EEG windows known as the window size. Choosing the right epoch size is an art and is associated with the proposed processing method. Some technical factors such as the stationary nature of the signal can limit the window size in statistical feature generation. Although almost all the papers mentioned their adopted epoch size, they mainly did not describe how it is determined. Window size can directly affect the result as mentioned in [98] and choosing a proper window length can enhance the results. It is recommended that studies report their investigation into the window size. Fig. 4 illustrates the statistical distribution of applied window size for each processing procedure in the form of a box plot. It can be seen that a 2 s length window was the most repeatable window size in all of the articles with 12 successful repeating times and the average window size for all the studies was equivalent to 17.32 s. Moreover, three quarters of the connectivity category are 20 s while this quarter for the rest of the processing procedures are 10 s. Moreover, the box plot for deep learning has the least range with a maximum of 10 s. It should be noted that 180 s and 120 s epoch sizes that exist in three studies were removed from the box plot to show the boxes in more comparing details.

4.4. Main processing

Adopting an effective methodology for introducing an EEG-based biomarker could be challenging since there are a reasonable number of processing methods categorized in slowing, complexity, connectivity, graph and network theory, and deep leaning groups in this paper. It should be noted that a reasonable number of studies generate feature sets from a combination of two or three categorized methods mentioned in section 3.3. Processing methods should meet the robustness since EEG signal is naturally very sensitive and vulnerable to noise and artifacts as mentioned in section 3. A robust-to-noise method in addition to an automatic noise reduction technique makes the designed system free from a specialist to manually remove or reconstruct the distracted signal. A processing procedure, in addition, should be optimized from recording protocol, channel number, window size and number, and computational operation points of view to be more practical for clinical use. However, there has to be a trade-off between the performance of the

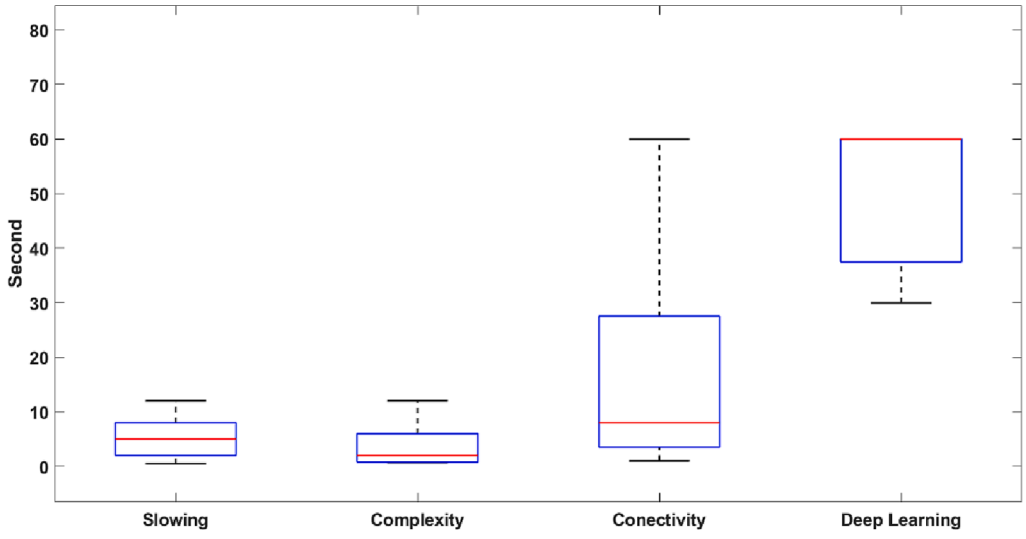

Fig. 4. Window size for each processing procedure.

designed automatic system and the optimization in the computational operation if designers want to practically use the system.

4.5. Decision-making

A considerable number of machine learning approaches, monitoring methods, and statistical evaluation techniques were applied in the past five years as reported in Table 7. Frequency distribution of them is shown in Fig. 5. According to this pie chart, machine learning methods contain 65% of the decision-making approach followed by statistical evaluations with 27%. It illustrates the significant number of efforts that scientists have made for developing automatic EEG-based systems associated with AD in the past decade. Among different machine learning techniques, the SVM family, with 19% of all the decision-making approaches, had the most repetition. SVM is applied in different kernels containing linear [46,83,86], and radial basis function (RBF) [46], different optimization techniques including Particular Swarm Optimization (PSO), Genetic Algorithm (GA), Grid Search (GS) [97], and different implementations contain multiple classification [73]. In the realm of detection, some studies applied several classifiers to find the best of them regarding their performance [46,75,83,90,97,106,119].

However, validation techniques in machine learning can be a prominent factor since the generalization of designed systems is directly investigated through validation. In validation, a portion of the learning matrix is considered as the test set to avoid the over-fitting of a classifier in training processes. K-fold cross-validation is a common form of validation techniques and applied in most of articles [46,91,106]. In the K-fold cross-validation techniques, some feature vectors from a particular subject may exist in train, validation, and test sets. Therefore, Machine learning is not necessarily blind to the subject in the training process while the designed system has never seen a new participant in real-world applications. Leave-one-person-out-cross-validation (LOPO-CV) is another form of validation that is completely blind to the test subject and it makes the reported results more reliable [55,75,83,88,90,104]. Moreover, two studies made it more challenging and used two different databases; one for training and the other for testing [48,89]. In this regard, Ali H. Al-Nuaimi et. Published an article in 2021 and used a recorded database in the UK for training LDA and another in Italy for testing it and they successfully diagnosed the AD patients [89].

The performances of these machine learning techniques according to their aim are reported in Table 10. It should be noted the best performance in multi-target studies is reported here. It can be seen that the SVM family and random forests classifiers have the best performance compared to other discrimination methods respectively with 6 and 3 repeating times.

4.6. Results

The results of studies, according to reported accuracy, across their corresponding target that looked for an automatic detection or prediction model are summarized and shown in Fig. 6. It should be noted that severe AD detection studies are omitted from the box plot to fairly compare the results in each category. It illustrates the capability of EEG-based biomarkers for AD problems and shows their performance and makes the targets comparable for researchers to propose their novel methods. While EEG-based biomarkers have been successful in a variety of mentioned targets in Table 1, reliable EEG biomarkers have not been proposed yet for the detection and prediction of AD in a preclinical stage.

Comparing the obtained results represents that a high average accuracy rate of 100% has been reported for mild AD detection [79], AD detection [45], and SCI/ MCI classification [86] in previous studies. However, full accuracy achievement in these studies does not mean the closing of that field since the proposed model should test for a considerable number of elderlies in a generalized validation like LOPO-CV. In addition, more optimized models are required for comparing and testing in issues associated with AD. Furthermore, comparisons of the results have confirmed that MCI has the widest range of performance with 62%

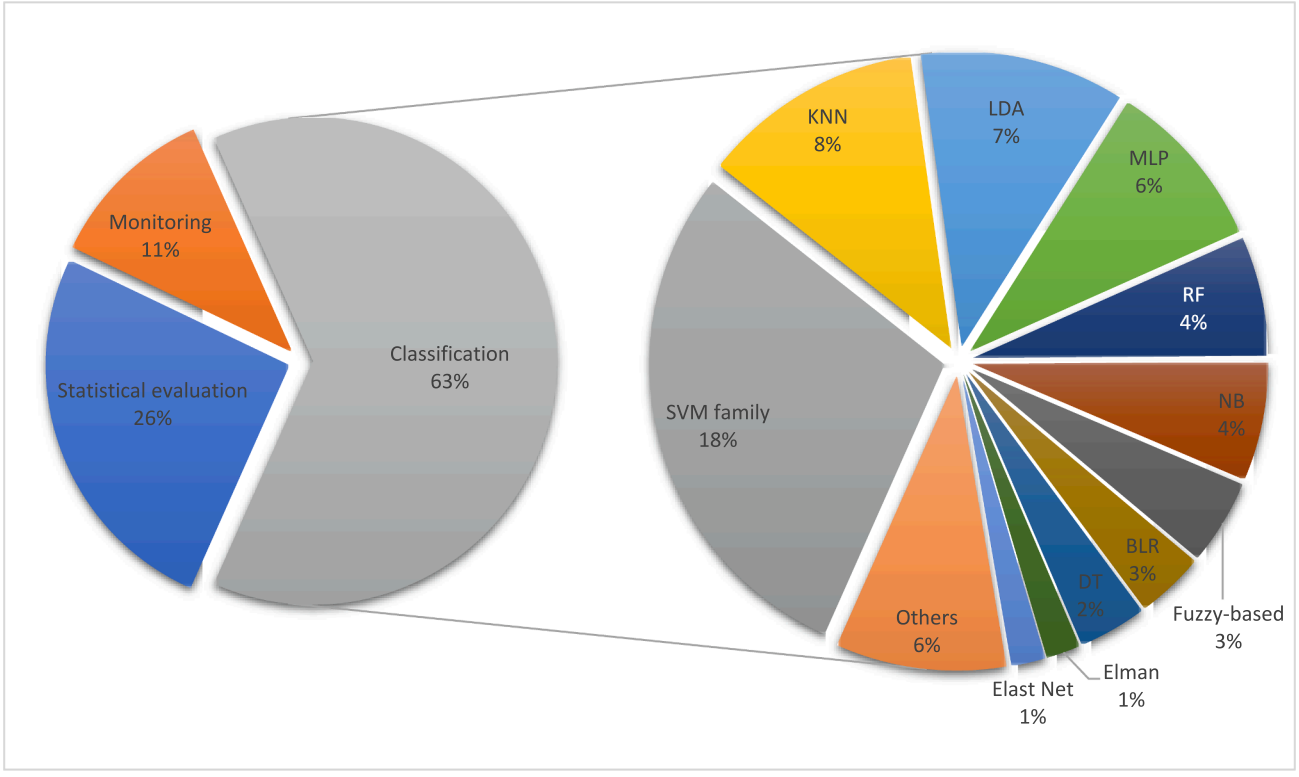

Fig. 5. This pie chart of the percentages of Decision-making approaches. Abbreviations: Support Vector Machine (SVM), K-Nearest Neighbor (KNN), Linear Discriminant Analysis (LDA), Multilayer Perceptron (MLP), Random Forest (RF), Naïve Bayse (NB), Binary Logistic Regression (BLR), Decision Tree (DT).

Table 10
Multi classifier studies according to their aim and performance in AD assessment.

Aim	Best classifier(Accuracy%)	Second classifier	Third classifier	Forth classifier	Fifth classifier	Sixth classifier	Reference
AD detection	**Random forests(99.10%)**	MLP	KNN	SVM	Naïve Bayse	Decision tree	[90]
	SVM (RBF)(92.50%)	SVM (Linear)	KNN	FDA	Naïve Bayse		[46]
	TSK [a](98.10%)	SVM	KNN	LDA	Naïve Bayse		[44]
	LDA93.18%	SVM	KNN	ANN	Naïve Bayse	Adaboost	[93]
Mild AD	**MC-DCNN [b](100%)**	Elman	LDA				[79]
Moderate AD detection	**Random forests(97.76%)**	SVM	KNN	Decision tree	Naïve Bayse	MLP	[106]
MCI detection	**SVM(80.39%)**	LDA					[75]
	SVM (GS)(86.60%)	SVM (PSO)	SVM (GA)	KNN	Naïve Bayse	MLP	[97]
	CKF-SVM [c](90.19%)	SVM	KNN	QDA [d]	LDA		[82]
	ELM [e](98.78%)	SVM	KNN				[98]
CI detection	**SVM(88.37%)**	Random forest	KNN				[83]
MCI / AD	**ANN(98.83%)**	SDT [f]	SVM				[107]
Nold/MCI/AD	**KNN(71.40%)**	LDA	SVM				[119]
	Bagged Trees(93.88%)	SVM	KNN				[87]
β-amyloid	**Random Forest (62%)**	LDA	SVM				[70]
Neurodegeneration	**LDA(61%)**	Random Forest	SVM				[70]

Abbreviation: [a] TSK: Takagi-Sugeno-Kang, [b] MC-DCNN: Multi-Channel-Deep Convolutional Neural Network, [c] CKF-SVM: Conformal kernel-based Fuzzy SVM, [d] QDA: Quadratic Discriminant Analysis, [e] ELM: Extreme Learning Machine. [f] SDT: Surrogate decision trees.

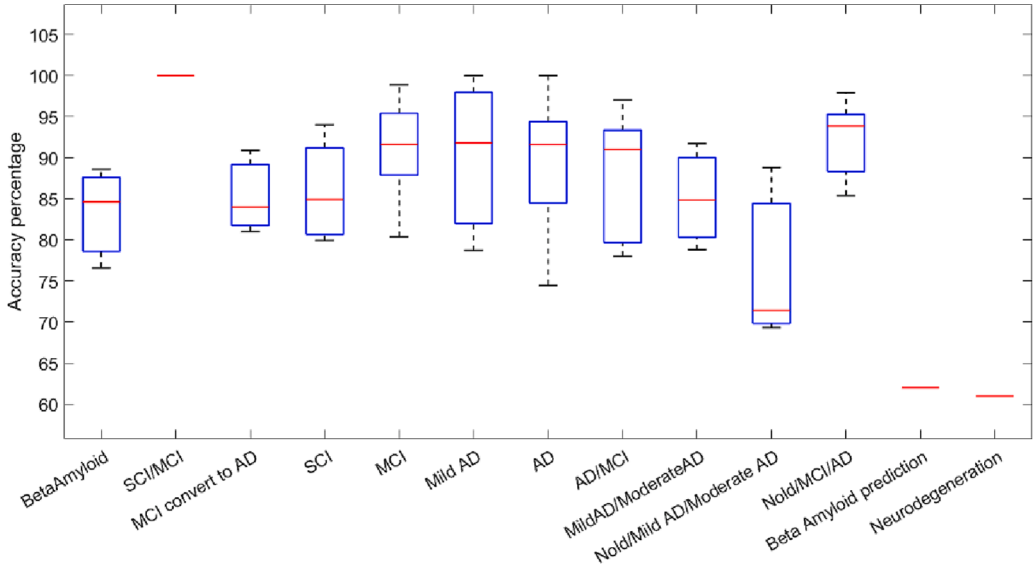

Fig. 6. Performance in each target group according to their accuracy.

up to 98% in accuracy followed by AD detection with 74% up to 100% of accuracy in monitored studies. The SCI/ MCI, mild AD, and AD detection have also provided 100% performance in accuracy, which is promising from the performance point of view.

4.7. Investigations

The efficiency of the EEG channels or ROIs in the processes of decision-making as well as the performance of the biomarkers in different EEG rhythms is usually reported in AD-related studies. These investigations are discussed in this section and finally, the trend of the studies in the realm of EEG-based biomarkers is investigated.

Some articles investigated the impact of EEG channels to find the most effective one in their studies. P4, P3, and PZ respectively reported as the top-ranked channel for AD detection in rs-EEG [89]. These channels were selected through a threshold on the T-test and their performance on the SVM classifier [89]. T3, T4, T5, and T6 channels that are located in the temporal area showing the most significant performance in a three-way classification of HC, AD, and MCI [88]. Furthermore, the O1 channel illustrated a sharp reduction in the performance of the classification according to EEG-based features in δ and θ frequencies in AD patients and it showed the roll of occipital area in AD and MCI [46]. This hypothesis was also introduced in another study that investigated predicting MCI to AD conversion by generating EEG-based biomarkers. However, it was not always true for the occipital area. FP2, Fz, F3, Pz, TP7, and T5 channels were found to provide the best performance in MCI classification while occipital channels were not found efficient in this issue [82]. Katz's fractal dimension (KFD) was applied in EEG channels for MCI detection and F7 met the largest weight in the sequential forward selection (SFS) feature selection algorithm [82]. The alpha coherence in the frontal lobe (F3–F7, F3 F4, F4–F8) and left frontal–central pairs (F3–T3, F7–C3) saw a significant reduction in AD patients compared to the healthy old group.

Selecting the most efficient EEG rhythms is also another challenging issue in the field of EEG-based biomarker generation. Decreased α oscillation power and increased θ oscillation power are reported in AD patients [68]. They also reported a decreasing trend in the spectral entropy of α oscillation and elevated spectral entropy in β rhythm in AD patients [68]. Decreased phase synchronization index in δ, θ, and β rhythms was also seen in AD [68]. AD patients clearly evidenced meaningful increases in Delta, and Theta frequencies and decreases in the Alpha, and Beta frequency bands in comparison to MCI and HC [88]. The EEG coherence was applied for detecting mild-AD and an increase was observed in the power across the θ rhythm in the mild AD patients

compared with the normal group (P = 0.1) [69]. In mild-AD detection, moreover, the alpha power in the parietal area saw a decrease (P = 0.4) but no significant differences were reported in δ, β, or γ EEG rhythms [69]. Increasing in the power of lower frequencies and decreasing in the power of higher frequencies were observed in AD and MCI compared with healthy old group [87]. However, delta bands could not make a significant difference between AD and HC groups in a study.

The number of published articles per year under the scope of EEG-based biomarkers related to AD is shown in Fig. 7. Generally, an increase in the number of publications is observed from 2018 up to 2023. A jump is also seen in the number of publications in 2021 which can be the result of scientists' attention to the capability of EEG signals in AD problems and discovering novel drugs.

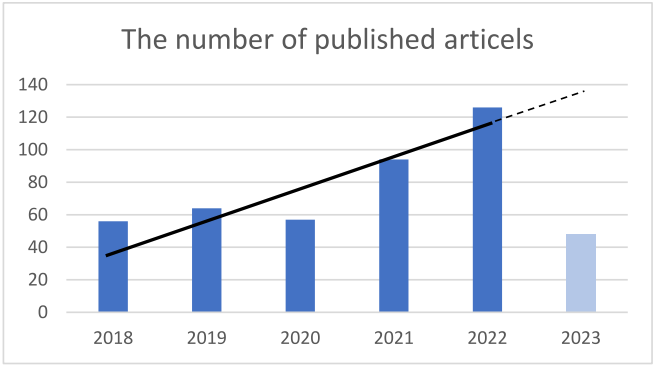

Fig. 7. The number of published articles per year in the last decade.

4.8. Advantages and disadvantages

The advantages and disadvantages of each processing step are discussed in this section. In the pre-processing step, most of the adopted approach such as frequency filtering and automatic artifact rejection techniques benefit from simplicity and efficiency. Meanwhile, manually segment selection and supervised artifact rejection approaches can be time-consuming and financially expensive. Next, in the main-processing step, univariate methods can be calculated by the minimum number of EEG electrodes. They usually follow less complicated algorithms and reduce the computational cost. While this type of features may not be very accurate in the AD detection and they may not be able to provide insight into the spatial pattern of the disease. On the other hand, multivariable methods can illustrate the relation between the different parts of the brain and provide insight into the affected regions which can be beneficial for neurologists. Moreover, they can be very accurate in AD detection. While it should be noted that multivariable methods generally require considerable number of EEG channel and powerful computer to handle their complicated calculations, especially for deep learning. Finally, when it comes to decision-making approaches, although statistical evaluation and monitoring methods can be simply applied to the extracted features, they are not able to distinguish patients from healthy control subjects. Classifiers can automatically detect the state of the subject from the extracted features. There are several types of classifiers and there is no guarantee for each of their preference until evaluates them under the test.

4.9. Implementation

In this section, some methods are recommended for reader to be implemented in their future works to improve the performance of their studies according to summarization of the eligible articles. First in the pre-processing, taking a proper artifact rejection procedure can fully automate AD detection algorithm from expert supervision. Furthermore, the use of dynamic bivariate or multivariate feature extraction methods helps in characterization of affected brain regions in AD combining spatial and temporal information which could further improve the detection. Binary classifiers are in the priority in the decision-making section when it comes to automatic AD detection. The severity of AD can also be estimated through multiclass classifiers.

5. Conclusion

This paper reviews EEG-based biomarkers and designed automatic patient detection by means of machine learning techniques in the realm of AD that published from 2018 up to 2022. The aims of these articles are categorized in detection, monitoring and prediction of AD. Detection methods tried to find AD patients in different stages or a degree of AD. However, monitoring approaches tend to estimate the severity of AD. Follow-up research is also required if the target of research is prediction. Methodologies for discovering the EEG-based biomarkers are divided into univariate and multivariate. Single-channel EEG can be enough for generating the biomarkers in univariable methodologies that contain slowing and complexity. In multivariable methodologies, EEG channels are not considered independent from each other and they include functional connectivity, effective connectivity, graph and network theory, and deep learning. Decision-making can be just based on statistical evaluation or automatic system through adopting machine learning algorithms. Results, investigations, and limitations of these studies are reported in the discussion section. 100% of accuracy was reported in the detection of AD patients in some stages while estimating the pathological factor or AD prediction seen low percentages of accuracy and they are still challenging. Some electrical evidence in EEG signal illustrates that AD onset is traceable in the occipital region. Decreased α oscillation power and increased θ oscillation power are reported in AD patients. limitations of studies mostly depend on the database. A considerable statistical population in the database gives the chance for researchers to evaluate the repeatability and generalization of the research methodology. An open-based database makes the research more comparable to find the best methodology. Pathological labeling makes the results more reliable that does not exist in some researches. Significant difference in effective factors such as age, gender, and educational level can make the bias in the reported results. Therefore, it is recommended to introduce an open-access database, adopting fare comparing subjects and methodologies according to the mentioned factors. Furthermore, it is recommended to more concentrate on CI detection, early AD detection and AD prediction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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