Signal Processing Methods of Diagnosing Alzheimer's Disease Using EEG A Technical Review

Bibina V C, Upasana Chakraborty, Mary Lourde R, Ajit Kumar

***Abstract*—**Alzheimer's is the most common form of Dementia prevailing in the elderly people. This review paper aims to put forward recent developments in the diagnosis of Alzheimer's disease (AD) using Electroencephalograms (EEG). The extraction of useful information from rough EEG signal using only mathematical algorithm is a tough but promising task. Various modern techniques have enhanced the computerized analysis of EEG in elderly people. All these techniques can exploit the information contained in the EEG signals in time, frequency and time-frequency domain analyses. This work provides an integration of various time, frequency and time-frequency domain methods which facilitate the analysis independently as well as combined thus making it easier to analyze nonstationary and non-deterministic EEG signals. Among these various methods, time-frequency domain tools offer most efficient methods as it can uncover features that remain invisible when only time or frequency domain methods are used. Several of the methods discussed here can be utilized to develop an efficient algorithm for early detection of Alzheimer's disease.

***Keywords*—**Alzheimer's disease, Dementia, EEG, Frequency domain analysis, Time domain analysis, Time-Frequency domain analysis.

I. Introduction

THE Alzheimer's disease (AD) is a neurodegenerative disease affecting one in fifteen people over the age of 65 [1]. The disease is named after German physician Dr. Alois Alzheimer. According to National Institute on Aging (NIA), Alzheimer's disease is a form of dementia that particularly affects regions of the brain that control thought, memory and language. Among all dementia cases, 50 to 70% falls into the category of Alzheimer's disease. As per Alzheimer's Disease International (ADI) report, the estimated number of people suffering from dementia in 2015 all over the world was 46.8 million and in 2017 this number could rise as high as 50 million.. In every 3 seconds, someone in the world develops dementia [2]. Fig. 1 shows a comparison of growth rate of people with dementia in high income countries with that in low and middle income countries [2]. In the United States of America, the sixth out of 10 leading causes of death is AD and it is the only one which cannot be cured or slowed as of now. Since 2000 the death rate due to cardiovascular diseases has reduced by 14% whereas the death rate due to AD has increased by 89% [3].

The brain of an AD patient contains abnormal deposits around the neurons and tangled bundles of fibers inside the neurons [4]. The abnormal clumps are due to the accumulation of extracellular Beta-amyloid plagues, formed when specific proteins in the neuron cell membrane are processed differently. Neurofibrillary tangles are formed when the intracellular protein called tau is modified. AD begins at hippocampus, the part of the brain where memories are first formed. Over many years, the plagues and tangles destroy the hippocampus and spread into different regions of the brain, killing cells and compromising the functions wherever they go.

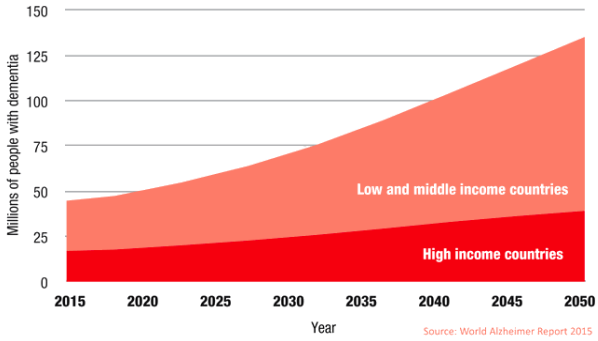

Fig. 1 The number of people with dementia in low and middle income countries compared to high income countries [2]

The growth of the disease can be categorized into four stages: Mild Cognitive Impairment (MCI), Mild AD, Moderate AD and severe AD [5]. The daily life of the patient is not altered seriously in MCI, as memory loss is the most common problem in this stage. Every year almost 25% of people with MCI is transformed to AD. Even though it is an incurable disease, medications are available to slow down the decay of the brain. Researchers are developing methods for protecting neurons from amyloid beta peptides and tangles [6].

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But most importantly the disease should be diagnosed in its early stage to avail the benefits of these medications.

As the symptoms of Alzheimer's disease are usually misinterpreted as normal consequences of aging, the medical diagnosis is very tough. Multiple exhaustive tests are conducted for the diagnosis. Basically, the AD diagnostic methods can be classified into invasive methods and non-invasive methods. Most commonly used invasive diagnostic methods for the Alzheimer's disease are the blood tests and examination of cerebrospinal fluid, which are painful to the patient. Researches claim that some blood tests can diagnose the disease even before evident symptoms appear [7]. With the blood tests, the disease is predicted based on the fat content in the blood and blood protein. Special peptides such as tau peptide and A beta peptide are found in cerebrospinal fluid of an Alzheimer's patient.

The non-invasive diagnostic methods for Alzheimer's detection include different neuroimaging modalities, neuropsychological assessment tests, electrophysiological recording etc. Neuroimaging methods like Single Positron Emission Tomography(SPECT), Positron Emission Tomography(PET), and Magnetic Resonance Imaging(MRI) are proven good diagnostic tools for AD. It has been found that there is a notable shrinkage in the size of the brain of Alzheimer's patient which is evident from fig. 2. Since the disease begins at hippocampus, the shrinkage also starts at hippocampus. Structural imaging techniques which include magnetic resonance imaging(MRI) and computed tomography (CT) reflect the information on shape, position or volume of brain tissue. Functional imaging techniques such as PET and functional MRI(fMRI) suggest that the cell activity has reduced in certain regions of the brain of Alzheimer's patients. These modalities provide the knowledge of the working of brain cells by showing their active usage of sugar or oxygen. Pittsburgh compound B (PIB) and Florbetaben (BAY 94-9172) are two molecular imaging compounds approved for clinical use and are capable of detecting beta-amyloid deposition during a PET scan [8]. Although neuroimaging techniques are good at diagnosing the Alzheimer's disease, they are inconvenient, expensive and imposing high radiation risks to the patient.

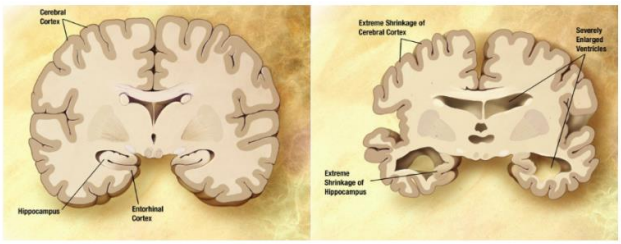

Fig.2 Structural differences of a normal brain (left), and the brain affected by Alzheimer's disease (right) [9]

Mini Mental State Examination (MMSE) which tests a person's mental abilities, is the most common neuropsychological test used for Alzheimer's diagnosis. The limiting factors of these are they are prolonged tests and by only this test the disease cannot be confirmed.

Electrophysiological recordings like Magneto encephalogram(MEG) and Electroencephalogram(EEG) are the next set of non-invasive tools for AD diagnosis. Again, MEG is expensive and poor at localizing exactly where the activity is occurring in the brain.

Among the means of diagnosing Alzheimer's disease, EEG is a repeatable, comparatively cheap and easily available technique. An enormous amount of researches have been reported on the capability EEG to detect Alzheimer's disease. EEG measures and records the electrical activity of the brain. It is observed that the full band EEG signal is combination of mainly five subbands [10], namely;

- delta rhythm (<4Hz) which occurs during deep sleep and has large amplitude,
- theta rhythm (4 – 7 Hz) appears during drowsiness and certain stages of sleep,
- alpha rhythm (8 – 13 Hz) is notable when the subject is relaxed and awake with eyes closed and has the largest amplitude in occipital regions,
- beta rhythm (14 – 30 Hz) is observed in the frontal and central regions of the scalp and has low amplitude and
- gamma rhythm (>30 Hz) related to the mechanism of consciousness.

Comparison of the distribution of power spectral density of three classes of subjects, viz. Healthy Control (HC), Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) has been shown in fig. 3 [11]. It can be perceived that the power distribution in alpha1 (8 – 10 Hz) subband and alpha2 (10 – 13 Hz) subband can effectively discriminate AD and HC.

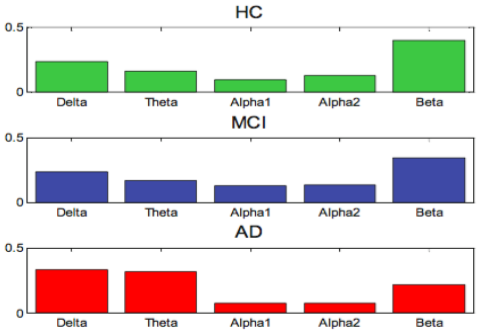

Fig. 3 Relative power content of frequency bands averaged [11]

The most accepted international standard for electrode placement is 10-20 system which often consists of 21, 32 or 64 electrodes. Fig. 4 depicts a 10-20 system with 21 electrodes. This system has been recommended by International Federation of societies and clinical neurophysiology. Electrodes are placed at every 10% of the distance between the two mastoids (electrodes on the ear tip). Similarly, electrodes are placed at every 20% distance of the total length between the forehead and back electrode. Thus, the name goes as 10-20 standards.

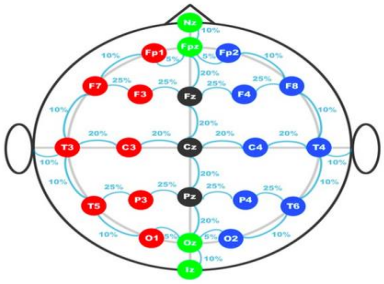

Fig. 4 10-20 International Standard of electrode placement [12]

This review paper is concentrated on various state-of-art signal processing techniques on EEG for the diagnosis of Alzheimer's disease. The arrangement of the paper is as follows; Section 2 gives a brief review on different AD diagnosing tools reported with EEG and its classification based on the domains of feature extraction, its subsections introduce each class briefly, and in final the paper is concluded with the remarks drawn from the review.

II. Classification Of Diagnostic Methods Currently In Use

EEG analysis is one of the standard methods used for the diagnosis of Alzheimer's disease. It also provides a best tool to mass screen the population at risk for AD. EEG based diagnostic methods are non-invasive, economical, side-effect free and easy to execute. The diagnosis with EEG is based on the fact from researches that the EEG of AD patients are abnormal compared to normal people. The major effects observed are slow down, complexity depletion and perturbation in synchrony of EEG signal. It has been deduced from the EEG frequency spectrum analysis that the low frequency bands such as delta and theta bands of AD patients show an increased activity while their high frequency bands like alpha and beta bands show decreased activity [13]. Fig. 5 is an illustration of slowing of EEG signal due to AD. In fig. 3, compared to HC, AD shows decreased activity in high frequency bands and MCI shows decreased activity especially in beta band, which are directing to the conclusion that slowing down occurs in both the MCI and AD patients, though at different levels.

The EEG record of the brain activity produced by electroencephalography as such may contain unwanted signals like interference from other electronic equipment, electrooculographic signal (EOC) due to eye movements, electromyographic signal (EMG) evoked from muscular activity etc. Hence a preprocessing stage is required to eliminate the artefacts before analyzing the EEG signals for the detection of AD as these noisy signals may bias the investigation [13]. One of the ocular artefact removing methods using Volterra filter has been delineated in [14]. After the preprocessing stage, the denoised signal is subsequently used for extracting the particular feature for diagnosis. With respect to the feature extracting domains, the prominent EEG biomarkers can be broadly grouped into three categories: time domain biomarkers, frequency domain biomarkers and time-frequency domain biomarkers.

The brain waves originate from deep inside brain sources and reach the surface of the scalp [15]. Studies have shown that EEG coherence can be used to quantify the functional connectivity between different brain units [16], [17]. Phase Locking Value (PLV) [18], [19], Phase Lag Index (PLI) [20]-[23] and Weighted Phase Lag Index (WPLI) [24], [25] are the phase synchronization indexes (PSIs) recommended for phase synchronization analysis of time series signals. Phase-locking indices can be calculated over time using sliding analysis windows. PSIs effectively describe the relationship between instantaneous phase extracted from signals. Let φ1(t) and φ2(t) be the instantaneous phase of two units. Then the two units are said to be in n:m phase synchronization, if the inequality $|n\varphi1(t) - m\varphi2(t)| <$ const. holds, where n and m are two positive integers.

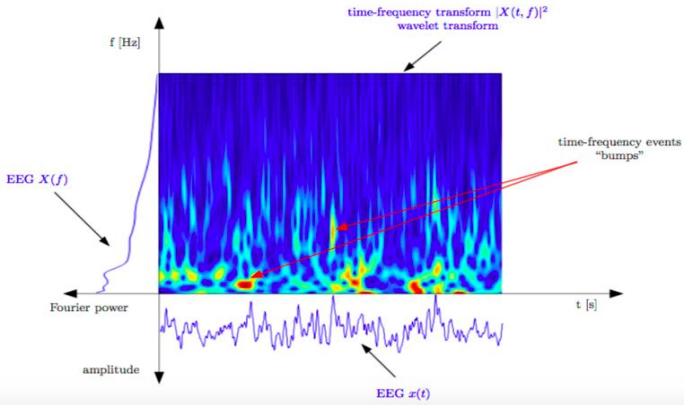

Fig. 5 Slowing of EEG signals: In time domain x(t), in frequency domain X(f) and time - frequency domain |X(t,f)|[13]

Mutual information, an information theory and coding parameter is another measure applied to find the functional connectivity between different brain units [26], [27]. Some other information theory parameters such as approximate entropy [28], multiscale entropy [29] - [31], Tsallis entropy [32], [33] are effective measures to quantify the complexity levels of EEG. Claude E Shannon introduced entropy, which gives the amount of uncertainty associated with a random variable [34]. Monitoring balance and gait duration of a person is claimed as potential tool for Alzheimer's diagnosis in [35]. Principal Dynamic Mode (PDM) analysis is also done in the time domain to EEG signal for the diagnosis of Alzheimer's [36]. This has been discussed in detail under the time domain analysis tools.

Power /energy of EEG signals, power spectral density of EEG subbands, frequency transform coefficients etc., are some of the classical biomarkers being used for the diagnosis of Alzheimer's disease in the frequency domain. One of the most basic analyses applied to time domain EEG signal obtained is Fourier transform to emphasize its frequency contents. The Fourier transform of an EEG type aperiodic signal x(t) is defined as,

$$\mathcal{F}\{x(t)\} = X(f)\int_{-\infty}^{\infty} x(t)e^{-j2\pi ft}dt \quad (1)$$

where X(f) is the frequency transform coefficient. The existence of Fourier transform is guaranteed by Dirichlet conditions. Fast Fourier Transform (FFT) is a computationally efficient algorithm to determine Discrete Fourier Transform (DFT). Though Fourier Transform is good in frequency domain feature extraction, it is zero in time localization. The solution to this problem is to adopt time-frequency analysis, which is the combination of time domain and frequency domain analyses.

Time Frequency Distribution (TFD) analysis has become one of the most attractive tools for feature extraction from EEG signals since it preserves both time and frequency information[1]. Short Time Fourier Transform (STFT) (also known as Gabor Transform) [37], Wavelet Transform (WT), and Wigner-Ville Distribution (WVD) are some of the most popular TFDs. STFT, the very basic TFD infers the strength of frequency in a signal around a particular time. In STFT the Fourier Transform of a windowed portion of the EEG signal is calculated as the window slides down the time axis. The portion of the nonstationary EEG signal within the window is assumed to be stationary, providing an efficient analysis of the entire signal in parts. The width of the window is decided by the time and frequency resolution required [38]. A wide window will give good frequency resolution but poor time resolution whereas a narrow window will give good time resolution but the poor frequency resolution. Wavelet Transform (WT) uses multiple window sizes making it as a better alternative of STFT. Commonly used basis functions (wavelets) in WT are Morlet and Daubechies wavelets. Wavelet Transform is a function of two parameters, scale and translation parameters. The scale parameter is a measure of frequency and the translation parameter is a measure of time. Wigner-Ville Distribution is a quadratic TFD which computes energy density by correlating the signal with its time and frequency translated version [39].

Another set of Time-Frequency biomarkers used for the diagnosis of AD is based on different parameters of amplitude modulation like modulation frequency [40], amplitude modulation energy [41], etc. Amplitude modulation can be considered as the multiplication of two or more sinusoidal signals. Since EEG displays the control, regulation, synchronization and intersystem interaction in the nervous and other body systems, the presence of amplitude modulation in EEG signal processing can be confirmed [42].

Neural network analysis is also used widely nowadays for the AD diagnosis. Artificial Neural Networks (ANN) finds its most wide use in the last step of EEG signal processing that is feature classification [22], [43] - [46]. In most of these works extension of low resolution brain electromagnetic tomography (LORETA) is used to extract the electrical activity of the neuron, for building the network. Another equally efficient method of feature classification is the Support Vector Machine (SVM) which is a statistic based method. Multiclass SVM with error correcting output codes (ECOC) is analyzed in [47] to explain how it can be used in the EEG classification with improved accuracy. SVM is a binary classifier to which several similar classifiers are combined to get a multiclass SVM.

A. Time Domain Analysis

AD has reduced the complexity of EEG signal. There have been several complexity measures used to quantify the complexity of EEG signal. Some of them come under information theory like approximate entropy [28], multiscale entropy [29] - [31], Tsallis entropy [32], [33] etc. EEG quantifies the combined activity of around 100 million neurons spotted in the vicinity of the recording electrode. The strong interactions between the neurons are the sources of regularity and complexity of EEG time series. As AD is the consequence of the replacement of neurons with plagues and tangles, it would severely impair such interactions and thereby reduces the complexity and enhances the regularity of EEG. The entropy measures may be used as an authentic index for inferring the complexity of EEG signal. Here all these entropy studies observed that the complexity of EEG signals is disturbed by MCI or AD. The patients seem to have more regular EEG than of age-matched healthy controls.

The approximate entropy [28], developed by Steven M Pincus, is a measure of likelihood which states that the patterns in a signal will not be followed by a further "alike" pattern. Let u(1), u(2), . . . , u(N) be a time-series of data from signal measurements equally spaced in time. A sequence vectors x(1), x(2), . . . , x(N-m+1) can be defined in Rm such that x(i) = [u(i), u(i+1), . . . , u(i+m-1)], where m is positive integer. For each i, $1 \leq i \leq N\text{-}m+1$, let

$$C_i^m(r) = \frac{number\ of\ j\ such\ that\ d[x(i),x(j)] \leq r}{N\text{-}m+1} \quad (2)$$

where r is positive real number and

$$d[x(i),x(j)] = \max_{k=1,2,\ldots,m} (|u(i+k\text{-}1)u(j+k\text{-}1)|) \quad (3)$$

From $C_i^m(r)$ it has been defined as

$$\Phi^m(r) = (N\text{-}m+1)^{-1} \sum_{i=1}^{N\text{-}m+1} C_i^m(r) \quad (4)$$

The approximate entropy is defined as

$$ApEn(m,r,N) = \Phi^m(r)\text{-}\Phi^{m+1}(r) \quad (5)$$

where

$\Phi^m(r)\text{-}\Phi^{m+1}(r)$ = average over i of log [conditional probability that $|u(j+m)\text{-}u(i+m)| \leq r$, given that $|u(j+k)\text{-}u(i+k)| \leq r$, for $k = 0, 1, \ldots, m-1$] (6)

The presence of similar patterns of fluctuations in a time series makes it more foreseeable than a time series which does not have such patterns. A relatively small ApEn for time series with many repetitive patterns and a higher ApEn value for the less predictable process. The work done in [48] has used ApEn to measure the complexity of EEG, recorded with 10 electrode system. With the help of 20 HC and 14 AD patients, detailed tests have been conducted by the authors and obtained the result indicating AD patients with less interaction and

communication of neural cells will have low ApEn value

In multiscale entropy analysis, consecutive coarse grained time series are constructed from the original time series, with an increasing coarseness parameter and entropy is calculated for each of the resulting time series [30]. Multiscale permutation entropy (MSPE) [31] is the extension of permutation entropy [49] which is based upon the comparison of the ordinal sequence of neighboring values. Here the permutation entropy is computed for each coarse-grained time series. The dataset consists of a group of 63 AD patients with an average MMSE score of 23.69 and 76 HC having the average MMSE score as 28.70. The data were collected during an episodic memory task. It has been seen that there is a reduction in the permutation entropy values for coarse grained scales (scale ranging from 5 to 8) especially at left and right centro-temporal regions which analogous to a reduction in complexity of the underlying signal.

In [33] Tsallis method, entropy is computed by quantizing the EEG amplitude and is calculated in both development and test phase of the analysis. A group of entropies described by a parameter q (a real number) is Tsallis entropy. Tsallis entropy is given,

$$S_q = (\sum_{i=1}^{N} P_i\text{-}P_i^q) / (q\text{-}1) \quad (7)$$

where N is the number of EEG quantization states, and Pi is the probability of ith state. The parameter q is the measure of the extent to which the system of interest is non-extensive. Tsallis entropy has been calculated for each subject's each EEG channel by quantifying the amplitude (with q = 0.5 for the sake of definiteness). To intensify the differences between the entropy of Alzheimer's patients and healthy control, the entropy values have been normalized and standardized with scale range method,

$$S_{q_i} = \frac{[S_q - \min(S_q) \times [\max(S_q) - \min(S_q)]}{c} \quad (8)$$

here S_{qi} is the scaled value of S_q with ith state and C is a constant. Two reference feature vectors, one for AD patients and one for HC subjects have been created with the normalized Tsallis entropy. The feature vector for the new subject is calculated in a similar manner. That feature vector has been compared with the reference vectors to differentiate AD and HC. For the reported work two datasets (A & B) have been used by the authors [33]. The dataset A had 3 AD patients and 8 age-matched HC and the recording has been done with the traditional 10-20 system. The dataset B had 17 probable AD patients and 24 not perfectly age-matched HC and modified Maudsley system was used to record EEG. During EEG recording the subjects were at states such as awake, drowsy, alert, and hyperventilation with periodically closing and opening eyes. During development for creating reference vectors, dataset B was used. For testing, dataset A has been used. The results emphasized the regularity of AD patients' EEG compared to HC by showing low entropy value.

In recent years, a new technique, called I-FAST (Implicit Function as Squashing Time) has emerged in EEG analysis [50]. The extraction of the spatial content of EEG signal voltage has been done by IFAST using artificial neural network in [50]. The huge bi-dimensional matrix of EEG data can be compressed into a one-dimensional vector, keeping all the key information using I-FAST technique. Here squashing of a multivariate data sequence into a finite number of variables is done. I-FAST is composed of three steps: (1) squashing phase (2) noise elimination phase (3) classification phase. The EEG data of 180 AD patients and 115 MCI have been considered in this study by the authors. The recording has been done on patients with their eyes closed at resting state. I-FAST approach has shown to be able to distinguish between AD, and MCI in a blind manner with an accuracy of 92.33%. The brain never rests even when the subject is with closed eyes and relaxed. This study didn't consider the subjects' contingent characteristics like age, emotions, cognitive status, etc.

Principal Dynamic Modes (PDMs) [51] and their Associated Nonlinear Functions (ANF) [51] have been proposed for modelling the causal dynamic relationship between EEG time series of frontal and occipital regions of the brain [36]. These PDMs comprised of a linear filter bank {Lj}and the outputs of filter bank flow into a polynomial of multi-input static nonlinearity form to yield a general model for the large class of Volterra systems as shown in fig.6. The impulse responses {bj(m)} of the filter bank is in the form of discrete Laguerre expansion which form a basis for the Volterra system kernel. Here the concept of principal dynamic mode is used to expand the dynamics of the nonlinear biological system into Volterra model. Most significant modes of the system are extracted from the decomposition. ANFs are the static nonlinear functions which report the probable nonlinearities of the system. In this work [36] the occipital (O1 or O2) signal is taken as the input x(n) of the system and the frontal (F3 or F4) as the output y(n). 17 Alzheimer's patients and 24 healthy control constitute the data set.

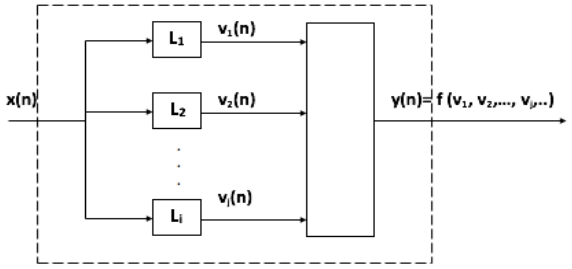

Fig. 6 The block structured model of discrete time Volterra class of systems. [36]

The EEG recording has been done with the international 10-20 system on subjects with their eyes closed at resting state. By modeling the nonlinear EEG system using the concept of PDMs, it has been found that a well diagnostic portrayal of Alzheimer's and normal person is possible with ANFs of two PDMs of O1 – F3 systems corresponding to alpha band and combination of theta and delta bands. The main drawbacks of

this work are the inadequate sample size to prove the clinical benefit of the method for the detection of AD, the average ages of the AD group and HC group are different and the case of doing some cognitive task during the test by the subjects is not included.

By assessing the brain connectivity, one can measure the integration of cerebral areas. Functional connectivity which is one of the subdivisions of brain connectivity can be defined as temporal correlation among the activity of different neural assemblies (distant brain regions) [52]. Perturbations in EEG synchrony is one of the major changes in EEG that have been reported in Alzheimer's disease [53]. An extensive study on methodological complications on inferring the functional connectivity with phase synchronization has been done in [17]. Phase synchronization is a nonlinear functional connectivity method, which measures the dynamics of an EEG signal. Phase synchronization is often found in high frequency (especially gamma frequency) large-scale oscillations that come into a precise phase-locking over a finite period of a cognitive task. Phase Locking Value is one of the representative methods which can be used to obtain the statistical measure of the phase synchronization strength in different brain areas.

Phase Locking Value (PLV) provides synchronization of large scale distance in EEG data for task-induced alterations in neural activity [19]. Since PLV cannot identify whether the signal came from a common source or from different sources, it is not a suitable tool for estimating the synchrony between signals observed at different points. Phase lag index measures the phase difference between two signals and can be used for signals from different points. Let a and b be two different points, and the PLI on signals between these points at time t_i can be obtained from,

$$PLI_{ab} = \left|\frac{1}{T}\sum_{i=1}^{T} \text{sign}\left(\Delta\Phi_{mod}(t_i)\right)\right| \quad (9)$$

$$\Delta\Phi_{mod}(t_i) = \Delta\Phi_{ab}(t_i) \bmod 2\pi \quad (10)$$

$$|\Delta\Phi_{ab}(t_i)| = |\Phi_a(t_i) - \Phi_b(t_i)| \leq \text{const.} \quad (11)$$

where Φ_a and Φ_b are the phase of signals at points a and b respectively [19]. PLIab $\approx$ 1 indicates moderate synchrony while PLIab $\approx$ 0 indicate randomness. PLI is less sensitive to common source effect (volume conduction) compared to similar phase synchronization indexes. Authors of reference [23] have considered 16 AD patients; 7 with MMSE >15 and 9 with MMSE $\leq$ 15, and 18 healthy control (HC) subjects. EEG data recording have been done with 18 channel system using 10-20 international standard. The subjects were at eyes-closed wakefulness state during the recording of EEG for 10-15mins. For the analysis, noise free epoch of continuous 60s have been extracted. For each subband of EEG, the PLI values were estimated. Their results demonstrated that AD patients show an increase in synchronization at alpha and theta waves compared to HC. But at beta and gamma waves HC group has high PLI value. At alpha, both AD and HC showed high correlation and it was highest at electrode pairs Fp2-T6 and P3-F7. Here the investigation has been done on a limited number of subjects, hence poor generalization ability on unseen subjects and did not incorporated the subjects' cognitive status.

As mentioned before, slowing of EEG is one of the consistent trademarks at different stages of Alzheimer's. In [54] the extent of slowing, by quantifying the changes in EEG amplitude in the time domain has been proposed by the authors as a biomarker of AD. The mean velocity of EEG is defined as the change in amplitudes over time and is given by,

$$M_c = \left(\sum_{1=1}^{N} \Delta EEG_A\right)/N \quad (12)$$

where

$$\Delta EEG_A = \frac{\sum \Delta x}{\Delta t} \quad (13)$$

Above equation determines the sum of differences between vicinal amplitudes EEG values per second. Two reference feature vectors have been created; one for AD and one for HC from the mean velocity values for all the channels. One feature vector is created for each new subject and to differentiate between AD and HC the Euclidean distance measure is used. Dataset A consists of 3 AD patients and 8 age-matched HC have been used for the development of reference feature vectors and dataset B consists of 17 probable AD and 24 not perfectly age-matched HC that were used in the testing phase. For each of the 21 channels, the p-values using t-test for Mc of both AD and HC have been calculated to determine the most significant channels to be employed to distinguish between AD and HC groups. It has been found that the minimum p-value is for PZ channel, followed by FZ, P4, CZ, F8, and T6. This was a clear illustration of the path of slowing of the brain activity due to AD, that is starting from the parietal lobe towards the frontal lobe and from right to left side. This study showed that AD patients have considerably lower mean velocity than normal people. Fewer dataset is the drawback of this study, hence this cannot be generalized for uncovered patients.

An Event Related Potential (ERP), Auditory mismatch negativity (aMMN) which appears mostly 100-200ms after a notable change in a sound sequence of repeated and deterministic nature, has been considered as an index of neuromodulatory deficit from MCI to AD in[55]. In the analysis, the Mismatch negativity (MMN) component was computed by measuring the mean amplitude of responses evoked by tones in the 150–180ms time window. In this experiment 19 AD patients, 12 amnestic MCI, and 18 age-matched HC took part. This investigation showed that at short (400ms) inter trail intervals aMMN evoked in AD at frontal locations and in MCI at temporal locations while in HC aMMN was elicited at both locations. At longer (4000ms) inter trail intervals only HC had aMMN and that too only at temporal locations.

Table 1 gives a comparison of different time domain based EEG biomarkers for the diagnosis of Alzheimer's disease. The various papers addressing the methods are discussed above and their respective results and challenges are tabulated below.

Table 1. Comparison of different Time domain methods of EEG analysis for AD diagnosis

References	Biomarkers used	Merits/ Results of the methods	Challenges
Zhenghui Hu and Pengcheng Shi [48]	ApEn	Effectively quantifies the regularity and complexity of EEG signal.	Computational complexity. Difficult to achieve proofs of asymptotic normality for ApEn
Gordon Morison. et, al. [31]	MSPE	Quantifies signal complexity at several differing time scales.	For smaller scales, no significant differences in EEG complexity between AD and HC.
Ali H Al-nuaimi. et, al [33]	Tsallis Entropy	Provides a basis for a real-time decision support tool and is computationally fast.	The smaller data set prevents it from generalizing on unseen subjects.
Buscema M. et, al [50]	IFAST	Distinguishes AD and MCI groups with an accuracy of 92.33% in a blind manner.	Ignored subjects' contingent characteristics.
Yue Kang. et, al. [36]	PDMS and their ANF	Focuses on the dynamic relationship between two EEG signals (at frontal and occipital lobes) and not the temporal or spectral structure of the signal themselves	Results are prone to various sources of noises. The average age of the two groups (AD and HC) were different.
Shinya Kasakawa. et, al. [23]	PLI	Shows an interdependence with MMSE score.	Poor generalization ability due to limited data size. Subjects' cognitive status were excluded.
Ali H. Al-nuaimi. et, al. [54]	M_c	Computationally fast. Reached 100% sensitivity.	Low data size

B. Frequency Domain Analysis

One of the methods to recognize the mental tasks starting from EEG signal is the feature extraction in frequency domain. The features extracted can be used to classify AD patients and healthy controls. Absolute and relative spectral power, distribution of spectral power, and measures of spatial synchronization are some of the spectral domain biomarkers which have been used to discriminate AD, MCI and healthy control groups.

The EEG biomarkers used in [56] are absolute spectral power, relative spectral power, distribution of spectral power and spatial synchronization indexes. Absolute spectral amplitude as a function of frequency has been used as an EEG biomarker for AD after applying FFT to EEG for frequency transformation. Relative spectral amplitude is the ratio of absolute spectral amplitude and sum of absolute spectral amplitudes in frequency band from 1.5-30 Hz. By estimating the locations of centroid (point of gravity) of spectral amplitude on a two-dimensional schematic electrode grid, the spatial distribution of spectral amplitude has been established. The biomarkers have been calculated from EEG signals of 197 (116 mild and 81 moderate) AD patients, 45 healthy control who were in eyes-closed resting state. The recording has been implemented with 19 electrode10-20 system. All these above-mentioned EEG features have been used as input for different classification algorithms such as, principal component linear discriminant analysis, partial least square linear discriminant analysis, principal component logistic regression, partial least square logistic regression, bagging, random forest, support vector machines, feed-forward neural network by authors of [56]. Even though some exhaustive modern computer-intensive classification algorithms slightly outperform these classifiers, they performed remarkably well. And the absolute and relative EEG power have been reported to be altered in AD patients, where the most prominent change is the increase of theta power in AD.

Measurement of linear functional connectivity in the frequency domain is made possible by the use of Magnitude Squared Coherence (MSC) or simply coherence in [16]. Coherence quantifies the spatial correlation among signals to be measured in different frequency bands [57]. The most commonly used linear synchronization methods are cross-correlation in time domain and MSC in frequency domain. MSC or simply coherence is calculated as the cross spectral density P_{xy} normalized by their autospectral density functions. Spectral density function is derived via frequency transformation of cross-correlation function. Let P_{xy}, P_{xx}, and P_{yy} represent the cross spectral density of x and y, power spectral density of x and power spectral density of y respectively. Then the coherence between x and y is given by

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \quad (14)$$

The estimated coherence value for a given frequency ranges from 0 (no interdependence) to 1 (maximum linear coupling). In [16] for a 16-channel bipolar montage, 18 channel pairs were selected which represent fiber pathways. The coherence has been calculated for those channel pairs and averaged over the following 6 frequency bands of equal width: 0.5 – 4 Hz, 4 - 8 Hz, 8 -12 Hz, 12 – 16 Hz, 16 – 20Hz, 20 – 24 Hz. The connectivity of fiber tracts corresponding to each channel pair can be quantified with the coherence. The coherence values across the groups of AD, MCI and HC were compared and the channel pair which shows a remarkable difference between MCI, AD and HC were determined here. An EID (enhanced-intact-damaged) model has been formed with the list of overall coherences for AD and MCI groups compared to HC, which can provide a quantitative, qualitative and graphical model of the brain connection attributes of Alzheimer's disease. 16 AD

patients, 24 MCI patients, and 16 age-matched healthy controls participated in this study. 10-20 system was used for the recording of eyes-closed resting state subjects. Any alteration in EEG coherence whether increased or decreased relative to HC was found to be a consequence of fiber damage. From the results, it has been concluded that more damaged pathways were found in AD patients' brain than MCI but both groups possess similar area of damage.

The functional synchronization of EEG data in frequency domain has been estimated by Global Field Synchronization (GFS) in [58]. Unlike coherence, GFS doesn't make any supposition on the spatial location of the activity. Global field synchronization measures the relative phase synchrony over all the electrodes at a specified frequency [59]. The calculation process of GFS consists of mainly 4 steps: (1) Compute the Fourier transform of the EEG signals and move apart the real and imaginary parts of the coefficients. (2) Concatenate all the real parts and imaginary parts of the coefficients into two columns. (3) Compute the covariance matrix of size 2x2 and calculating 2 Eigen values. (4) Global field synchronization is defined as

$$\frac{|E(f)_1 - E(f)_2|}{E(f)_1 + E(f)_2} \quad (15)$$

where $E(f)_1$ and $E(f)_2$ are the two Eigen values at the given frequency f. 22 Alzheimer's patients and 23 healthy control have taken part in the testing, whose potential at 18 scalp locations have been recorded with 10-20 system. The subjects were asked to open and close their eyes periodically for 10mins in resting condition. It has been seen that the GFS values of AD patients in beta1(13-18 Hz), beta2 (19-21 Hz), beta3 (22-30 Hz), and full bands (1-70 Hz) are lower than of HC. There has been a positive correlation between MMSE scores and GFS values in alpha, beta1, beta2, beta3, and full bands.

The paper [60] discusses the relation between EEG synchrony markers and severity levels of Alzheimer's disease. In this work, the EEG synchrony markers have been derived from the spectral density and information theory and investigation done on the correlation of these markers with MMSE score, was used to perceive the severity level of the disease. The spectral density of multivariate EEG signal (x(t)) over the frequency range, $\lambda \in [-\pi, \pi]$ can be obtained from,

$$f(\lambda) = \frac{1}{2\pi} \sum_{s=-\infty}^{\infty} e^{-\lambda s} \gamma(s) \quad (16)$$

where, $\gamma(s)$ is the covariance function of (x(t)) defines as $\gamma(s) = \mathbb{E}x(t+s)\,x(t)'$ with a time lag $s \in Z$. Instead of analyzing the synchrony between each EEG channels, the channels are grouped into clusters and the synchrony between the clusters are analyzed. As a first step to that, the overall EEG channels have arranged into five clusters, viz. anterior (Fp1, Fp2, F3, F4), temporal/left (F7, T7, P7), central (Fz, C3, Cz, C4, Pz), Temporal/right (F8, T8, P8), and posterior (P3, P4, O1, O2). The principal component analysis (PCA) has been done on each cluster. Since first two principal components (PCs) together can represent 90% of the information in the respective channel data, the synchrony investigation has been done between first two PCs of one cluster and the first two PCs of another cluster. And the third step was to maximize the correlation between MMSE score and synchrony biomarker in terms of coefficients of determination R2. 8 synchrony markers have been analyzed in this work.

1. Coherence, $C_{ij} = \frac{|f_{ij}(\lambda)|^2}{f_{ii}(\lambda) f_{jj}(\lambda)}$
2. Partial coherence, $pC_{ij}(\lambda) = \frac{|g_{ij}(\lambda)|^2}{g_{ii}(\lambda) g_{jj}(\lambda)}$; $g = f^{-1}$
3. Phase shift, $\Phi_{ij}(\lambda) = phase\ of\ f_{ij}(\lambda)$
4. Granger causality (G): to find the direction of dependence between EEG channels.
5. Conditional Granger causality (cG)
6. Canonical correlation (ρ^c): provides the information of dependence between multivariate processes (EEG signals)
7. Dynamic canonical correlation ($d\rho^c$): coefficients are defined as the maximum correlation $\sum_s a_i\,(t\text{-}s)\,'x_I(t)$ and $\sum_s b_i\,(t\text{-}s)\,'x_J(t)$; $a_i, x_I(t) \in \mathbb{R}^p$ and $b_i x_J(t) \in \mathbb{R}^q$
8. Cross mutual information, $\mathrm{cMI}(X, Y) = \sum_{x,y} P_{XY}(x,y) \log_2 \frac{P_{XY}(x,y)}{P_X(x) P_Y(y)}$; x and y are the observations of discrete random variables X and Y with joint probability distribution P_{XY} and marginal probability distributions of P_x and P_y respectively.

EEG recording has been done on 79 subjects with probable AD in resting state and during a cognitive task. The results showed that EEG synchrony of most of the biomarkers (C, ρ^c, $\Phi_{ij}(\lambda)$, cG, $d\rho^c$, cMI) increases with MMSE score from 26 till 20 and below that it decreases and the effect is most evident during cognitive tasks. At resting phase, significant results were obtained between the anterior-temporal and posterior-temporal regions whereas during cognitive phase most prominent results were between anterior-central, central-posterior and central-temporal sites. The authors have considered the patients' demographic variables like, age, sex education level and AD duration to improve analysis. It has been observed that age and level of education have significant influence on MMSE score.

Various papers addressing frequency domain based EEG biomarkers for the diagnosis of Alzheimer's disease are discussed above and their relevant results and challenges are tabulated in table 2.

C. Time – Frequency Domain Analysis

Time - Frequency analysis preserves the time and frequency information of non-stationary signals. Researches are being conducted on amplitude modulation analysis of EEG for AD diagnosis [40]. Due to impaired cerebral flow in AD, a neuromodulatory decline may exist. In [40], primary step done was to measure the rate at which subband EEG amplitude modulations change over short periods of time and then compare such spectro-temporal signal representations between AD and healthy control.

Table 2. Comparison of different Frequency domain methods of EEG analysis for AD diagnosis

References	Biomarkers used	Merits/ Results of the methods	Challenges
Christoph Lehmann. et, al. [56]	Absolute & relative spectral power, distribution of spectral power, and spatial synchronization measures.	Determines optimal statistical classification algorithm for differentiating between different stages of the disease with remarkable sensitivity and specificity.	Not considered subjects cognitive status.
Kwaku Akrofi. et, al. [16]	Coherence	Adequately quantifies the connectivity of fiber tracts. EID model yields a quantitative and qualitative illustrative model of the brain connection characteristics of the Alzheimer's disease.	Coherence is subject to both change in phase and change in power relation. Usage of 16 channel system and limited data size.
Young-Min Park. et, al. [58]	GFS	The difference in GFS values between AD and HC can effectively delineate the severity of AD.	Considered only resting state EEG of subjects. The limited ability of MMSE score to evaluate AD severity. Not incorporated the possible effects of psychotropic drugs taken by the subjects.
Markus Waser. et, al. [60]	Multiple synchrony markers	AD severity can be assessed with the synchrony markers used. To improve the robustness, clusters of EEG channels are considered for synchrony analysis. Usage of quadratic regression. Incorporating demographic co-variables could improve the performance.	Synchrony markers used showed non-monotonic trends with decreasing MMSE score. Sensitivity and specificity obtained for the classifier based on combination of all markers were not satisfying. The relations obtained for overall patient groups were not strong enough to be used as a separate criterion for individual diagnosis.

Dataset consists of a total of 32 subjects which include 3 groups MCI, AD, and HC. EEG recording was performed with subjects in awaken state followed by resting state with closed eyes using 10-20 system. The percentage modulation energy (PME) which is given by,

$$PME_{i,j} = \frac{\bar{\varepsilon}_{i,j}}{\sum_{i=1}^{5}\sum_{j=}^{4}\bar{\varepsilon}_{i,j}} \times 100\% \quad (17)$$

is calculated for each signal. After computing the temporal envelope of each subband, modulation band decomposition has been performed on these envelopes. $\bar{\varepsilon}_{i,j}$ represents the average modulation energy of the ith subband signal which is grouped by the jth modulation filter. The authors in [40] listed out top 35 principal PME features in their ranking order. It has been found that percentage modulation energy features extracted from theta and beta frequency bands could effectively discriminate AD vs HC. The proposed analysis also allows direct characterization of EEG cross-frequency interaction effects and their changes with AD. The observations showed that the theta-beta interaction is reduced with AD.

In [61] the feature used in time-frequency domain is the sparse oscillatory events extracted from EEG signals, for the diagnosis. A model has been used for extracting the oscillatory events in EEG called the sparse bump model [62] which consists of high magnitude time-frequency bumps (patterns). It conveys the information on cognitive and sensory processing by representing the transient synchronization of neuronal groups. Here the Morlet mother wavelet has been used to represent the EEG signals in time-frequency domain. Time-frequency domain relative power of each of the frequency bands, viz. theta, alpha1, alpha2, and beta, were computed after computing the wavelet coefficients. Generally, the oscillatory events (bumps) are assumed to be due to the local synchrony of neuronal groups seen in the vicinity of recording electrode. The bumps can be extracted with sparse bump modeling. After applying wavelet transform, the z score normalization has been done on each trail as,

$$z(f,t) = \frac{W(f,t)-\mu_f}{\sigma_f} \quad (18)$$

where W(f,t), μ_f and σ_f are the complex Morlet wavelet coefficient, mean and standard deviation of the wavelet map W respectively. The bump models are approximated from the normalized z-score maps z(f,t) as mentioned below,

$$z(f,t) \approx z_{bump}(\theta) = \sum_{k=1}^{N_b} b(\theta_k) \quad (19)$$

where b is the ellipsoid basis function with parameter $\theta_k; k = 1,2,..,N_b$. The number of bumps and two sets of relative powers for each frequency band were computed; one before bump process and one after bump process. Figure 7 shows the mapping from wavelet time-frequency representation to sparse bump model. The subject group consists of 25 MCI with MMSE 26 and 56 HC with MMSE 28.5. The recording has been done with 21 electrodes using 10-20 system during the phase when the subjects were at resting state with their eyes closed. It has been seen that AD patients show strong low frequency (0.5 – 8 Hz) activity. The bump modeling has amplified this effect of AD on EEG. The increase in theta band activity has been taken as a feature for discriminating AD and HC subjects.

As has been mentioned earlier that AD impairs cognitive memory, Ghorbanion et al. conducted an experiment based on

it to examine the impacts. EEG recording started with resting conditions with eyes closed initially and then open followed by states of attention, identification, card flipping cognitive tasks, Paced Auditory Serial Addition Test (PASAT) and finally auditory stimulations. They again measured EEG in eyes open and closed condition to conclude the session. Each of these tasks has been explained in [63]. Dataset used consists of a total of 24 subjects out of which 10 have AD and 14 are normal age matched subjects. DWT has been used to divide the signal into its sub-bands. For this the mother wavelet used is Daubechis2 and at each sub level statistical parameters like mean, median, etc. are calculated using the wavelet coefficients. Two tests namely t-test and Kruskal-Wallis [64] test have been used to identify statistical features that can help in significant distinction between AD and controls. Also, to judge the dominant feature, Decision tree algorithm was used. The t-test is a statistical examination for which data needs to follow a Gaussian or normal distribution which was not the case with the dataset used thus they shifted to a non-parametric chi-square based test called Kruskal-Wallis test. The final outcome was that mean values of delta, beta bands and standard deviation of theta band was found to be more for AD patients compared to normal.

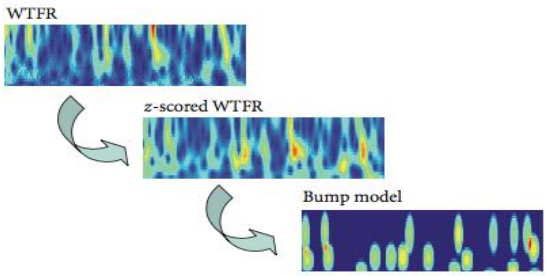

Fig. 7 Mapping from wavelet time frequency representation (WTFR) to sparse time frequency bump model [60].

Neurophysiological correlation has been proposed as a biomarker for detecting MCI using group Independent Component Analysis (gICA) in [65]. EEG data is decomposed using group Independent Component Analysis (gICA) [66] and the neuronal components were analyzed using Phase Intertrail Coherence (PIC) and Phase shift Intertrail Coherence (PsIC). Independent component analysis (ICA) estimates the maximally independent and non-Gaussian components of a mixture of signals. Each electrode in EEG measures the weighted sum of electrical activity of many brain areas. ICA enables the identification of underlying component signals and the sources associated in the data. The model can be expressed as,

$$x = As \quad (20)$$

where x is the recorded signal, A is the mixing matrix and s denotes the number of independent source signals. The study has been conducted on several sets of data. x is measured for different subjects under different experimental conditions. Hence gICA has been used for analyzing a group of subjects. The neuronal components thus obtained were analyzed with PIC and PsIC. The phase locked activity of trails in an Event Related Potential (ERP) can be quantified with PIC measure [66]. The phase and non-phase activity of the events can be captured with PsIC measure [67]. The PIC and PsIC are defined as,

$$\mathrm{PIC} = \left|\frac{\sum_i X_i[k,n]}{\sum_i |X_i[k,n]|}\right| \leq 1 \quad (21)$$

$$\mathrm{PsIC} = \frac{[\sum_i |X_i[k,n]|^2]}{\max_{k,n}[\sum_i |X_i[k,n]|^2]} \leq 1 \quad (22)$$

where i is the number of trials, X denotes the coefficients obtained using a complex wavelet transform, n is the point of time and k is the frequency value. The data subject consists of a group of 12 MCI and another group of 12 age-matched HC. The gICA was performed on each group. It has been shown that there is an increase of PIC in theta band of MCI patients and an increase in PsIC in alpha band of healthy control. The main pitfall in this research is the limited number of subjects which has been considered for analyzing and concluding, thus it is difficult to generalize the result and apply on unseen subjects.

In table 3, the various EEG analysis techniques for the diagnosis of Alzheimer's in time-frequency domain are tabulated with their merits and challenges.

III. Summary And Conclusion

The constant increase in rate and inability to treat the AD has created a great concern especially in developed countries. Hence there is a need to do in-depth research for the advancement of biomarkers to help towards early detection of AD so that its progression can be slowed down. Neuroimaging techniques show precisely how people suffering from Alzheimer's have a smaller brain compared to the normal ones, due to the shrinkage of the hippocampus. But its high cost and radiation risks make it less feasible to be used. Also, MMSE and MEG are equally efficient, but only these tests cannot confirm the prevalence of the disease. Thus, the feasible option left is methods based on low cost EEG. Several features of EEG like PSD distribution, coherence, mean velocity etc help in distinguishing MCI, HC and AD. Equally important are the information theory parameters like entropy.

Several signal processing steps that need to be performed on EEG signals include preprocessing, feature extraction and feature classification. Time frequency tools of feature extraction have become most effective because of their ability to analyse signal in both domains thus unshielding features that remain hidden when only time or frequency domain tools are used.

Wavelet transforms among linear TFDs, and Wiener distribution and Spectrogram among quadratic, prove to be the most efficient ones for non-periodic signals like EEG. ANN and SVM form an important part of EEG classifiers which can differentiate between normal, MCI and AD patients. An efficient diagnostic portrayal of AD and normal people can be achieved using ANS and PDM. Tsallis method was used to calculate entropy which gave lower value for HC compared to AD, thus showing more regularity in the EEG signals of AD.

Table 3. Comparison of different Time-Frequency domain based EEG analysis for AD diagnosis

References	Biomarkers used	Merits/ Results of the methods	Challenges
Tiago H Falk. et, al. [40]	PME features	Provides a spectro-temporal semi-automated diagnostic tool for AD. A classifier trained on PME features outperforms those trained on spectral peak parameters.	Limited dataset leading to poor generalization ability. Artefact removal and its effect on PME features are not considered
Francois-B. Vialatte. et, al. [61]	Sparse oscillatory events	The bump modeling magnified the statistical differences in theta band activity between HC and MCI patients with a maximal specificity.	The bump modeling has limits in lower frequency bands. Choosing the bump model should be done carefully, otherwise, background noise could be modelled instead of bump bursts.
Ghorbani on. et, al [63]	Statistical parameters of WT coefficients	Amount of data to deal with is efficiently reduced to few wavelet coefficients which make it easier to analyze. Signals can be localized in both time and frequency domains simultaneously.	Determination of the suitable type of wavelet and the number of levels of decomposition to be performed for a particular study is challenging. Can be computationally cumbersome for fine analysis.
John F. Ochoa. Et, al. [66]	PIC & PsIC	Shows a proportional relationship with MMSE score.	Inadequate data size. Strategies not included to quantify specificity and sensitivity.

Latest time domain method named I-FAST enabled differentiating AD and MCI with an accuracy of 92.33%.

Combining EEG markers that capture the change in signal complexity, synchrony and frequency content and relating them with neuropsychological assessments of AD severity could yield a remarkable tool for early detection of Alzheimer's disease. We have simulated some of these reported works such as Tsallis entropy analysis, mean velocity of EEG, etc. using the data obtained from the TUH EEG Corpus [68]. It has been found that the results obtained were agreeing well with the results published in [32], [33] and [54].

Several other methods like gICA, PIC, aMMN etc. helps to differentiate between AD, MCI and HC.

All the different methods of EEG signal analysis for the detection of Alzheimer's disease are summarized in table 4 shown below along with the observations from each of these works.

Table 4. Summary of effects of AD on EEG signal analysis

Domain	Method	Biomarker/Feature	Effect of AD in EEG / Remarks
Time	Information theory analysis	Approximate entropy Multiscale entropy Tsallis entropy	Low entropy values for AD
	Principal dynamic mode	Associated nonlinear functions of PDMs of O1-F3 system.	ANFs of PDMs corresponding to alpha band and combination of theta and delta bands have much deviated from that of HC.
	Phase synchronization analysis	Phase lag index	At alpha and theta bands: PLIAD > PLIHC At beta and gamma bands: PLIAD < PLIHC
	EEG amplitude analysis	EEG mean velocity (Mc)	Reduced mean velocity for AD
	Event related analysis	Auditory mismatch negativity (aMMN)	AD at short inter trial intervals: aMMN at frontal locations MCI at short inter trial intervals: aMMN at temporal locations HC at short inter trail intervals: aMMN at both locations At long inter trail intervals: only HC had aMMN
Frequency	FFT	Spectral power	Increased theta power in AD
	Spectral synchrony analysis	Coherence between channel pairs which represent fiber pathways	More damaged pathways for AD
	Functional Synchronization analysis	Global field synchronization (GFS)	GFS values in AD at beta1, beta2, beta3 and full band are lower than that of HC
Time-Frequency	Amplitude Modulation Analysis	Percentage modulation energy (PME)	PME features from theta and beta frequency bands showed a significant difference from normal. Reduced theta-beta interaction in AD.
	Sparse Bump model	Sparse oscillatory events	Increased EEG power in theta range
	Wavelet transform	Statistical parameters – Mean and Standard deviation of coefficients	Increase in mean values of delta, beta bands and standard deviation of theta band.
	Complex Wavelet Transforms.	Phase Intertrail Coherence (PIC) in theta band and Phase Shift Intertrail Coherence (PsIC) in alpha band	PICAD > PICHC PsICAD< PsICHC

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