Clinical Neurophysiological and Automated EEG-Based Diagnosis of the Alzheimer's Disease

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Key Words

Alzheimer's · Plaques · Tangles · Donepezil · Apraxia · Neurodegeneration · Aphasia

Abstract

Alzheimer's disease (AD) is a progressive disorder affecting intellectual, behavioral and functional abilities. It is associated with age and pathological alterations leading to the formation of amyloid plaques and tangles. It is the most common source of dementia in the older population, which varies in its degrees of severity. We are yet to find efficient methods of diagnosis of AD, as its symptoms vary among individuals. This paper presents a review of recent research on the clinical neurophysiological and automated electroencephalography-based diagnosis of the AD. Various therapeutic measures are also discussed briefly.

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Introduction

Senescence is defined as the normal aging process where the human body undergoes several physiological changes. It affects cognition, thought process, learning

ability, and emotions and reduces the tempo of one's daily activities. Aging is not pathology but a normal physiological change leading to memory disorders. Dementia is a neurological disorder characterized by memory, language and cognitive impairment and loss in behavioral abilities. It is caused by brain cell death and worsens with age but is not linked to the typical aging process [1, 2]. Other potential causes of dementia are head injury, brain tumor, stroke, cerebral nervous system infection, vitamin deficiency, alcohol, exposure to heavy metals, and so on. Alzheimer's disease (AD) is the common basis of dementia in the elderly population [3].

AD is a progressive brain cell death and an irreversible process that happens over a course of time resulting in memory loss, inability to learn new things and perform calculations, unbalanced perception of space, depression, delusions and cognitive decline. These impairments hamper patients' social functioning and behavioral abilities [4, 5]. Cera et al. [6] studied the effect of AD on different cognitive functions such as orientation, language, attention, praxis, visual perception and executive function. They report that severity of language impairment and orofacial apraxias in the individuals with AD is directly proportional to the gradual progression of AD. The clinical features of AD are summarized in table 1.

Table 1. Main features of AD [98–100]

Clinical features of AD	
Memory deficit	Learning disability
Aphasia	Language impairment affecting speech and information processing
Apraxia	Motor disorder
Agnosia	Inability to recognize and identify people or objects

Table 2. Different stages of AD [18]

Stages of AD	Symptoms of AD
Mild AD	Memory loss, poor judgment Mood swings, repetitive questions Difficulty in doing mathematical calculations
Moderate AD	Unable to learn new things Difficulty in recognizing family members and friends Possesses hallucinations, delusions, paranoia and impulsive behavior
Severe AD	Dependent and bedridden

AD is the sixth leading cause of death in the United States [7]. Patients die due to fall, malnutrition, dehydration, traumatic brain injury, and complications such as ab-ingestis pneumonia, pneumonia, bladder infection, and diabetes. AD often becomes fatal within 10 years of its commencement. According to the Alzheimer's Association, 13% of people over 65 years and 45% of people over 85 years have AD [8]. Some of the potential risk factors associated with AD are age, inheriting apolipoprotein E (APOE) gene [9] and sleep apnea [10–12]. Females are more prone to AD than males. AD progresses in prevalence after the age of 65. Prevalence rate increases by 2-fold every 5 years between the ages of 65 and 95. It rises from ~2% in those aged 65–69, 4% in 70–74, 8% in 75–79, 16% in 80–85 and ~35–40% over the age of 85 [13]. Neuro-researchers are trying to analyze possible age-related changes in the AD brain. Some of these changes include inflammation of the brain, atrophy, mitochondrial dysfunction and production of unstable molecules in the brain [13]. AD can also be inherited. Individuals with primary relative having AD show a 3–4-fold increase in AD risk and it increases to a fold of 7.5 in individuals who have two or more primary relatives with AD [14].

Early onset of AD is seen in people between 30 and 60 years of age due to inherited genes in an autosomal-dominant manner [15, 16]. The younger population with early-onset AD possesses a distinct cognitive profile reflecting different distribution of underlying neuropathology [17]. Ossenkoppele et al. [17] observed that increased amyloid-beta ($A\beta$) deposition in the parietal lobe and metabolic dysfunction contribute to the distinct cognitive profile of patient's with AD.

AD is broadly classified into 3 stages [18] listed in table 2. AD commences with signs of mild cognitive impairment (MCI) [19]. Individuals with MCI have significantly high memory loss compared to individuals with normal aging but possess normal behavioral abilities. As AD progresses, memory loss worsens and leads to mild AD characterized by poor judgmental ability, emotionally disturbed mind frame and inability to perform simple calculations [18].

Moderate AD is the second stage of AD where sensory processing and conscious thought process are hampered. Individuals with moderate AD experience hallucinations, delusions, paranoia and impulsive behavior are unable to recognize their kith and kin. The third stage of AD leads to severe symptoms resulting in cognition impairment, behavioral disabilities and atrophy when the patient becomes completely dependent on others [18].

After the detection of early symptoms of AD (mild AD) as indicated in table 2, a neurologist conducts a physical examination and differential diagnosis in order to dismiss other potential diseases or neurological disorders [7, 13]. These examinations include thyroid and vitamin B12 deficiency tests. After ascertaining that the memory loss is not due to hormonal deficiencies, clinicians recommend the brain-imaging technique. Generally, CT and MRI are used to identify the structural changes in the brain [7, 13]. Single photon emission computerized tomography and photon emission tomography (PET) can detect activities like blood flow or metabolism in the brain. In recent years, researchers have attempted to develop computer algorithms for automated electroencephalography (EEG)-based diagnosis of the AD and their precision for detection of AD is being evaluated [4, 10, 38, 75, 76].

Section 2 provides a brief overview of the pathology of AD. Section 3 describes the layout of this review, which is the latest research on the early diagnosis of AD including the application of the EEG signal analysis. Various therapeutic measures are discussed in Section 4. Section 5 concludes the paper.

Fig. 1. Pathological alterations resulting in the formation of plaques and tangles.

Pathology and Pathogenesis of AD

The main pathological alterations observed in the AD brain are neuritic plaques and neurofibrillary tangles (fig. 1). They are tiny inclusions, abnormal protein clumps found in the AD brain tissue during autopsy. Plaques are formed by the accumulation of a protein called beta-amyloid between the dying brain cells. These plaques are globular microscopic lesions composed of extracellular A β in the core surrounded by degenerating axonal endings. The degeneration of a protein called tau gives rise to tangles that are fibrillary, cytoplasmatic structures within the neurons [20–23]. Neuropil threads, amyloid angiopathy and granulovacuolar degeneration are some of the pathological features observed in the AD brain [5].

Bie et al. [24] found that amyloid-induced neuroinflammation leads to epigenetic suppression [25] of NLGN1 (neuroligin1) expression and microglia-mediated inflammation may advance the activity of transcriptional receptors damaging central glutamatergic synapses and memory in the brain. Lunnon et al. [26] analyzed methylomic variation in AD using samples from four human postmortem brain cohorts. They observed differentially methylated region in the ANK1 (ankyrin1) gene

[27] associated with the superior temporal gyrus and pre-frontal cortex (entorhinal cortex), a primary symptom of AD.

Abnormal protein deposition spreads to hippocampus leading to memory loss. As more neurons die, the brain regions shrink, resulting in atrophy. The progression of neuronal vulnerability is related to the morphological and biochemical characteristics of AD. The number of nerve cells in the brain tissue progressively decreases and the neuronal connectivity weakens [28]. The total brain size shrinks due to the degeneration of nerve cells [29].

Neurodegeneration of hippocampus and the variation of resting eyes-closed EEG signals are major features observed in MCI and AD [30]. The progressive atrophy of hippocampus is also correlated with the reduction of cortical alpha power [30]. Migliaccio et al. [31] mapped the succession of gray matter atrophy in early-onset AD and late-onset AD. MRI scans of patients who met AD criterion and who showed AD symptoms before the age of 65 were obtained. Voxel and tensor-based morphometry [32] is used for diagnosis. They reported that medial temporal or lateral neocortical regions underwent atrophy in the beginning and AD progressed to medial parietal cortices and medial precuneus regions in the later stage.

Madeira et al. [33] measured D-serine levels in the postmortem hippocampal, cortical samples and cerebrospinal fluid (CSF) from the control group and subjects with AD. They observed difference in the brain and CSF D-serine levels of AD and control group. D-Serine levels in parietal cortex, hippocampus and CSF were higher in individuals with AD than the control group. Some of the neurochemical changes associated with AD are reduction in cholinergic activity, insufficiency in glutamate, serotonin, somatostatin, norepinephrine, and corticotrophin-releasing factors [34].

Neuroglial cells are a group of heterogeneous cells responsible for neuroprotection and defense against exogenous and endogenous entities. At the onset of neurodegenerative disorders, neuroglial cells become asthenic and lose their neuroprotective, defensive and homeostatic capabilities. It is found that paralytic neuroglial cells are responsible for the progression of AD [35].

Goll et al. [36] demonstrated that auditory scene analysis is susceptible to the neurodegenerative process in AD. Auditory scene analysis describes the processing of vocal and non-vocal sounds. Neuroanatomical changes in auditory scene analysis are identified in posterior cortical areas. They found that AD is linked to the primary and generic disruption of the auditory scene analysis.

Clinical Neurophysiological Diagnosis of AD

In preclinical AD, the pathology of AD represents an insidious process that starts years before the occurrence of clinical manifestations. Early diagnosis of AD and need for its biomarkers becomes challenging because of the delay between the pathological and behavioral symptoms [21, 37]. Neurologists, neuro-scientists and neuro-researchers are all involved in the Alzheimer's research [38, 39] for its early intervention, to predict the rate of cognitive decline and to measure the impact of drug treatments.

Mattsson et al. [40] studied the correlation between CSF and PET A β in AD. They observe that reduction in CSF and increase in PET A β is strongly related to early-stage AD and the disease progression respectively. Hence, they concluded that these parameters can be considered the biomarkers of AD.

Using PET for diagnosis of AD, Viola et al. [41] found that A β oligomers are responsible for memory loss in patients with AD. The oligomer-specific antibodies, binding to A β oligomers, are induced into brain tissues and cells. They can generate MRI signals that help in identify-

ing the early-stage AD. The magnetic nanostructures targeting neurotoxic A β oligomers can also provide feedback on the effects of antioxidants.

Moyse et al. [42] study the concept of perception processing in social cognition among AD patients. They evaluated the impairment of facial-age estimation in patients with mild and moderate AD. They observed individuals with mild AD-faced difficulties in estimating the age of middle-aged adults, whereas individuals with moderate AD had difficulties in calculating the age of young adults. However, it is surprising to find individuals with AD accurately assessing the age of older adult faces compared to the control group.

Oleson and Murphy [43] reported ApoE ϵ 4 gene as the major risk factor of AD associated with olfactory and cognitive deficits. Individuals carrying more than one allele of ApoE gene (ϵ 4/4) are at greater risk of developing AD. Olfactory functioning was examined in homozygous ϵ 4/4 adults with probable AD. These individuals showed deficits in odor memory and identification compared to individuals with heterogeneous ϵ 3/4 ApoE carriers. Thus, the odor tasks may prove to be helpful in the early diagnosis of AD.

Lopez-de-Ipina et al. [44] discuss a noninvasive methodology for early diagnosis of AD based on speech analysis and emotional temperature. Speech features such as spontaneous speech and emotional response are extracted from the suspected AD patients. Machine learning algorithms [45–47] are applied to the significant features, and the severity of AD is evaluated.

EEG-Based Diagnosis of AD

The advent of neuroimaging techniques such as EEG [48, 49], magnetoencephalography [19, 50], MRI [51, 52], functional MRI (fMRI) [53, 54], structural MRI (sMRI) have increased the study of cognitive neuroscience. They facilitate the noninvasive research of human brain mechanism and study of its complex connectivity [55, 56]. MRI and fMRI [57], however, are costly and not clinically valuable at the onset of AD. On the other hand, EEG is a non-invasive and cost-effective technique with a potential to detect AD in its early stages.

The EEG signals are highly nonlinear in nature. Variation in the EEG signals cannot be deciphered by mere ocular assessment. Earlier, Smith [58] reported that EEG signals are normal during the early stage of AD, but as the disease progresses, alpha waves disappear and slow waves become more apparent. In some cases, periodic sharp

waves are also visible but minute variations occurring in the EEG signals during the early onset of AD remains undetermined. Computer-aided diagnostic tools can be used to identify the subtle variations in the EEG signals [59–61]. Time-domain, frequency domain, time-frequency analysis [62, 63] and nonlinear methods can be used to analyze the EEG signals. In recent years, Adeli and associates [48, 64, 65] have advanced the idea that adroit integration of three computing paradigms, time-frequency signal processing [66–68], chaos theory and nonlinear methods [69, 70], and pattern recognition techniques such as artificial neural networks [71–73] is the best approach to analyze nonstationary and highly chaotic signals. Significant features can be extracted by nonlinear dynamics and classified using different data-mining techniques and neural networks [74].

Adeli et al. [75] presented a review of research on computational modeling of AD employing computer imaging, classification models, connectionist neural models, and biophysical neural models up to 2005. Adeli et al. [76] summarized the early efforts on the use of EEG for diagnosis of AD. Adeli et al. [62] present a spatiotemporal wavelet-chaos methodology for analysis of EEGs and their delta, theta, alpha, and beta sub-bands for the purpose of discovering potential markers of AD. The nonlinear dynamics of the EEG and EEG sub-bands are quantified employing the correlation dimension representing system complexity, and the largest Lyapunov exponent representing system chaoticity. They report potential markers for the diagnosis of AD using a sample of 20 subjects diagnosed with probable AD and 7 controls.

Dauwels et al. [77] report that slowing of the EEG in patients with AD, reduced complexity [78], and perturbations in EEG synchrony [79] are the major effects in Alzheimer's EEG signals. Trambaiolli et al. [80] apply support vector machine (SVM) [81] to identify significant patterns in Alzheimer's and normal EEG epochs. A quantitative EEG-processing method is used to differentiate between AD and normal patients. A classification accuracy of 87% and sensitivity of 91.7% is obtained using SVM.

Sankari et al. [82] investigate interhemispheric, intrahemispheric and distal coherence in individuals with AD. The EEG electrode coherence is computed over all the frequency bands. An increase in the characteristic pattern of the left intrahemispheric frontal coherence in the alpha, theta, delta frequency bands, left intrahemispheric temporo-parietal coherence in all bands and a decrease in the right temporo-parieto-central coherence in all bands is observed in patients with AD, whereas an increase in

left temporo-parietal, temporo-central and frontal coherence in specific bands implied progression of AD leading to loss of memory and cognitive decline.

Using the concept of fractality dimension (FD) Ahmadlou et al. [63] present a wavelet-chaos methodology for EEG-based diagnosis of AD. They determine the most discriminative FD and the corresponding loci and EEG sub-bands for discriminating between AD and healthy subjects. They report an accuracy of 99.3% for diagnosis of the AD based on Katz FD using a sample of 20 subjects diagnosed with probable AD and 7 controls.

Yang et al. [83] applied multiscale entropy (MSE) [84] to identify the variations in the AD EEG signals. Consistency of MSE measures in different EEG epochs and their correlation to cognitive and neuropsychiatric symptoms is assessed. They report that decreased MSE complexity measured by short-time scales and increased MSE complexity measured by long-time scales are associated with increased severity of AD, and the MSE complexity of temporal and occipitoparietal regions is related to cognitive and neuropsychiatric manifestations. Al-Jumeily et al. [85] compare EEG signals of left and right temporal regions of brain with the rest of the brain regions and report reduced synchronization in Alzheimer's EEG signals compared to normal EEG signals.

Labate et al. [86] measure the EEG signal complexity to predict the disease progression and also to differentiate brain states that are proportional to the varying stages of AD. They applied three entropic complexity measures (permutation entropy, Lempel-Ziv complexity, sample entropy) to the EEG signals and performed a multi-scale multivariate analysis. They observe significant inter-channel correlation among the EEG channels and conclude that the severity of the disease is prominent in the EEG dynamic complexity and that EEG is a potentially useful tool for early diagnosis of AD.

Waser et al. [87] study univariate and multivariate spectral densities to measure slowing and decreased synchrony in the EEG signals. Coherences, partial coherences, bivariate Granger causality and conditional Granger causality are analyzed to measure EEG synchrony and spectral power in the predefined frequency bands is calculated to measure signal slowing. These measures are computed for resting-state EEG signals for subjects with AD. They conclude that automated analysis of variations in the EEG signals of individuals with AD may contribute to the medical diagnosis of the disease.

The amplitude of alpha rhythms is related to AD neurodegeneration along with pathologic aging. Babiloni et al. [88] observed abnormality in alpha rhythms obtained

by occipital sources of resting-state EEG in patients with amnesic MCI and AD. Gallego-Jutgla et al. [89] analyze changes in EEG synchrony in the theta band and observe an increase in the EEG synchrony in its narrow frequency ranges. They also propose a synchrony ratio to enhance the difference between subjects with AD and control group.

McBride et al. [90] use scalp EEG-based causality measurements and perform Sugihara causality analysis [91] to differentiate among normal aging, MCI and AD patients as these measurements have different distribution for different cognitive groups. A reconstruction model for each EEG channel is developed to predict the signal in the current channel using data of the remaining channels. The leave-one-out principle is used for training and Sugihara causality between different channels is described by a quality score obtained by comparing the reconstructed and original signals. They report an average classification accuracy of 96.5% after a 3-way classification.

Therapeutic Interventions

AD cannot be cured, but measures can be developed to delay its symptoms and help the AD population live with ease. Enhanced and efficient care quality and public awareness on AD can support people with AD and their families. Current AD treatments are classified as neuroprotective approach using antioxidants [92] and symptomatic approach based on the enhancement of neurotransmitter system.

Drugs such as donepezil, alantamine, rivastigmine, and tacrine can be used as acetylcholinesterase inhibitor [93] that enhances cholinergic system of the brain. Acetylcholine plays a major role in the manifestation of cognitive and behavioral symptoms in AD [94]. The latest addition for treatment of AD is memantine that blocks N-methyl-D-aspartate receptor receptors and acts on the glutamatergic system. Ahnaou et al. [95] studied the effects of cognition enhancers such as donepezil, galantamine, tacrine on the EEG oscillations for cortical and subcortical networks. These enhancers help in the systematic development of cortical slow theta and gamma oscillations. Improved neuronal connectivity revealed elevated coherent slow theta activity in parieto-occipital and in between interhemispheric cortical areas. The study concluded that therapeutic drugs such as donepezil, galantamine, and rivastigmine have cognition-enhancing potential that can delay the commencement of AD.

Blurton-Jones et al. [96] found that neural stem cell transplantation enhanced synaptic connectivity and improved cognition in AD patients. Stem cells of AD patients are genetically modified and implanted in their brain hallmarks. They observed that neural connectivity between the brain cells increased, whereas accumulated A β protein degenerated. Modified stem cells increased the level of neprilysin, an enzyme that breaks down A β and lowers its activity in the AD brain. Chancellor et al. [97] explored the art therapy on AD patients and observed that it improved social behavior, self-respect and neuropsychiatric symptoms. Immunization therapy, cognitive training and physical activities are some of the therapeutic measures applied on subjects with AD. Effects of cardiovascular and diabetes treatments on AD patients are also being explored.

Conclusion

AD is a neurocognitive disorder that progresses after its commencement in the older population. It is characterized by behavioral variability, cognitive decline, depression, delusions and memory loss. Studies reveal that formation of neuritic plaques, tangles, neuropil threads, granulovacuolar degeneration and amyloid angiopathy are some of the pathological variations causing AD. Neuroprotective and symptomatic approaches such as antioxidants and neurotransmitters have proved to be effective in the treatment of AD symptoms and found to delay their development. The paragraph has been simplified as follows: there are no treatments that can cure AD, but drugs have been developed and continue to be developed that can treat symptoms of the disease and delay its progression. As such, early diagnosis is the key in the treatment of the disease. Advances in neuroimaging technology, cognitive neuroscience, psychopathology, neuropathology and neurobiology are leading to the discovery of AD biomarkers for its early diagnosis. Researchers are also working on refining and improving the accuracy of the EEG-based diagnosis of AD [101]. The dream research and discovery is to develop an algorithm for early onset diagnosis of the AD but that will be sometime in the future.

Disclosure Statement

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