Analysis of EEG characteristics in Alzheimer's disease

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Abstract:

Alzheimer's disease (AD) brings a heavy burden to society and families because of the high misdiagnosis rate, prevalence rate, and disability rate. At present, the treatment of AD still faces great challenges. Early intervention can effectively delay the disease progression and improve the burden of symptom care. However, the key to early intervention is accurately identifying and assessing the disease. The examination is difficult to be widely used because of its high invasive cost. There is an urgent need for a simple, convenient, and non-invasive diagnosis of AD. Studies have shown that the brain number of AD patients is slower than that of healthy people, and the complexity of EEG is disturbed. Clinical practice has proved that the specificity and sensitivity of α, β, δ, θ absolute power and α/θ absolute power ratio, especially θ absolute power and α/θ absolute power ratio in the model, are important electrophysiological indexes for AD diagnosis EEG. Non-invasive and economical electrophysiological techniques can characterize and identify the EEG characteristics of AD patients from different angles. They are relatively simple to implement, and patients have a high degree of cooperation. Therefore, EEG, as a diagnostic method of AD, can improve the accuracy of differential diagnosis and early detection of AD and quantify the severity of the disease. It has the advantage of non-invasive convenience and price, which is of great significance for early diagnosis of AD.

Keywords: Alzheimer's disease; EEG; Dementia.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by insidious onset, predominant cognitive impairment, and accompanying behavioral abnormalities and decline in social functioning. Its core symptom is extensive cognitive dysfunction primarily manifested as memory impairment, often accompanied by hallucinations, delusions, anxiety, depression, and behavioral disturbances. Social functioning is severely impaired, ultimately leading to death. Due to its high misdiagnosis rate, prevalence rate, and disability rate, AD imposes a heavy burden on society and families. According to authoritative statistics, approximately 4.7 million people worldwide were estimated to have dementia in 2019, with an expected increase to 13.8 million by 2050. China's AD Report for the year 2021 showed that AD ranked fifth among the causes of death for both urban and rural residents. Currently, the treatment of AD still faces significant challenges. Early intervention through medication therapy or physical and psychological interventions can effectively delay disease progression while improving symptoms and reducing caregiving burden.

The key to early intervention lies in accurately identifying and assessing the disease process. However, the clinical diagnosis of AD still has significant limitations. Traditionally, invasive methods such as extracting relevant serum or protein analysis are used for diagnosing AD, but these approaches may cause irreversible damage to patients' brain structures. Routine diagnosis based on clinical manifestations or cranial magnetic resonance imaging makes it difficult to detect early; molecular biology diagnostics require cerebrospinal fluid or brain PET marker imaging analysis, which are invasive procedures with high costs that make them less accessible. To address this issue, there is an urgent need for a simple, non-invasive diagnostic method for AD, which has become a pressing problem in geriatric medicine. The main purpose of monitoring electroencephalogram (EEG) is to understand the brain's functional state and its close association with neural functions. The changes in EEG are also related to cognitive function. Therefore, exploring the value of EEG as a diagnostic tool for AD is currently an important research direction. EEG signal monitoring is a simple, non-invasive, cost-effective electrophysiological technique compared to traditional examination methods. Combining domestic and foreign studies indicates that cortical EEG signals originate from postsynaptic potentials of cortical pyramidal cells, providing real-time reflection of brain neural activity and representing the integrity of specific neurophysiological

pathways, consciousness, and sleep states, as well as precise temporal dynamics of brain function. With advancements in computer technology and EEG signal processing techniques, resting-state EEG technology has become increasingly mature. It can characterize and identify specific EEG features in AD patients from different perspectives while being relatively easy to implement with high patient cooperation.

Power spectrum analysis of different frequency bands provides valuable clinical information for diagnosing AD and evaluating cognitive abilities, which helps identify early-stage AD cases. Power spectral changes in the EEG signals of AD patients have been widely observed over the past few decades. Both absolute and relative power proposed to eliminate inter-individual differences yield consistent results: decreased power in high-frequency bands but increased power in low-frequency bands. Recent clinical studies have found that the alpha to theta power ratio in brain electrical signals (i.e., α/θ power value) can be used as one of the diagnostic criteria. The research indicates that patients with AD have significantly lower α/θ power values compared to healthy controls. With the continuous development and improvement of computer analysis techniques, many parameters analyzing the complex features of brain electrical signals have been successfully applied in AD research. For example, the complexity of brain electrical activity is lower in AD patients, higher in healthy controls, and intermediate in individuals with mild cognitive impairment (MCI), suggesting a correlation between changes in complexity and progression of AD. The reduced complexity of brain electrical activity observed in AD patients is attributed to neuronal and synaptic apoptosis and decreased cortical connectivity among various brain regions, resulting in simpler changes in brain electrical activity. Early studies believed that cognitive impairments in AD patients were caused by focal abnormalities within specific brain regions, such as medial temporal structures and association cortices [1].

Because of the high misdiagnosis rate, morbidity rate, and disability rate of AD, it brings a heavy burden to society and families, so early detection is very important for the rehabilitation treatment of patients. This research will analyze the EEG characteristics in AD. As a simple, non-invasive, and economical electrophysiological technology, EEG monitoring can improve diagnostic accuracy and become an important means of early diagnosis of AD in the future.

2. Brainwaves

Different frequency bands are grouped according to the logarithmic increase in central frequency and bandwidth.

The brain rhythm bands include δ (0.5~4 Hz), θ (4~8 Hz), α (8~13 Hz), β (12~30 Hz), as well as low-frequency γ (30-80 Hz) and high-frequency γ (80~150Hz). This grouping is determined by neurobiological mechanisms of brain oscillations, including synaptic decay and dynamic signal transmission. The α, β, and γ bands are also known as fast wave frequencies, while the δ and θ bands are referred to as slow wave frequencies. Individual differences in peak frequencies are also related to characteristics such as brain structure, age, working memory capacity, and brain chemistry. In a normal awake adult's EEG, the basic frequency is dominated by α waves with intermittent β waves and a small amount of low-amplitude slow waves. The frequency of δ waves ranges from 0.5 to 4 Hz and represents the slowest frequency with the largest amplitude among all EEG waves. The δ waves start appearing in stage three of sleep and peak in stage four when almost all spectral activity is dominated by δ waves. Stage three sleep is characterized by deep sleep, which is difficult to wake up easily. Brain wave changes during this stage mainly manifest as slowly increasing amplitudes on the curve. The frequency range for θ waves is 4-8 Hz, which commonly appears in EEGs of older children and adults during meditation or drowsy states like hypnosis or sleepiness. Theta oscillations in the frontal cortex are behaviorally associated with spatial memory performance, particularly after learning processes show prominent effects. Alpha waves, 8 to 13 Hz, are the primary frequency observed in the human brain when awake, calm, and with closed eyes. The most prominent regions where alpha waves are observed are the occipital and parietal lobes, and they diminish as the eyes open and external noise decreases. When a person falls asleep, alpha waves typically disappear and are replaced by mixed low-frequency waves. Beta waves have a frequency range of 12 to 30 Hz. They can be further divided into three subcategories: low-frequency beta (12 to 16 Hz), mid-frequency beta (16.5 to 20 Hz), and high-frequency beta (20.5 to 30 Hz). Beta waves with multiple frequency bands often correlate with active thinking processes or engaging conversations. Gamma waves operate at a frequency range of 30 to 80 Hz and serve various functions. They are considered important rhythms for brain signal transmission and are associated with cognitive processing.

3. The limitations of traditional AD inspections

In the NIA-AA 2018 diagnostic framework developed by the National Institute on Aging and Alzheimer's Association, AD diagnosis revolves entirely around the disease defined by biomarkers based on ATN status. According

to this criterion, even in the absence of cognitive impairment symptoms, abnormal β-amyloid and tau biomarkers (amyloid-positive and tau-positive) is also defined as Alzheimer's disease. However, controversy has sparked three years after introducing the NIA-AA criteria due to conceptual and pathology-based reasons. Firstly, it has low predictive accuracy. Its low predictive accuracy is a major limitation of defining AD based on biology. The presence of tau and β-amyloid positive expression alone is insufficient to reliably predict symptom occurrence (mild cognitive impairment or dementia) in individuals without clinical impairments. Secondly, there may be other pathologies involved. Another issue with using biomarkers for diagnosing AD is that these biomarkers indicating the presence of Alzheimer's pathology are often used as a primary basis for diagnosis; however, such pathologies are commonly found in individuals with other neurodegenerative diseases, most notably Lewy body dementia.

For example, doctors usually make accurate diagnoses of Lewy body dementia based on clinical symptoms or indirect biomarkers. However, in the case of AD, biomarkers may show positive expression, confusing: what is the final diagnosis? Is it AD or Lewy body dementia? According to NIA-AA 2018 criteria, it is considered AD. Using pure biomarkers of AD for diagnosis without other proteinopathy biomarkers remains controversial. On the contrary, even though AD is defined as the primary diagnosis in neuropathology terms, it may also be associated with other pathological changes. Although reign of interest (ROI) analysis, which combines non-invasive medical imaging techniques such as magnetic resonance imaging (MRI), has advantages such as safety and high sampling rate, there are three drawbacks: firstly, extracting ROIs based on whole-brain requires a large amount of manpower and time-consuming process; secondly, brain structures are exceptionally complex demanding strict capabilities from clinical workers; thirdly, poor adaptability when dealing with a large number of data samples.

4. Brainwave characteristics of AD patients

The resting-state EEG of patients with AD refers to the spontaneous brain electrical activity recorded without stimulation, known as the background EEG activity. Due to the lack of specific tasks required, particularly for elderly patients, acquiring EEG data in a resting state without cognitive load is simpler and more comfortable. Resting-state EEG includes recordings during wakefulness with eyes open and eyes closed and sleep monitoring. In AD patients during this state, four typical patterns can be observed: slow wave activity, a common evolution from high-frequency to low-frequency EEG waves. This change is believed to be a consequence of cholinergic neuron loss associated with AD progression and has some predictive value for assessing cognitive impairment severity.

De-complexification: Compared to the healthy control group, AD patients show a decrease in the complexity of their brain electrical activity. This simplification is believed to be primarily caused by extensive neuronal death and reduced cortical connectivity.

De-synchronization: Reduced connectivity between cortical regions has been observed in the brain electrical activity of many AD patients, which is thought to be associated with neural network dysfunction. Interestingly, some studies suggest that MCI patients exhibit enhanced synchronization in their brain electrical activity compared to healthy controls, possibly indicating compensatory mechanisms in the brain.

Neuroregulatory deficits: Recent analysis of quantified brain electrical rhythms and neuroregulatory activities through amplitude modulation analysis have revealed a decline in neuroregulatory rhythm function among AD patients compared to healthy controls. An EEG analysis conducted at Shanghai Mental Health Center on AD patients found the following changes: (1) an abnormality rate of 80.4% (45/56); (2) predominant abnormal EEG patterns characterized by frequencies below 8.5Hz, alpha waves, and diffuse slow waves beta and theta waves; (3) an increase in EEG abnormality rate with age, with more severe cases exhibiting more pronounced changes.

The findings of this examination are as follows: α slow wave activity, with most healthy elderly individuals maintaining a frequency of 9-10 Hz; if it is less than 8 Hz, it is abnormal. In individuals over 80, a posterior rhythm below 8.5 beats should be suspected as abnormal. θ and β waves show significant increases. Although there is no specificity in the EEG of AD patients, and the direction of EEG changes in AD patients is similar to that of normal elderly individuals, AD patients can still be distinguished from normal elderly individuals. The EEG changes in AD further intensify based on changes seen in normal aging, including slowing down of α activity and the appearance of diffuse β and θ activities, which differ from age-related EEG changes in older adults. Therefore, EEG has certain significance for the preliminary diagnosis of AD patients and can be used for further differentiation through neuroimaging studies. The specific origin analysis within the brainwave changes observed in AD patients indicates that the slowing down of α rhythm is due to reduced cerebral blood flow. Fast waves are believed to result from specific subcortical systems regulating cortical responses. Slow waves are related to alterations in cholinergic activity within the brains of AD patients. Additionally, Meyment

basal nuclei are areas containing cholinergic-dependent neurons, which have been reported to decrease significantly during pathological examinations conducted on individuals with AD. This also contributes to enhanced power output observed within slow wave activities in brainwave patterns exhibited by those with AD [2].

When dividing AD patients into mild, moderate, and severe groups according to the severity of their condition, it was found that there were no statistically significant differences between the mild AD group, moderate AD group, and severe AD group in terms of age, gender, EEG open-closed eye test, flash stimulation-induced test, and hyperventilation-induced test. However, there were statistically significant differences in terms of disease duration, mini-mental state examination (MMSE) total score, Montreal cognitive assessment (MoCA) total score, activities of daily living (ADL) total score, EEG background rhythm pattern modulation amplitude adjustment ability epileptiform discharge form changes in EEG patterns and EEG grading. In terms of MMSE item scores, time orientation ability, location orientation ability, attention, and calculation abilities, language abilities showed statistically significant differences among all three groups as well as pairwise comparisons; immediate memory showed no statistically significant difference between mild AD patients and moderate AD patients; delayed memory and visuospatial abilities showed no significant difference between moderate AD patients and severe AD patients. In terms of MoCA item scores, visuospatial/executive function abilities, naming abilities, and attention showed statistically significant differences among all three groups as well as pairwise comparisons; language abilities delayed recall orientation did not show a significant difference between moderate AD patients and severe AD patients; abstract thinking skills did not show a statistically significant difference among all three groups.

EEG abnormalities were found in 87.5% of AD patients, primarily characterized by background rhythm slowing and the presence of varying degrees of sharp waves, slow waves, spike waves, and spike-and-slow wave discharges in unilateral or bilateral frontal regions [3]. The mild AD group showed predominantly mild EEG abnormalities, accounting for 53.3%, while moderate and severe AD groups exhibited moderate to severe EEG abnormalities, accounting for 78.9% and 85.7%, respectively. Diffuse changes were observed in 75% of the EEG recordings. The mild and moderate AD groups mainly presented diffuse abnormalities (60.0% and 73.7%, respectively), whereas the severe AD group showed a combination of focal and diffuse changes (64.3%). Epileptiform discharges on EEG and the form and severity of EEG alterations impacted cognitive function assessment results: individuals with epileptiform

discharges scored lower on MMSE and MoCA. Comparing different forms of EEG alterations, the normal group had higher MMSE scores than those with only diffuse abnormalities or only focal abnormalities; meanwhile, those with both focal and diffuse abnormalities had lower scores than all other groups mentioned above. Furthermore, there was a negative correlation between the severity of EEG alterations and MMSE/MoCA scores–indicating that more pronounced changes in EEG corresponded to greater cognitive decline.

Based on the above statistics, the conference draws three conclusions: Firstly, as dementia severity increases, the degree of changes in the EEG becomes more severe, and cognitive decline becomes more evident. At the same time, EEG can be a reliable, objective indicator for reflecting cognitive function and assessing AD severity. Secondly, patients' EEG can manifest as diffuse or focal changes, with diffuse changes being the main form of AD-related EEG alterations. Thirdly, patients' EEG may exhibit epileptiform discharges characterized by varying degrees of sharp, slow, spike, and spike-slow wave complexes appearing unilaterally or bilaterally in frontal-temporal regions. Epileptiform discharges can exacerbate cognitive impairment [3].

5. Reasons for the popularization of manga

Acetylcholine (ACh) is an excitatory neurotransmitter widely distributed in the central and peripheral nervous systems. Its deficiency in the cerebral cortex and hippocampus affects dementia severity in AD patients. Choline acetyltransferase (ChAT), a key enzyme involved in ACh biosynthesis, is present within cholinergic neurons and measures their functionality. Decreased ChAT activity leads to reduced ACh levels. Overphosphorylation of tau protein can damage cholinergic neurons, weakening neuronal function when ChAT activity is diminished, ultimately leading to AD onset. Since ChAT synthesizes Ach, dysfunctionality within cortical cholinergic neurons has been considered one of the causes of memory impairment and other cognitive dysfunctions. The Meynert basal nucleus serves as a major source for neocortical cholinergic fibers. Therefore, decreased cholinergic neuron count within this region during the early stages of AD indicates prominent and sustained insufficiency in Ach synthesis.

The decrease in ChAT also correlates with dementia severity, increased senile plaques, and neurofibrillary tangles observed within the amygdala nucleus and cortical nerve fibers. Research conducted at Xuanwu Hospital of Capital Medical University on 22 AD patients with an average age of 68 found that the ACh levels in these patients

were significantly reduced compared to the control group. Furthermore, this decrease was positively correlated with scores on the MMSE, a simple psychiatric assessment tool. ACh is an important neurotransmitter that maintains higher cognitive functions and is closely associated with memory, thinking, and intelligence. The decline of ACh in the cerebrospinal fluid of AD patients reflects overall damage to the cholinergic system and increased impairment in ACh metabolism, which may be related to oxidative damage caused by glucose metabolism dysfunction and decreased catalase activity (CAT). The consistency between the degree of reduction in cerebrospinal fluid ACh levels and disease severity confirms that there are indeed changes in brain ACh levels among AD patients [4].

6. Comparison of EEG between patients with AD and normal individuals

The EEG records the brain's electrical activity by placing electrodes on the scalp. The EEG results show changes in brain activity, which can help diagnose brain disorders. There are two reasons for a thorough analysis of EEG in patients with AD: firstly, AD is cortical dementia, and abnormal EEG can directly reflect cortical damage and functional deficits; secondly, EEG can non-invasively assess impaired synaptic plasticity. The EEG signals slow down in AD patients. Conventional visual analysis of EEG in AD patients shows predominantly posterior rhythm slowing and diffuse slow wave activity increase. AD affects the EEG in specific ways. Moreover, there is a significant correlation between cognitive impairment and the degree of abnormality in EEG spectra measurements, indicating disrupted information processing within the cortical networks of individuals with AD, leading to cognitive dysfunction.

Human biological signals, including electrocardiogram (ECG) and EEG, accurately reflect an individual's physiological and pathological conditions. The decreased complexity in EEG induced by AD is related to the slowing down EEG signals, as slower signals are inherently more regular. Disturbances affect the coherence of EEG. Although the EEG signals from different brain regions appear random, they are interrelated. Coherence analysis of EEG has been used to estimate the degree of functional connectivity between cortical areas and examine cognitive decline. A prominent characteristic of AD is the functional disconnection between cortical areas, which is significantly associated with cognitive impairment. This is due to the loss of cortico-cortical fiber connections, as long-distance connections between different cortical regions are essential for brain functional interactions [5].
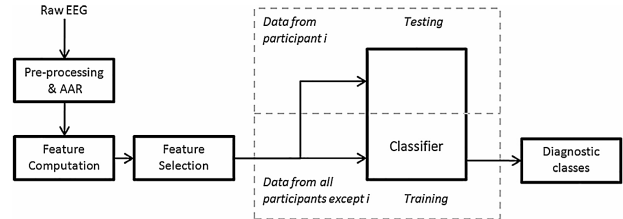

Fig. 1 Scheme of EEG-based AD diagnosis system [6].

7. The significance of EEG in the diagnosis of AD

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) categorized AD into three stages: preclinical, prodromal, and dementia. The introduction of these concepts incorporated the asymptomatic stage of preclinical AD into the scope of AD, significantly advancing the timing of diagnosis. As brain electrical activity is closely related to cognitive function, EEG may hold a certain value as a diagnostic tool for AD, as shown in Fig. 1. For instance, absolute power in alpha and beta frequency bands, as well as the ratio between alpha and theta absolute powers, show positive correlations with MMSE and MoCA scores. In contrast, theta absolute power exhibits a negative correlation with MoCA scores. In a study involving 496 elderly participants from abroad, resting-state EEG in the frontal lobe region was compared with MMSE scores. The results revealed that slower resting-state EEG activity was associated with lower overall MMSE and cognitive domain scores, particularly regarding time and location orientation.

The absolute power of α, β, δ, and θ frequencies and the ratio of α/θ absolute power are included in the model. Particularly, θ absolute power and the α/θ absolute power ratio exhibit good specificity and sensitivity in the model, indicating that EEG is an important electrophysiological indicator for diagnosing AD. Combining EEG with neurocognitive and cardiovascular factors has shown advantages in accurately identifying dementia and mild cognitive impairment, increasing diagnostic accuracy from 82% to 92%. EEG may have significant value in AD diagnosis, with θ absolute power and the α/θ absolute power ratio possibly having the strongest correlation with AD. The role of EEG in diagnosing and clinically evaluating AD has become increasingly important. EEG can improve the accuracy of differential diagnosis and early detection of AD, quantify disease severity, assist in clinical treatment for patients with AD, and facilitate the necessary planning of social healthcare resources. Neurophysiology is an important indicator that reflects the state of brain activity. Diagnosis of AD still faces great challenges.

EEG examination has advantages such as portability and non-invasiveness. Electroencephalographic diagnosis of AD is currently a research hotspot with promising potential for early detection. It also holds significant advantages for intervention effect evaluation in later stages, where brainwave characteristics can be directly utilized through neurofeedback techniques.

8. Conclusion

Because AD is a neurodegenerative disorder characterized by insidious onset, cognitive impairment, and accompanying behavioral abnormalities and functional decline, with high misdiagnosis rates, prevalence rates, and disability rates, it imposes a heavy burden on society and families. Traditional AD examinations involving cerebrospinal fluid or brain PET imaging analysis are invasive and costly, making them difficult to be widely accessible. Moreover, without other proteinopathy biomarkers available for diagnosis purposes, using pure biomarkers for AD remains controversial. This greatly complicates early diagnosis of AD. In comparison to healthy individuals, AD patients exhibit focal or diffuse changes in their EEGs, which become more severe as the disease progresses. Therefore, EEG can serve as a reliable, objective indicator that reflects cognitive function in AD patients and assesses the severity of the condition. Clinical practice has also demonstrated that combining EEG with neuropsychological and cardiovascular factors can improve diagnostic accuracy. With continuous advancements in computer analysis technology and improvement in analytical techniques—particularly the development of artificial intelligence technology—and the application of big data models, EEG will become an important tool for early diagnosis of AD.

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