Advances in Sleep EEG Signaling in Alzheimer's Disease Prediction

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Abstract: With the acceleration of global aging, Alzheimer's Disease (AD) has emerged as a grave public health issue. At present, the commonly employed diagnostic methods have certain drawbacks. In contrast, sleep electroencephalography (EEG) signals have garnered significant attention in the area of AD prediction, mainly because of their non - invasive nature, repeatability, and low cost. In this paper, we review the research progress of sleep EEG signals in AD prediction, elaborate the pathological mechanisms of AD, compare the advantages and disadvantages of traditional detection methods, and analyze the current status and development of sleep stage classification system technology is ongoing. When concentrating on the connection between non - rapid eye movement (NREM) sleep stages and AD, it has been discovered that in AD patients, the σactivity shows a decline and the EEG undergoes a slowdown during NREM sleep, and that σ power during NREM sleep is positively correlated with cognitive ability, which may be used as a reference standard for AD detection. Future research efforts should be dedicated to optimizing the algorithm in order to enhance the precision of sleep stage classification, integrate multimodal data to explore the relationship between sleep and AD, and carry out a large-scale longitudinal study to validate the sleep EEG indexes, so as to promote the development of early warning and precise intervention for AD.

1 INTRODUCTION

In today's society, with the acceleration of global aging, Alzheimer's Disease (AD), as a neurodegenerative disease, is the most common form of dementia, the third most expensive disease and the sixth leading cause of death worldwide. It has become a serious public health challenge.

Following the deposition of insoluble amyloid-β (Aβ), tau accumulates in neocortical cells, leading to neuronal cell death, synapse loss, brain volume reduction, and cognitive impairment. In the absence of cognitive symptoms, the progression of Alzheimer's disease (AD) involves the gradual accumulation of pathological changes, creating a critical window for timely therapeutic intervention. Sleep patterns are now emerging as a potential biomarker for AD pathology and a predictor of future cognitive decline Lucey, et al.,2019).

AD is difficult to diagnose, and symptoms can be easily misinterpreted as a normal consequence of aging, requiring multiple investigations and the exclusion of other causes. Two significant pathological changes occur: the deposition of β - amyloid plaques and the formation of hyperphosphorylated tau neurofibrillary tangles. Biomarkers like cerebrospinal fluid (CSF) analysis and positron emission tomography (PET) imaging, when integrated with clinical evaluations, are commonly employed to diagnose the disease, but the former is an invasive procedure that causes physiological discomfort to the patient such as the risk of infection and pain at the puncture site, and the latter is expensive to perform with expensive equipment and a high cost of learning, which greatly limits its popularity. The latter is expensive and costly to learn, which greatly limits its popularity. On the other hand, sleep electroencephalography (EEG) signal acquisition EEG devices are affordable. In recent years, the progress of sleep stage recognition technology has been remarkable. Due to the limitation of manual scoring, the development of automatic sleep stage classification system (ASSC) has been accelerated, using the PhysioNet Sleep EDF database and a decision tree classifier, the model achieved an average sensitivity of 89.06%, specificity of 98.61%, and accuracy of 93.13%., which improved the feasibility and speed of practical application of ASSC (Lucey, et al.,2019). feasibility and speed of practical application (Aboalayon, et al., 2016).

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During sleep, the electrical activity of the brain exhibits a rich variety of regular changes, which contain a vast amount of information regarding the state of brain health. Sleep is mainly classified into two stages: Rapid Eye Movement (REM) sleep and Non - Rapid Eye Movement (NREM) sleep, and each of them has unique electrical characteristics and physiological functions, and may play different but interrelated roles in the development of AD.

Given the unique advantage of sleep EEG signal in reflecting the functional state of the brain, as well as its noninvasive, reproducible, and relatively low-cost features, investigating the use of sleep EEG signals for AD prediction not only broadens our comprehension of AD pathogenesis but also offers innovative approaches for its early detection. The present study aims to review the research progress of sleep EEG signaling in AD prediction in recent years, focusing on the changes of EEG characteristics during REM and NREM sleep stages and their correlation with the pathophysiological process of AD, evaluating the strengths and weaknesses of current research methods and exploring future directions, this study aims to establish a solid theoretical foundation and practical guidance for early AD detection and targeted intervention.

2 AD PATHOGENESIS

2.1 Mechanisms of Aβ and Tau in the Induction of AD

Aβ is produced by cleavage of amyloid precursor protein (APP) by β - secretase and γ - secretase. Under normal conditions, Aβ can be cleared, but in AD patients, there is an imbalance between the production and clearance of Aβ, leading to the abnormal deposition of Aβ in the brain and the formation of senile plaques. Aβ oligomers have neurotoxicity, which can bind with receptors on the cell membrane of neurons, these disruptions impair neural signaling and synaptic plasticity, while simultaneously promoting the generation of reactive oxygen species. This leads to oxidative stress, which damages cell membranes, proteins, and mitochondria, ultimately causing the death of neurons.

Normally, tau protein promotes the assembly of microtubules and maintains their stability to ensure intra-neuronal substance transportation. In AD, tau protein is abnormally hyperphosphorylated and its ability to bind to microtubules decreases, resulting in microtubule depolymerization, which destroys the cytoskeleton structure of neurons, affects axonal transport, and prevents neurons from taking up nutrients and transmitting signals normally. Over-phosphorylated tau protein aggregates to form neurogenic fiber tangles. These tangles accumulate in neurons, hindering normal physiological activities of neurons, and can spread among neurons, accelerating neurodegeneration.

2.2 Other Relevant Pathological Factors and Interactions

Aβ deposition, tau protein abnormalities, impaired mitochondrial function, and cerebrovascular pathology all play key roles in the complex pathogenesis of AD.

Aβ is produced by cleavage of APPs by specific enzymes and is normally cleared. In AD patients, the balance between Aβ production and clearance is disrupted, leading to its excessive accumulation in the brain. tau proteins become abnormally hyperphosphorylated, disrupting their ability to bind to microtubules and interfering with intra-neuronal transport of substances. the deposition of Aβ and the abnormalities of the tau proteins activate microglial cells and astrocytes. Activated microglia release pro - inflammatory cytokines, such as interleukin - 1β (It seems there might be a mistake in your original "interleukin - 1 Aβ", perhaps you meant interleukin - 1β) and tumor necrosis factor - α, while astrocytes expand in reaction to inflammatory signals, releasing a variety of cytokines and chemokines, which triggers neuroinflammation and damage to neuronal cells. Mitochondrial function is also impaired in the brain of AD patients. Mitochondrial dysfunction can trigger oxidative stress, partially clarifying the intricate mechanisms behind oxidative damage in AD. Beyond ATP production, mitochondria play a key role in controlling cell death by storing various apoptotic factors, which are released during apoptosis. In AD patients, mitochondrial impairment, elevated oxidative stress, and neuronal apoptosis have been observed (Moreira, et al., 2012). These findings imply that mitochondrial malfunction could be the impetus behind neuronal degeneration and demise in AD. Disruptions in the mitochondrial respiratory chain and impaired electron transport lead to a decline in membrane potential and diminished energy generation. At the same time, reactive oxygen species production increases, exceeding the cellular antioxidant capacity and oxidatively damaging lipids,

proteins, and other biomolecules, making neurons more susceptible to oxidative stress damage.

Certain gene mutations are closely related to AD, such as mutations in APP, progerin 1 (PS1) and progerin 2 (PS2), which can lead to familial AD; and the ε 4 allele of the apolipoprotein E (APOE) gene significantly heightens the risk of developing sporadic AD (Scheltens, et al., 2021).

Cerebrovascular lesions are equally important in the development of AD. Chronic hypertension also impairs the integrity of the blood-brain barrier (BBB), leading to cerebral edema and the introduction of systemic elements into the brain parenchyma, and chronic hypertension also impairs the integrity of the BBB, resulting in brain swelling and the infiltration of systemic components into brain tissue (Santos, et al., 2012). Cerebrovascular endothelial dysfunction affects vasodilatation and vasoconstriction, resulting in reduced cerebral blood flow, inadequate nutrient supply to brain tissue, and accumulation of metabolic wastes. The damage to the blood-brain barrier is even more serious, its permeability increases, harmful substances enter the brain tissue, triggering inflammation and immune damage, and it also affects the removal of Aβ, prompting the further deposition of Aβ and accelerating the development of AD disease. These pathologic processes interact with each other and jointly promote the development and deterioration of AD.

3 PROGRESS IN DETECTION RESEARCH

3.1 Traditional Testing Methods and Limitations

3.1.1 Mini-Mental State Examination (MMSE)

The MMSE is a widely used clinical instrument for AD detection. This 30-question test evaluates cognitive abilities, including attention, orientation, memory, calculation, language, and visuospatial skills, such as drawing complex shapes (Arevalo, et al., 2012). The MMSE score offers a quantitative measure of cognitive decline in older adults, aiding doctors in diagnosis and treatment planning. However, the assessment dimensions of MMSE are limited, mainly focusing on several major aspects of cognitive function, and the assessment of some complex cognitive functions, such as executive function and social cognition, is not comprehensive enough. If the elderly has a high level of education, there may be cases where the MMSE score is still in the normal range even though there is some cognitive impairment, thus masking the condition. For some specific cognitive dysfunctions, such as executive dysfunction, the MMSE may not be able to detect them accurately, which may lead to an incomplete assessment of the patient's cognitive function. Patients with AD may develop these impairments during the course of the disease, but the difficulty of detecting them on MMSE may affect the overall judgment of the patient's condition.

3.1.2 CSF

Biomarkers in CSF can directly reflect the pathophysiologic process of AD in the brain. Pathologic changes, such as A β deposition, may occur in the brain before the onset of clinical symptoms of AD, and biomarker levels in the CSF may change accordingly. The most intensively investigated biomarkers of Alzheimer's disease (AD) are the cerebrospinal fluid proteins that are pathologically related, namely β - amyloid 42 (A β 1 - 42), total tau (t - tau), and tau phosphorylated at amino acid 181 (p - tau181). Many laboratories use enzyme-linked immunosorbent assays (ELISA) to detect these proteins (Wang et al., 2012). By immobilizing an antibody that specifically recognizes A β 42 on a solid-phase carrier and adding it to a CSF sample, the A β 42 in the sample will bind to the antibody, and then an enzyme-labeled secondary antibody will be added, which will produce a color change through the reaction between the enzyme and the substrate, and then the absorbance will be measured by using an enzyme marker, and compared with a standard curve. If the level of A β 42 in the CSF decreases significantly, it suggests that Alzheimer's disease may be present. However, the CSF test requires lumbar puncture to obtain CSF, which is an invasive operation that may bring some pain and risk to patients, and the CSF test involves special testing equipment, reagents, and specialized technicians, and the overall cost is relatively high, which may bring some financial burden to patients and the health insurance system, and to a certain extent, limit its wide application.

3.1.3 PET

PET technology allows for the evaluation of various functional processes in the brain of AD patients

during their survival. This method allows for the 3D visualization and quantification of metabolic (glucose metabolism) and neurotransmitter activity. It also provides insights into the pathological mechanisms of AD. PET scans enable clinicians to visually analyze results through color coding and, crucially, gather quantitative data on brain regions. This data supports objective evaluation of diagnostic precision and treatment outcomes. PET can identify early metabolic and pathological brain changes before noticeable clinical symptoms appear. With specific tracers, such as the glucose analog of brain glucose metabolism, 2-[18F]-fluoro-2-deoxygenase, PET is able to detect subtle metabolic and pathological changes in the brain before they become clinically apparent.

Oxygen-d-glucose (18F-FDG) can be used to monitor cerebral glucose metabolism (Nordberg,et al., 2012). This tracer has been widely used in radiopharmaceutical imaging studies and clinics of AD, which can clearly show the metabolic or pathological changes in different regions of the brain and help doctors accurately determine the site and extent of lesions. In AD diagnosis, it can clarify the functional abnormality of brain areas closely related to cognitive function, such as hippocampus, internal olfactory cortex, etc., which can provide an important basis for localized diagnosis of the disease and evaluation of the disease, and help to differentiate it from other diseases that may lead to cognitive disorders. PET test not only shows the anatomical structure of the brain, but also more importantly reflects the functional state of the brain, such as the metabolic activity of the neurons, neurotransmitter changes and so on, neurotransmitter changes, etc. However, the PET test itself is expensive, and with the cost of the tracer, the overall cost of the test is usually high. PET equipment is expensive, with high maintenance costs and high requirements for installation environment and technicians, resulting in its limited popularity in medical institutions. At the same time, the analysis and interpretation of PET images require specialized nuclear medicine doctors or specially trained personnel who are not only familiar with the normal anatomy and physiological functions of the brain, but also understand the characteristics of PET performance in various disease states.

Therefore, in Alzheimer's disease detection, EEG has outstanding advantages over mainstream methods. Firstly, it is non-invasive. CSF requires lumbar puncture, which is risky, while EEG only places electrodes on the scalp. Secondly, it has a higher detection accuracy and can capture early abnormalities in neuronal electrical activity. Furthermore, in terms of economy and popularity, CSF and PET testing equipment and process costs are high, while EEG equipment is cheap, with low learning costs, and can be operated by primary healthcare professionals after short-term training, which is more conducive to popularization, and more patients can benefit from early diagnosis, which has a great potential for the detection of AD.

3.2 State of the Art and Development of Sleep Stage Classification System Technology

Classifying sleep stages is essential for studying sleep, diagnosing sleep disorders, and assessing treatments. It enhances our understanding of sleep mechanisms and offers a foundation for managing sleep-related conditions. At present, the sleep stage classification system technology presents diverse characteristics in methods and applications, and also faces many challenges, and the future development direction is becoming clearer.

Sleep specialists usually perform manual sleep stage scoring through the analysis of neurophysiological signals gathered in sleep laboratories. This process is often challenging, monotonous, and time-intensive. Scoring is usually based on polysomnographic (PSG) data recorded during overnight hospital stays. In traditional practice, overnight PSG recordings consist of EEG, electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG) data. These recordings are manually assessed by sleep specialists based on the 1968 guidelines established by Rechtschaffen and Kales (R&K) (Konkoly, et al., 2012). PSG recordings are divided into 20- or 30-second intervals and classified into wakefulness (W), REM sleep, and NREM sleep. Due to their multi-channel signals and expert-based visual analysis, PSG remains the gold standard for assessing sleep in laboratory studies. Polysomnography offers comprehensive insights into sleep architecture, duration, and quality. However, it is costly, labor-intensive, and unsuitable for field applications, as it requires a sleep technician to install equipment and place multiple electrodes on the face and scalp (Arevalo, et al., 2012).

Consequently, the process of sleep stage scoring incurs high costs, is prone to human mistakes, and is frequently tiresome and demands a significant amount of time. Analyzing overnight sleep recordings usually requires 2 to 4 hours, and in some studies, there has been a 90% expert agreement on sleep stage

classification (Konkoly, et al., 2012). In addition, sleep stage scoring using PSG usually requires a hospital setting where subjects have to wait on a waiting list for some time. Due to the limitations of manual sleep stage scoring, there is an increasing demand for the development of automated sleep stage classification systems (ASSC).

The research divides dual-channel EEG signals into quasi-steady-state segments, extracts features using Short-Time Fast Fourier Transform (STFT), reduces dimensionality with the fuzzy C-Means algorithm, and constructs an ASSC system employing a multi-class SVM. The system achieved an accuracy of 70.92% (Al-Aloqaly, et al., 2012). To improve the classification accuracy, the researchers tried to fuse multiple physiological signals. In addition to EEG, EOG, and EMG, signals such as heart rate, respiratory rate, and oxygen saturation were incorporated. Multimodal data fusion can provide more comprehensive sleep information, adopt more advanced algorithms, study new deep learning architectures, such as models based on the attention mechanism, which can better focus on key sleep signal features; and explore the application of generative adversarial networks (GANs) in sleep data augmentation and model optimization, to improve model performance. We will further improve the multimodal data fusion method, combine artificial intelligence and big data analysis technology, mine the complex relationship between sleep data, and realize the comprehensive assessment of sleep quality, early warning of sleep disorders, and the formulation of personalized treatment plans.

3.3 Association between NREM Sleep Stages and AD and Research Progress

3.3.1 The Relationship between non Rapid Eye Movement (NREM) and AD

Starting from the prodromal phase of AD, patients exhibit slower EEG rhythms while awake, potentially linked to poor sleep quality. To explore the connection between arousal and sleep, we analyzed EEG activity during sleep, as well as before and after sleep, in patients suffering from Alzheimer's disease (AD), those with mild cognitive impairment (MCI), as well as healthy individuals used as controls. It was found that individuals with AD, as well as those suffering from mild cognitive impairment, presented a longer sleep latency and less slow-wave sleep. The NREM sleep phase is typically characterized by reduced σ activity, which reflects the absence of the sleep spindle. For both AD and MCI patients, EEG slowing is characteristic of REM sleep and wakefulness, and there is a strong correlation between these two phenomena, suggesting a common neuropathological mechanism.

Furthermore, EEG changes from evening to early morning during wakefulness revealed a gradual reduction in nocturnal δ activity in both MCI and AD patients. This suggests a progressive decline in the restorative effects of sleep on circadian rhythms, aligning with the impaired high-frequency sleep activity observed in AD patients.

In this process, NREM stage sleep is crucial for memory consolidation. It plays a facilitating role in transforming short - term memory into long - term memory. Moreover, it is of great significance in maintaining learning ability and cognitive functions.

3.3.2 Power of EEG During NREM Sleep

The histograms of the spectral power at cortical sites and bands from Figure1 show the power of the two groups in the α and σ bands. Looking at the graph as a whole, there is a difference in the α and σ band power between the AD and HC groups at different cortical sites. The α and σ bands were chosen because the σ band is associated with the relaxation and attentional states of the brain, and in AD patients, altered brain function may affect their relaxation and attentional regulation mechanisms. σ band is associated with the sleep spindle wave, which is critical for memory consolidation, and AD patients with impaired memory may have characteristic changes in this band. Other frequency bands, such as the δ band, are potentially related to AD, but the two more distinguishable frequency bands are discussed briefly here. α and σ power in AD patients at T3 and T5 correspond to the temporal lobe region of the brain, and the reduced α and σ power at these locations may indicate abnormal neuronal activity in the temporal lobe region. α power is reduced, reflecting the impaired function of relaxation and attentional regulation of the brain, and the reduced α power suggests a weakening of the activity of sleep spindles and impairs memory consolidation. Reduced α power suggests that sleep spindle wave activity is impaired, affecting memory consolidation. This difference may reflect the alteration of cortical function in AD patients, which to some extent provides data support for the study of the neurophysiological mechanism of AD, and helps to further explore the characteristics and patterns of the abnormalities in the brain function of AD patients.

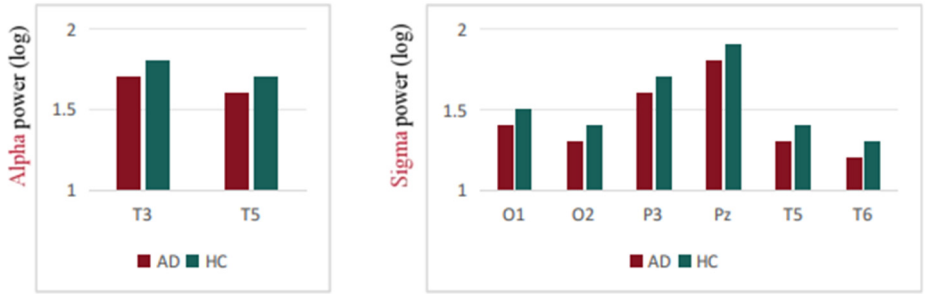

Figure 1: Spectral Power Histograms of Cortical Sites and Frequency Bands in AD (Alzheimer's Disease) and HC (Healthy Control) Groups.

3.3.3 Correlation between σ Power and Cognitive Ability

From Table 1, it is possible to evaluate the association between the level of cognitive ability and the σ power (sigma power) during NREM sleep. The graph clearly shows that there is a significant correlation ($p \leqslant 0.0054$) between MMSE scores and σ power during NREM sleep at different EEG loci (O1, O2, P3, Pz, T5, T6) (D'Atri, et al., 2012). The correlation coefficients r values ranged from 0.28 - 0.32 and the p values were extremely small, indicating that this correlation was highly statistically significant. Based on this, we can basically conclude that there is a positive correlation between σ power and cognitive ability, i.e., the higher the σ power during NREM sleep, the higher the corresponding MMSE score and the stronger the cognitive ability.

Table 1: Correlation (Pearson's R) between MMSE Score and Sigma Power During NREM Sleep, and EEG Slowing Index During REM Sleep ($P \leqslant 0.0054$) (D' Atri, et al., 2012).

EEG site	σ power in NREM sleep	
	r	p
O1	0.32	0.000077
O2	0.32	0.000055
P3	0.28	0.0006
Pz	0.31	0.000093
T5	0.31	0.00014
T6	0.29	0.00033

Given this association, σ power during NREM sleep has the potential to be used as a reference standard for EEG to detect AD levels. In clinical practice and research, detecting the power in this frequency band of the EEG may be able to assist in determining the cognitive state of an individual and provide valuable information for early screening and assessment of AD. However, more studies are needed to further validate its accuracy and reliability.

4 CONCLUSION

With the limitations of traditional AD detection methods, sleep EEG signaling has become a hot research topic due to its unique advantages. This paper comprehensively analyzed the pathological mechanisms of AD, the advantages and disadvantages of traditional detection methods, and the current state of the art of sleep stage classification system, and focused on the association between NREM sleep stages and AD, and found that the cortical functional activities of AD patients differed from those of healthy controls in terms of α and σ band power, and clarified the positive correlation between the σ power and the cognitive ability.

However, the accuracy and reliability of sleep EEG signal for AD prediction still need to be improved. In the future, we can focus on conducting large-scale and multi-center clinical trials to further validate the relevant indexes, exploring more frequency bands and brain regions, optimizing the detection techniques and analysis algorithms to enhance the precision and steadiness of the prediction, and promoting the development of AD early diagnosis and intervention techniques.

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