Changes in electroencephalography and sleep architecture as potential electrical biomarkers for Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by dementia and mental illness. The main pathological changes of AD are the accumulation of amyloid β (Aβ) and phosphorylated tau. With the increase in the aging population, the prevalence among adults aged ≥60 years will be growing from 5.4% (2015) to 6.7% (2050) in China.[1] At the present stage, the diagnosis of AD is primarily based on the long term clinical observation. Neuro-imaging and invasive cerebrospinal fluid (CSF) measurement of Aβ and tau may help making a differential diagnosis, but the cost to conduct these examinations is high and they are only applicable for the middle to late stages of the disease.[2] Furthermore, there is still no effective treatment to reverse the clinical symptoms and the pathological changes of AD because most of the patients when they are seen by specialists have already lost the majority of AD-related cortical and hippocampal neurons.[3] Therefore, the early detection of AD is of importance in order to monitor the AD progression and provide early intervention of the disease. Accordingly, there is a great need to develop low-cost, noninvasive measurement for the early detection of AD. Among many recent research advances, electroencephalography (EEG) has become an effective measurement aiding AD diagnosis and monitoring the disease progression. It has been reported that sleep architecture alteration, decreased θ and δ power could manifest before AD neuropathology.[4] In this review, we update the recent findings on EEG spectrum analysis, sleep architecture measurement, brain networks research, and their correlation with AD disease progression. We also discuss the potential application of EEG and sleep monitoring in the research of AD pathogenesis, and use them to evaluate the possibility of early AD detection.

Research on the relationship between sleep disorders and neurodegenerative diseases usually focuses on rapid eye movement (REM) sleep behavior disorder in Parkinson's disease or dementia with Lewy bodies. However, an increasing number of studies have discovered that sleep disorders also occur in diseases such as frontotemporal dementia, amyotrophic lateral sclerosis, and AD. Several reports indicated that AD is accompanied by abnormal sleep-wake cycles, excessive daytime sleep, reduced non-rapid eye movement (NREM) and slow-wave sleep time, and frequent awakenings at night.[5] Recently, researchers have found that Aβ is related to the loss of slow-wave activity (SWA) in NREM sleep (<1 Hz)[6]; tauopathy is related to the loss of SWA in NREM (1–2 Hz) sleep, and SWA-sleep spindle coupling could predict medial temporal lobe tau burden.[5,7]

In addition, recent studies have found that AD patients have a higher incidence of respiratory diseases, such as obstructive sleep apnea (OSA) and sleep-disordered breathing. Compared with healthy control (HC) individuals, Aβ in blood and $A\beta_{42}$ and phosphorylated tau in CSF have increased in patients with OSA.[8] Longitudinal studies have reported that apnea and hypopnea are associated with the annual rate of change in CSF $A\beta_{42}$.[9]

Not only can AD affect sleep, but sleep disorders also can lead to Aβ clearance impairment. Aβ is cleared by the lymphatic system, which mainly works during sleep and gradually decreases with age; thus sleep disorders may be one of the main factors leading to the accumulation of Aβ and eventually progression to AD. More studies, moreover, have shown a close association between AD and sleep disorders. Such as the accumulation of Aβ and tau pathological proteins in critical sleep regulatory centers may lead to sleep impairment.[6] Similarly, if sleep is affected, the pathological protein is accumulated. Current studies propose that the association between sleep disruption and the AD pathway is a two-way relationship.

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Table 1: Correlation of potential EEG changes and AD related pathological biomarkers.

AD pathology	Increased δ and θ power	Decreased α and β power	Increased connectivity of δ and θ band	Decreased connectivity of α and β band	Increased α3/α2 ratio	Decreased SWS and SWA
Decreased CSF Aβ$_{42}$	++	−	++	++	−	−
Increased CSF p-Tau and t-Tau	−	++	−	++	−	++
Hippocampal atrophy	+	+	−	−	++	−

++: Strong correlated; +: Weak correlated; −: Not correlated; Aβ$_{42}$: Amyloid β$_{42}$; AD: Alzheimer's disease; EEG: Electroencephalogram; CSF: Cerebrospinal fluid; SWA: Slow-wave activity; SWS: Slow wave sleep.

Impaired sleep architecture is associated with AD pathology, and sleep duration alteration during lifespan could predict late-life Aβ and tau burden.[7] A recent longitudinal study reports that midlife insomnia and late-life terminal insomnia are related to higher dementia risk.[10] In sleep architecture studies, the lower REM sleep proportion and longer REM sleep latency are higher dementia risk; each percentage reduction in REM sleep increased the risk of incident dementia by 9%.[11] Both cross-sectional and longitudinal experimental studies suggest that impaired sleep may increase the risk of AD. Based on the latest research, the quality of sleep has already altered prior to AD pathology.[12]

Results from these studies might warrant further investigation to use EEG as a noninvasive biomarker of disease progression in preclinical AD.[13] To accurately describe the interaction between AD pathology and sleep disorders, further research is needed to define the relationship between sleep disorders and disease progression and to verify whether any neurophysiological factor is specific for AD, which can differentiate it from other neurological diseases.

It is known that the pathological changes of AD can affect neuronal activity in the brain; therefore, EEG might be a promising noninvasive electrical biomarker for AD.

Research on the relationship between EEG and AD usually focuses on the frequencies of brainwaves. The analysis of the relative power of frequencies and the loss of complexity of low frequencies could be a useful tool for the early diagnosis of AD.[14]

In clinical studies, researchers have found that decreased CSF Aβ$_{42}$ levels are correlated with increased θ and δ power; increased p-tau and t-tau are correlated with decreased α and β power.[15] Furthermore, in AD patients, there are increased θ and δ power and decreased α and β power. Moreover, peak frequency of AD patients shifts toward lower frequencies in the power spectra and relative θ power increases.[16]

Existing studies have reported that early AD affects relative α power and α cortical neural synchronization. Recent studies try to determine which frequency band/bands are more specific. Prodromal AD patients have decreased α1 (6.9–8.9 Hz). AD patients showed dramatically lower posterior α2 power (8.9–10.9 Hz). The increases in α3/α2 (α3: 10.9–12.9 Hz) power ratio have been demonstrated as a biomarker characteristic of prodromal AD. Patients with

higher α3/α2 have greater cortical atrophy and a lower perfusion rate correlated with memory impairment. The increase in α3/α2 power ratio could be useful for the early diagnosis of AD.[17]

In the study of event-related potentials (ERPs), AD patients have low ERP amplitudes and P300 (peak at 300 ms) response which is significantly associated with AD severity. AD patients also have reduction in P1 (peak at 100–130 ms) and N1 (peak at 150–200 ms) visual evoked potential amplitudes. Moreover, it is reported that AD patients have lower visual sensory-evoked oscillations over the left hemisphere in the 0 to 200 ms time window at 25 to 30 Hz and delay event-related oscillations at the γ band.[18]

Pathological changes in the brain usually affect brain networks. By studying brain networks, we can better understand the brain functions and pathological alterations in AD patients. Hippocampal volume is associated with decreased α and increased δ, β, and γ connectivity.[19] Additionally, AD patients display a loss of resting-state functional connectivity in lower α and β bands.

At present, researchers believe that the most significant changes in EEG connectivity of AD are in the θ band or the α band.[16] In terms of information processing, AD patients have lower global information processing ability (integration) and higher local information processing ability (segregation) than HC.[20] In addition, AD patients have lower global connectivity and higher local connectivity in the α and β bands than HC.[21] Possibly due to reinforced local circuits and weakened network connectivity and activity, AD patients have hyperexcited sensorimotor systems or long-distance frontoparietal effective connections. Moreover, decreased CSF Aβ$_{42}$ and increased p-tau and t-tau are associated with lower global connectivity of the α and β bands as well.[15] AD also affects the phase synchronization in different wavebands of brain networks, showing a decline of lagged phase synchronization between most cortical regions in the δ band, between the right dorsolateral prefrontal cortex, the right posterior-inferior parietal lobule in the θ band and within the middle temporal gyrus in the β band.[22]

This review presents an overview of EEG and sleep analysis in AD and its potential value as a biomarker measurement [Table 1].[5,23] In AD, changes in α waves and θ waves are usually considered the most important manner. However, recent studies have begun to focus on the γ band and the relationship between γ waves, cognitive function, and AD. With the advances in AD research, the relationship

between sleep and AD has become more deeply understood. In recent years, new studies have found that sleep disorders occur in the early stage of AD. More studies are needed to determine the role of sleep disorders in the development of AD.

Spectrum analysis of EEG is helpful for AD research to some extent, but accumulating evidence indicates that simple spectrum analysis of EEG can no longer satisfy the clinical studies of brain networks in AD. The dominant frequency, band connectivity, ERPs provide reliable performance of AD monitoring. Still, more crossover research works are needed to determine the specific brain electrical activities and dysfunction in the AD brain networks, which may be of significance to help understand the underlying mechanisms of progressive neurodegeneration in AD. In future research, sleep architecture and EEG crossover research could be a useful tool to aid AD diagnosis.

Conflicts of interest

None.

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