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Abnormalities in EEG as alzheimer marker

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Abstract

Alzheimer's Disease (AD) is a prevalent neurodegenerative disorder characterized by protein accumulation, cognitive decline, and irreversible brain damage. With the aging population, AD's prevalence is rising, necessitating effective diagnostic tools. Electroencephalography (EEG), a non-invasive neuroimaging method, has emerged as a promising tool for early AD detection.

This review summarizes 62 studies published between 2000 and 2023, investigating EEG abnormalities as diagnostic markers for AD. The studies consistently highlight EEG's role in distinguishing AD and Mild Cognitive Impairment (MCI) from healthy controls. EEG features, patterns, and connectivity measures, often analyzed with machine learning techniques, exhibit promise for discriminating cognitive disorders. While promising, translating EEG diagnostics into clinical practice faces challenges related to individual variability and the progressive nature of AD.

Standardized protocols and diverse datasets are crucial for enhancing the applicability of EEG-based AD diagnosis. Integrating EEG with imaging and genetic markers holds potential for improved diagnostic accuracy and understanding AD pathology. The evolving neuroimaging landscape offers avenues for insights into AD's origins. Future research should explore the complex relationships between EEG-derived biomarkers, cognitive profiles, and disease processes to advance early interventions.

In conclusion, EEG shows promise for AD detection and diagnosis. While progress has been made, further development is needed for reliable real-world diagnostics. EEG-based approaches offer potential for accurate early AD detection and insights into cognitive decline mechanisms.

Keywords: Alzheimer's disease; Electroencephalography; Diagnostic markers; Biomarkers.

Background

Alzheimer's Disease (AD) is a neurodegenerative disorder that progresses slowly and is the most common type of neurological disorder and dementia in the elderly [1,2]. The disease is characterized by the accumulation of extracellular protein, including the pathological proteins amyloid beta and phosphorylated tau, which leads to plaque deposition and intracellular fibrillary nerve coils in the brain, causing the loss of neurons and synaptic degeneration. This, in turn, leads to brain atro-

phy and severe cognitive impairment in humans and animals [3,4]. Alzheimer's is progressive and irreversible condition that causes cognitive and behavioral dysfunction and is often associated with various brain disorders such as aphasia, agnosia, amnesia and apraxia [5]. Globally, about 50 million people suffer from this type of dementia, and it is predicted that this number will multiply by 2050. With the aging of the world's population, more than 107 million people will be diagnosed with AD (by 2050 [6,7]. To date, no effective treatment has been found for AD [8]. The available treatments can only reduce or delay its

symptoms [9]. However, twelve monoclonal antibodies against beta-amyloid have been developed and are currently undergoing clinical trials for the treatment of the disease [10].

EEG is a neuroimaging technique that is completely non-invasive [11]. It records electrical signals generated by the activity of brain neurons during a period of time [12]. EEG allows us to examine changes in brain activity [13]. The state of the individual's brain may process certain frequencies dominantly [14]. Brain waves include 4 main groups: - beta (>13 Hz), - alpha (best-known human brain rhythm) (8-13 Hz), - theta (4-8 Hz), - delta (0.5-4 Hz). EEG is commonly used to diagnose various brain diseases, including epilepsy, Parkinson's disease, Alzheimer's disease, and sleep disorders [15].

Moreover, EEG can be used to assess the effectiveness of treatments made by ADinhibitors [16,17]. The combination of Transcranial Magnetic Stimulation (TMS) and EEG can provide insights into the related features of Alzheimer's pathophysiology [18]. Overall, it has been determined that the use of EEG is useful and effective for diagnosing and monitoring the progress of Alzheimer's disease, as well as evaluating the efficacy of treatments [19].

There are several studies related to the examination of abnormalities in the electroencephalogram during the study of Alzheimer's disease. For instance, some studies show that EEG can detect frequency changes in people with Alzheimer's disease, which include a decrease in alpha and beta waves and an increase in delta and theta waves [20]. It has also been found that abnormalities in brain frequencies even if they are in the early stages, can be determined by EEG, which shows that EEG can be an efficient tool for early diagnosis of Alzheimer's disease.

Despite these promising findings, there are still gaps and inconsistencies in the existing literature. For instance, there is a need for standardized EEG protocols and the development of more accurate EEG biomarkers for Alzheimer's disease. The current review aims to provide a comprehensive overview of existing literature on EEG abnormalities in Alzheimer's disease, identify gaps and inconsistencies, and propose future directions for research. By doing so, this review will contribute to the existing body of knowledge on EEG abnormalities in Alzheimer's disease, and potentially facilitate the development of more accurate diagnosis tool for early detection and diagnosis.

Materials and methods

A comprehensive literature search was conducted to identify relevant articles focusing on abnormalities in EEG as potential markers for Alzheimer's disease. The search covered the period from 2000 to 2023 and encompassed the PubMed, IEEE Xplore, Science Direct, and Google Scholar databases. The search utilized the keywords "Alzheimer," "EEG," and "Abnormalities" to ensure a comprehensive retrieval of relevant studies.

The inclusion criteria comprised English-language articles published between 2000 and 2023 that investigated abnormalities in EEG as potential markers for Alzheimer's disease. Studies that explored the diagnostic potential of EEG abnormalities or alterations in EEG patterns in Alzheimer's patients were considered. Conference papers, reviews, and non-English articles were excluded.

The initial search yielded a total of approximately 150 articles. After removing duplicates, the titles and abstracts of the remaining articles were screened for relevance. This led to the identification of approximately 78 potentially relevant articles. Full-text examination was then performed to further refine the selection. Ultimately, 62 English articles met the inclusion criteria and were included in this review article. For each included article, the abstracts were carefully read and analyzed. The main focus was to identify studies that specifically investigated EEG abnormalities as potential markers for Alzheimer's disease. The articles were assessed for their objectives, methodologies, findings, and implications related to the diagnostic utility of EEG abnormalities in Alzheimer's disease.

The abstracts of the selected articles were examined to determine whether there were agreements or disagreements between the studies regarding the potential of EEG abnormalities as diagnostic markers for Alzheimer's disease. Emphasis was placed on identifying consistent findings and divergent results that could provide a comprehensive overview of the current state of research in this field.

The findings from the selected articles were synthesized to provide a comprehensive overview of the studies that have explored EEG abnormalities as potential markers for Alzheimer's disease. The review article is structured to present the similarities and contrasts across the studies, the methodologies employed, key findings, and the implications for the diagnostic utility of EEG abnormalities in Alzheimer's disease.

The comprehensive search and selection process ensured the inclusion of relevant studies that investigate EEG abnormalities as potential markers for Alzheimer's disease. By analyzing the selected articles' abstracts, this review article aims to provide insights into the consensus and discrepancies among studies and to contribute to our understanding of the diagnostic potential of EEG abnormalities in the context of Alzheimer's disease.

EEG and alzheimer's disease: Insights over time

In 1931, Hans Berger initiated Alzheimer's-EEG studies, observing slowed rhythms and coherence reduction in EEGs of patients. Subsequent research in 1989 and 2001 linked EEG abnormalities to disease severity. EEG usage in Alzheimer's investigation is motivated by its sensitivity to cortical dysfunction, reflecting functional and anatomical brain defects. EEG coherence offers insights into synaptic plasticity's connection to cognitive function. Non-linear EEG analysis reveals disease-related complexity reduction and functional impairments, providing unique disease progression insights [21].

In 2000, studies focused on EEG frequency band generators to describe Alzheimer's-related changes and predict the disease, identifying alterations in power across delta, theta, alpha, and beta bands [22]. The role of the cholinergic system in EEG was explored, linking EEG changes to Alzheimer's progression and symptoms [23]. Cognitive decline in Alzheimer's was associated with EEG slowing and defects in cholinergic and monoaminergic systems [24].

In 2001, spectral indices were examined for Alzheimer's diagnosis, showing accurate results except for frontal regions affected by eye movement [25]. Cross-Mutual Information (CMI) analysis revealed lower information transmission in Alzheimer's

patients, particularly between distant electrodes and across the right hemisphere [26]. Nonlinear dynamic analysis highlighted decreased complexity in EEG patterns of Alzheimer's patients [27].

In 2003, synchronization probability analysis demonstrated reduced beta band synchrony in mild Alzheimer's patients, linked to cognitive impairment [28]. EEG studies in 2004 found alpha wave analysis effective in distinguishing mild Alzheimer's from vascular dementia and healthy elderly individuals [29]. EEG abnormalities in Alzheimer's were associated with lower frequencies, decreased coherence, and disrupted functional communication in cortical areas [30].

Between 2005 and 2009, research advancements in Alzheimer's and EEG provided valuable insights. Studies in 2005 explored EEG irregularities in Alzheimer's, revealing reduced disorganization [31]. Additionally, reduced synchronization in alpha and high beta bands was observed [32]. Artifact removal using ICA improved Alzheimer's pattern detection [33], while EEG preprocessing using blind source separation enhanced diagnosis [34]. Coherence disruptions in alpha bands indicated potential brain connection issues [35]. Age-related changes in EEG rhythms were discovered in 2006, hinting at dementia prediction [36]. Non-linear analysis unveiled lower complexity in Alzheimer's brain signals [37]. In 2007, higher theta power and lower alpha response were found in AD patients [38], and algorithms identified AD through EEG [39]. Some EEG rhythms were linked to memory and attention tasks [40]. The ApoE gene was linked to altered brain activity [41], while GBP indicated cognitive dysfunction [42]. Alzheimer's EEG changes in various frequency ranges were explored in 2008 [43], and qEEG and ERP became biomarkers for early detection [44]. Brain wave analysis revealed potential Alzheimer's signs [45], and EEG complexity alterations across frequencies were detected [46]. In 2009, EEG incoherence was explored as a diagnostic indicator for early-stage Alzheimer's [47]. Lastly, communication dynamics between brain regions provided insights into memory disturbances [48].

In 2010, an article highlighted Alzheimer's effects on EEG: Slowing, complexity reduction, and synchrony disorders. Specific EEG markers were identified, including alterations in frequency bands, connectivity, and synchronization. The article explored EEG's diagnostic utility, addressing methods, analysis types, and limitations due to signal variability and standardization challenges. Advantages of EEG for Alzheimer's diagnosis were discussed, including non-invasiveness and potential early detection. Future directions envisioned machine learning integration [49].

A 2010 study investigated synchronization measurement methods for AD diagnosis, suggesting combined methods could enhance accuracy [50]. In 2011, nonlinear complexity measures were applied to EEG signals, showing improved AD detection accuracy when combined [51]. EEG and ERPs were considered for low-cost, non-invasive assessment in high-risk groups [52].

In 2012, a study correlated the alpha3/alpha2 power ratio in EEG markers with hippocampal atrophy in MCI and Alzheimer's patients, suggesting diagnostic potential [53]. Studies in 2014 recognized the challenge of understanding EEG brain signals and proposed computer-assisted analysis to enhance brain issue identification for effective Alzheimer's diagnosis [54]. A 2014 study at the Institute of Information Technology in Thessaloniki focused on Alzheimer's research using EEG and recent

studies [55].

In 2015, studies focused on EEG's potential for early Alzheimer's diagnosis, revealing intricate signals in AD individuals. Techniques measuring neural synchrony (phase, coherence, cross-correlation) were tested on databases, particularly in temporal brain regions affected early in AD. A study employed deep learning networks on EEG data, improving accuracy [56,57]. In 2016, a new EEG biomarker (Δ EEG A) was proposed for early AD detection, outperforming existing methods [58]. Abnormal neural coordination and connectivity were observed in AD and MCI resting-state EEG [59]. Delta and theta band synchronization disturbances were identified as potential AD biomarkers [60]. In 2017, algorithms and machine learning enhanced EEG biomarker classification accuracy, highlighting its potential in clinical trials [61].

In 2018, EEG's relationship to cognitive disorders and dementia diagnosis was explored, suggesting its usefulness but calling for larger studies [62]. Clinical EEG data was used to differentiate cognitive conditions, achieving high classification accuracy [63]. qEEG power alterations were observed in AD and MCI, correlating with neuropsychological measures [64]. TMS-EEG study linked frontal brain connections to cognitive decline [65]. A multi-task learning approach with EEG images improved AD detection accuracy [66].

From 2020 to 2023, research milestones in AD diagnosis emerged. In 2020, an article underscored AD's increasing prevalence and suggested EEG's cost-effective role in monitoring cognitive decline [67]. Electrophysiology's relevance in understanding AD's impact on brain activity was highlighted [68]. In 2021, EEG gained prominence for early AD detection and identifying biomarkers [69,70]. "Lacsogram" introduced EEG-based AD diagnosis [71]. EEG studies focused on different stages and disease connections, often combined with MRI. Resting/task-oriented EEG and machine learning aided early detection, revealing cognitive impairment indicators [72,73]. Combining Hjorth parameters and features improved AD diagnosis [74]. In 2022, finite response filters and machine learning improved EEG-based AD diagnosis [75,76]. ERP and deep learning models were explored [77]. In 2023, Deep learning's impact on AD diagnosis was evident [78]. Early AD diagnosis's significance was emphasized [79]. Intelligent models like Adazd-Net demonstrated high AD diagnosis accuracy [80-82]. EEG-based models distinguished between AD, mild cognitive impairment, and healthy aging [81]. EEG in clinical trials and AD monitoring platforms highlighted its potential [75,80].

Discussion

While the primary diagnosis of cognitive disorders relies on clinical assessment, EEG plays a crucial role in evaluating, classifying, and monitoring specific conditions [82-92]. EEG's potential has been demonstrated in appraising neurological disorders like AD, autism, Parkinson's Disease (PD), and ADHD [83]. Changes in Quantitative EEG (QEEG) have been observed in PD and ADHD, with QEEG variables correlating over time with cognitive assessment tools and predicting PD-related dementia [84]. Notably, distinct EEG spectrum and Event-Related Potential (ERP) changes emerge in motor abnormalities and cognitive decline, particularly in PD, while connectivity disruptions manifest in schizophrenia spectrum disorders [85,86]. Despite EEG's reliability and noninvasiveness, its clinical use requires advancements in analytical techniques and technologies [87]. Recent validation of the theta/beta ratio as an ADHD diagnostic marker

highlights EEG's role, albeit with specificity challenges [88]. In Autism Spectrum Disorders (ASD), EEG research uncovers power anomalies, functional connectivity disruptions, and the impacts of GABAergic transmission [89,90]. Furthermore, dementia reveals individual-level biomarkers in EEG, such as decreased dominant frequency and increased θ power, signifying cognitive decline [91]. Although EEG holds promise for understanding brain function and clinical applications, further research is vital to establish its diagnostic utility in conditions like dementia and mild cognitive impairment [92-94]. Alzheimer's disease is a global healthcare challenge characterized by cognitive decline and neurodegeneration. The introduction of the literature underscores the urgency and importance of finding effective diagnostic tools and therapeutic strategies for this condition [21]. EEG, as a non-invasive and cost-effective neuroimaging technique, has gained prominence in the field of AD research. The literature synthesizes the findings from 64 reviewed studies, collectively reinforcing its role in understanding the pathophysiology and diagnosis of AD [21]. One key finding highlighted in the literature is the presence of EEG abnormalities as potential AD biomarkers. These abnormalities encompass rhythmic slowing, reduced interregional coherence, increased theta/delta, and decreased alpha/beta activities [21]. These EEG changes are shown to correlate with the severity of AD and offer diagnostic potential [23]. Additionally, altered EEG generators, particularly global field power in various frequency bands, have been identified as discriminators between AD patients and control subjects [22]. This emphasizes the potential of EEG in aiding the diagnosis of AD. Longitudinal studies mentioned in the literature suggest that EEG has predictive power for tracking AD progression, especially from the stage of Mild Cognitive Impairment (MCI) [22]. This indicates the potential utility of EEG as a tool for early diagnosis and monitoring of the disease. The literature also highlights the connection between EEG abnormalities and the cholinergic system, offering insights into both diagnostic and therapeutic avenues [23]. Cognitive symptoms in AD are strongly associated with EEG slowness and cholinergic deficits [24], suggesting that targeting these aspects could be beneficial in managing AD. Furthermore, the involvement of the monoaminergic system suggests potential treatment options alongside cholinergic therapies [24], indicating a multifaceted approach to tackling AD. EEG spectral indices, such as fast/slow power ratios, are shown to have high diagnostic accuracy [25]. This indicates the potential for EEG to serve as a reliable diagnostic tool in the clinical setting. Cross-information analysis reveals impaired cortical connectivity in AD [26], emphasizing the importance of understanding the neural network disruptions associated with the disease. Non-linear EEG analysis also identifies complexity reductions in AD patterns, advocating for non-linear approaches [27], which could provide novel insights into the disease's mechanisms. EEG synchronization measures show promise in both diagnosis and assessing disease progression [28], further highlighting the versatility of EEG as a diagnostic tool. Individual EEG frequencies, such as decreased alpha and increased delta/theta, are identified as differentiators between different types of dementia [29], underlining the specificity of EEG patterns in AD. The literature also underscores the diagnostic and neuropathological value of EEG, particularly in cortical involvement and synaptic dysfunction [30]. This suggests that EEG could be a valuable tool for understanding the pathological changes in AD. Moving forward, the literature discusses several advanced techniques and approaches in EEG research. Approximate entropy (ApEn) analysis is mentioned as a potential tool for understanding brain dysfunction in AD patients [31]. How-

ever, cautious optimism is warranted due to sample size limitations. EEG synchronization dynamics are explored, revealing lower synchronization levels in specific frequency bands, which shed light on functional connectivity disorders and self-organized criticality in neural networks [32]. Advanced preprocessing techniques like Independent Component Analysis (ICA) are mentioned, which can improve EEG data interpretability and diagnostic accuracy, particularly in early AD stages [33]. Blind Source Separation (BSS)-based preprocessing is also highlighted as a method that enhances EEG classification [34]. Altered functional connectivity patterns, especially reduced coherence in the alpha band, are found to contribute to cognitive decline in AD [35]. Classification algorithms using EEG features are shown to demonstrate high diagnostic accuracy [36], suggesting the potential for machine learning in improving AD diagnosis. The complex relationship between EEG measures and cognitive decline is explored [37], emphasizing the need for a nuanced understanding of the data. Quantifying EEG slowing and analyzing individual frequencies show promise for early AD detection and differentiating dementia types [38,39], underlining the specificity of EEG markers. Genetic risk factors in AD underscore EEG's diagnostic and research value [40,41], highlighting the potential for personalized medicine in AD management. The literature also discusses the diagnostic potential of gamma band power enhancement [42,43] and quantitative EEG (qEEG) as a reliable biomarker for early AD cognitive impairment [44]. Signal processing and machine learning techniques are presented as essential for enhancing AD diagnosis accuracy, revealing neural synchronization patterns and complexity changes [45-50]. Combining nonlinear signal complexity measures with machine learning is shown to greatly improve diagnostic accuracy [51], promoting a multimodal approach. EEG is positioned as a valuable tool for understanding normal and abnormal brain aging, aiding individual-level assessment [52]. Correlations between EEG markers and hippocampal atrophy are highlighted, underscoring diagnostic and prognostic potential [53]. Computational methods, data mining, and machine learning are found to support automated AD diagnosis [54], offering potential for streamlining the diagnostic process. EEG's versatility spans differential diagnosis, prognosis, and drug effectiveness monitoring [55]. Advanced signal processing and deep learning networks achieve high accuracy in AD classification [56-58]. Disturbances in functional connectivity are identified as potential neurophysiological biomarkers of AD [60]. The literature presents an EEG-based index utilizing 14 biomarkers, achieving significant classification accuracy and showcasing the potential for improved diagnostic accuracy in clinical trials [61]. Distinct EEG patterns in cortical oscillatory activity and functional connectivity are revealed in different cognitive disorders, such as Frontal Dementia (FTD) and AD [62]. A novel approach involving epoch-based entropy and spike modeling achieves efficient discrimination between various patient groups, enhancing early AD detection [63]. Early changes in qEEG power, particularly relative theta power, are discussed as potential markers for AD-related cognitive decline and differentiation between AD, MCI, and healthy controls [64]. The integration of EEG with other neuroimaging methods, such as transcranial magnetic stimulation, offers a deeper understanding of AD pathophysiology and personalized therapeutic possibilities [65]. Deep learning techniques, including Convolutional Neural Networks (CNN) and Deep Neural Networks (DNN), show promise in AD diagnosis and differentiation from other cognitive impairments [76]. A multi-task learning strategy with a discriminant convolutional high-order Boltzmann machine proves effective for feature extraction and classification

accuracy [66]. The literature emphasizes the importance of non-invasive and cost-effective diagnostic tools, like EEG, for early AD detection and tracking cognitive decline [67]. EEG's integration with MEG biomarkers in clinical trials is advocated to provide insights into neural dynamics, network behavior, and support drug discovery initiatives [68]. EEG is positioned as a practical and accessible biomarker for early AD detection, highlighting its advantages over molecular markers [69]. The economic and social consequences of AD underscore the significance of EEG in early diagnosis [70]. The "Lacsogram" tool is introduced for EEG signal processing to describe AD activity and diagnose disease stages, showcasing promising machine learning-based classification accuracy [71]. Combining Hjorth parameters with various features and analysis methods in early AD detection from EEG signals yielded high classification accuracy [74]. Standardization in EEG recording methods and data analysis is emphasized for monitoring disease progression and interventions, with EEG feature extraction and supervised machine learning achieving high classification accuracy between healthy subjects, MCI, and AD patients [77]. A computer-based system for AD diagnosis using EEG signals from a limited number of electrodes, implementing deep learning techniques, achieves high accuracy [78]. Combining EEG signal processing with gait analysis through a deep learning strategy demonstrates potential for comprehensive AD patient monitoring and diagnosis [79]. Focusing on periodic components in EEG analysis shows promise in distinguishing between healthy subjects, MCI patients, and AD patients [80]. The Adazd-Net framework for automatic AD detection using EEG signals achieves high accuracy and provides explanations for predictions [81]. An interdisciplinary approach combining EEG signals and gait monitoring offers potential benefits for early AD diagnosis and monitoring [82]. The literature provides a comprehensive overview of the role of EEG in understanding and diagnosing Alzheimer's disease. It highlights the potential of EEG as a valuable biomarker, emphasizing its versatility, diagnostic accuracy, and integration with advanced technologies like machine learning. While there is a wealth of promising findings, the literature also acknowledges the need for further research, larger sample sizes, and standardization to fully unlock the diagnostic and prognostic potential of EEG in the context of AD. EEG research in AD is a dynamic field, offering hope for earlier and more accurate diagnosis, as well as insights into the underlying pathophysiological mechanisms of the disease.

Conclusion

In conclusion, EEG holds promise as a valuable tool for diagnosing and monitoring AD. The reviewed studies demonstrate consistent findings in using EEG features, patterns, and connectivity to distinguish AD and MCI from healthy controls. Machine learning techniques enhance diagnostic accuracy, but challenges in clinical translation remain. Integration of EEG with other biomarkers and advancements in technology offer potential for more accurate diagnosis and understanding of AD. However, further research is needed to address individual variability, comorbidities, and the dynamic nature of AD progression. EEG-based approaches show potential for early AD detection and insights into cognitive decline mechanisms.

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