

Wavelet Entropy Analysis of EEG Signals During Wake and Sleep in Patients with Alzheimer's Disease: A Pilot Study

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Purpose: Our primary objective is to delve into the wavelet entropy of EEG during wake and sleep in patients with Alzheimer's disease (AD). This is a pilot study aimed at exploring the potential of wavelet entropy as an indicator of EEG complexity in AD patients.

Patients and Methods: This study enrolled 30 participants (15 AD patients vs. 15 age-/sex-matched healthy controls). Wavelet entropy analysis was conducted on the electroencephalogram (EEG) signals recorded from all participants across the two groups. A comparative analysis was undertaken between the integral wavelet entropy (En) and individual-scale wavelet entropy (En(a)) during wakefulness and distinct sleep stages in the two patient groups.

Results: Compared with the healthy control group, the entropy of AD group was significantly lower in wakefulness and significantly higher in N3 stage (all $P < 0.001$). AD patients demonstrated lower En(a) in the β and α frequency bands during wakefulness, compared to the healthy controls (all $P < 0.001$). Conversely, during N3 stage, these patients displayed higher En(a) values across β , α , and θ frequency bands compared to the control cohort (all $P < 0.001$).

Conclusion: Wavelet entropy can be used as a reliable indicator of the complexity of EEG signals during waking and different sleep stages in patients with AD. This provides a new insight into the pathophysiological mechanisms of dementia. Due to the limited sample size, larger-scale studies are needed in the future to validate these findings.

Keywords: dementia, sleep stages, brain electrophysiology, wavelet entropy, cognitive function

Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disorder, manifests as memory decline and multi-domain cognitive dysfunction, accounting for 60–80% of global dementia cases.¹ Its neuropathological hallmarks include extracellular amyloid- β (A β) plaque deposition and intraneuronal hyperphosphorylated tau protein aggregation, collectively driving synaptic degeneration and neuronal apoptosis through protein misfolding mechanisms. Current diagnostic protocols prioritize cerebrospinal fluid (CSF) analysis, with reduced A β 42 levels and elevated phosphorylated tau-181 (p-tau181) serving as gold-standard biomarkers. Notably, the 2024 diagnostic guidelines now recognize plasma p-tau217 and GFAP as equally valid alternatives to CSF testing, reflecting advancements in minimally invasive detection methods.² Despite the diagnostic value of CSF biomarkers and neuroimaging techniques (such as amyloid-PET and MRI), their clinical use is limited by invasiveness (lumbar puncture), radiation exposure (PET/CT), and high costs.

Electroencephalography (EEG) is a noninvasive, cost-effective, high-temporal-resolution technique that monitors synchronous neuronal activity, reflecting neuronal degeneration and synaptic loss, which are crucial for cognition.³ EEG has shown promise in diagnosing dementia by identifying cognitive impairment before significant brain atrophy or behavioral symptoms

emerge.^{3,4} Extensive research has been conducted on analyzing brief intervals of awake resting-state EEG (rsEEG) to develop EEG biomarkers for AD.⁴⁻⁷ Methods based on power spectrum and functional connectivity have been extensively employed to characterize rsEEGs in individuals with MCI and AD.^{5,8} The diagnostic accuracy of rsEEG for AD is still debated, and both the 2024 NIA-AA and European Neuroscience Societies guidelines exclude rsEEG biomarkers from standard protocols for cognitively impaired older adults.^{2,9}

Wavelet entropy is based on the concept of disorder in thermodynamics and is a more comprehensive measure of signal complexity compared to traditional methods. It measures how signal energy is distributed across time and frequency, reflecting the level of organization in neural oscillations across multiple scales, providing a more comprehensive assessment of brain activity. Traditional spectral methods assess power within separate frequency bands.¹⁰⁻¹⁴ In contrast, wavelet entropy evaluates both regular rhythmic activity and irregular changes across multiple scales. Low entropy indicates more synchronized brain activity, such as the large slow waves observed during N3 sleep. High entropy indicates more irregular and less synchronized activity. Alzheimer's disease is characterized by synaptic loss and disruption of large-scale brain networks. These changes may alter neural synchronization and oscillatory patterns. Sleep, especially slow-wave sleep, is a highly synchronized brain state and may help detect abnormal neural dynamics.

In this context, sleep-stage-dependent neural synchronization may be differentially affected in AD. Many studies have looked at EEG entropy during wakefulness or specific sleep phases, but how neural complexity changes across sleep stages in AD and its link to disease progression is still unclear. Our study uses wavelet entropy to measure EEG complexity during wakefulness and different sleep stages in AD patients. H. Azami et al¹⁵ reported reduced entropy during REM sleep in AD patients but did not assess NREM stages. A. Cacciotti et al¹⁶ reviewed entropy-based methods in neurodegenerative disorders and highlighted their sensitivity, though most studies focused on resting-state EEG. Similarly, M. A. Zúñiga et al¹⁷ emphasized the need to explore entropy changes across sleep to better capture disease progression. However, sleep-stage-specific EEG entropy patterns in AD remain underexplored. Therefore, the present study applies wavelet entropy to characterize EEG complexity across wakefulness and multiple sleep stages in AD, with the goal of identifying stage-related electrophysiological alterations and enhancing our understanding of the disease-related disruptions in brain network dynamics.

The present study applies wavelet entropy to characterize EEG complexity across wakefulness and multiple sleep stages, including N2 and N3, in individuals with AD. The aim is not to focus solely on early diagnosis but to explore electrophysiological changes that reflect underlying neurophysiological alterations. By examining stage-dependent entropy patterns, this study seeks to improve understanding of sleep-related network dysfunction and its potential association with disease severity and progression. Based on previous findings, we hypothesized that patients with Alzheimer's disease would exhibit altered EEG complexity across wakefulness and sleep stages compared with healthy controls, which could be detected using wavelet entropy analysis.

Materials and Methods

Participants

A total of 30 patients from the outpatient and inpatient departments of Tianjin Union Medical Center were included in this study, which comprised 15 AD patients (7 male, mean age 69.93 ± 4.86 years) and 15 health controls (HC) (8 male, mean age 68.73 ± 5.56 years) individuals.

The inclusion criteria for patients with AD were stipulated as follows: (1) fulfilling the diagnostic standards set forth by the NIA-AA Diagnostic Guidelines Writing Group in 2011; (2) exhibiting deficits in two or more cognitive domains, encompassing memory, language, visual spatial abilities, executive functions, as well as alterations in personality and behavior; (3) being over 50 years of age and possessing an educational background beyond primary school education; (4) suffering from impairment in activities of daily living, indicated by a score of more than 22 on the Abilities of Daily Living Scale (ADL), stemming from a non-somatic structural disorder that significantly compromises social functioning, and a Clinical Dementia Rating Scale (CDR) score ranging from 0.5 to 3 points.

The exclusion criteria were defined as follows: (1) Patients who have a past medical history of neurological or psychiatric disorders that can potentially induce dementia unrelated to AD-specific cognitive decline, including but not limited to fronto-temporal dementia, Lewy body dementia, vascular dementia, Parkinsonism, and epilepsy. (2) Patients with a documented history

of significant internal medical conditions affecting the heart, liver, lungs, and kidneys. (3) Patients who exhibit significant structural abnormalities in memory-related brain regions, such as the frontal lobe, medial temporal lobe, hippocampus, and thalamus, as evidenced by head computed tomography (CT) or magnetic resonance imaging (MRI) examinations. (4) Patients with severe anxiety and depression, as indicated by Hamilton Depression Rating Scale (HAMD) scores exceeding 24 and Hamilton Anxiety Rating Scale (HAMA) scores exceeding 21. (5) Patients with a history of drug, toxin, or alcohol abuse. (6) Patients suffering from severe dementia, reflected by a Clinical Dementia Rating Scale (CDR) score of 3, and who are unable to cooperate in completing neuropsychological assessments. (7) Patients with Hachinski Ischemia Scale scores surpassing 4.

There were no significant differences in age, sex, or years of education between the two groups ($P > 0.05$). Prior to the start of the study, all participants voluntarily enrolled and provided written informed consent. The study protocol was approved by the Institutional Ethics Committee of Tianjin Union Medical Center (Approval No. 2025-B115) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Due to participant availability and strict inclusion criteria, the final sample consisted of 15 AD patients and 15 healthy controls. Therefore, this study should be considered a pilot study.

Neuropsychological Assessments

Comprehensive data were collected on the medical history and medication of patients diagnosed with AD. The participants underwent evaluations utilizing various scales, which were administered either by the participants themselves or by a guardian who had intimate knowledge of the participant's condition. The degree of cognitive impairment is determined by a brief mental state examination (MMSE). Patients whose condition prevented them from cooperating or completing any part of the assessment were recorded as unable to complete, and their score on the incomplete cognitive assessment was recorded as 0.

EEG Recording and Analysis

EEG Data Acquisition

Participants were instructed to refrain from taking any medications (eg., antipsychotics, antidepressants, benzodiazepines, or other sleep-inducing drugs) or substances (eg., coffee and alcohol) that could disrupt sleep for two days prior to and on the day of the examination. They were also instructed to wash and thoroughly dry their hair on the day of the examination. The scalp was sanitized with alcohol before EEG recording. Data acquisition took place in a serene and comfortable EEG room, where participants were seated in a quiet environment and instructed to keep their eyes closed.

The EEG data were recorded using an EB-neuro Be-light EEG system (Firenze, Italy) with scalp disc electrodes, following the internationally standardized 10–20 system. A total of 20 electrodes, including bilateral auricular electrodes, were placed, with the auricular electrodes serving as reference points for the 16-channel EEG recording. Electrode contact impedances were kept below 5 k Ω , and the analog-to-digital conversion was set to a sampling rate of 512 Hz.

For overnight EEG recording, participants were fitted with the EEG device on the evening of the first day, and recording continued until 7:00 AM the following morning, resulting in a total acquisition time of over 8 hours. During this period, participants were instructed to rest and sleep in a quiet, undisturbed environment to ensure the natural quality of sleep and the reliability of EEG signals.

In data processing, all EEG data were manually interpreted and annotated by a qualified EEG technician according to standard sleep staging rules. Ten-second segments of EEG signals (16 channels) were selected from annotated periods for each sleep stage (eg., Wake, N2, N3, REM), ensuring no obvious artifacts. The same number of segments were extracted from each stage for each participant, and wavelet transform and entropy calculations were performed for each second of the EEG segments.

Wavelet Analysis

Wavelet analysis is a digital signal processing technique that decomposes signals through cross-correlation with scalable basis functions. By applying time-scale operations, it enables multiscale decomposition of complex signals into localized frequency components.^{18–20} These wavelet bases, derived from a mother wavelet via translation and scaling, represent finite-duration physical events or localized oscillations.

This study utilizes the continuous wavelet transform (CWT), defined for EEG signal $s(t)$ as:

$$W_s(a, b) = \int_{-\infty}^{+\infty} s(t) \overline{W_{ab}(t)} dt \quad (1)$$

The family of wavelet functions is generated from the mother wavelet $W(t)$ through translation (parameter b) and scaling (parameter a) transformations:

$$W_{ab}(t) = \frac{1}{\sqrt{a}} W\left(\frac{t-b}{a}\right) \quad (2)$$

In the present investigation, the EEG signals underwent analysis at numerous scales employing the Continuous Wavelet Transform (CWT), with a minimum scale set at 0.00075 seconds and a scale magnification factor of 1.5. A comprehensive analysis was conducted encompassing a total of 30 wavelet scales. The correspondence between different wavelet scales and their central frequencies is shown in Table 1. To ensure comprehensive coverage of the EEG signal frequencies, unfiltered raw EEG signals were utilized, encompassing a broad spectrum of frequencies for analysis.

Multiscale Power Spectral Analysis

The scale-dependent power of the EEG signal $s(t)$, derived from the wavelet coefficients $W_{ab}(t)$, can be quantified by the wavelet power spectral density function at each scale. This function characterizes the power distribution across distinct temporal scales of the EEG signal:

$$P(a) = \frac{2}{C_W} \int_{-\infty}^{+\infty} |W_s(a, b)|^2 db \quad (3)$$

The total power of the EEG signal is the summation of power contributions across all scale-specific components:

$$P = \int_0^{+\infty} P(a) da \quad (4)$$

By normalizing with respect to $P(\text{total})$, the relative percentage of scale-specific power within the total signal power is obtained:

$$\tilde{P}(a) = \frac{P(a)}{P} \quad (5)$$

Wavelet Entropy Analysis

The $En(a)$ and En were used as dimensionless parameters in this study, and were calculated according to following formulas:

$$En(a) = -\tilde{P}(a) \ln \tilde{P}(a) \quad (6)$$

$$En = \int_0^{+\infty} En(a) da = - \int_0^{+\infty} \tilde{P}(a) \ln \tilde{P}(a) da \quad (7)$$

where En represents integral wavelet entropy of EEG signals from 16 channels, and represents individual-scale wavelet entropy of EEG signals from 16 channels.

Table 1 The Correspondence Between Different Wavelet Scales and Central Frequencies

Scales Frequency (Hz)	3 117.06	4 78.04	5 52.02	6 34.68	7 23.12	8 15.41	9 10.28
Scales Frequency (Hz)	10 6.85	11 4.57	12 3.04	13 2.03	14 1.35	15 0.90	16 0.60

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics 25. The statistical analyses were performed to test the hypothesis that EEG complexity, measured by wavelet entropy, differs between AD patients and healthy controls across wakefulness and sleep stages. Demographic and clinical variables were summarized as mean $\pm$ SD or median (IQR), according to the data distribution. Group differences were assessed using Student's t-tests for approximately normally distributed continuous variables and χ^2 -tests for categorical variables. For comparisons involving more than two groups, one-way ANOVA was used for normally distributed data, and the Kruskal–Wallis H-test was used for non-normal data, with post-hoc tests performed where appropriate.

For EEG-derived wavelet entropy across multiple sleep stages, a repeated-measures analysis of variance (ANOVA) was applied to account for within-subject correlations. In this analysis, sleep stage was treated as a within-subject factor, and group (AD vs. control) was treated as a between-subject factor.

Effect sizes (Cohen's d) and their 95% confidence intervals were calculated to assess the practical significance of group differences. Statistical significance was set at $\alpha = 0.05$.

Results

Clinical Data

The clinical data comparison between the two groups is presented in [Table 2](#), while [Supplementary Table 1](#) illustrates the clinical data of each individual in the AD group. No significant differences were observed in age, sex, or education level between the groups. The MMSE scores of the AD group were significantly lower than those of healthy individuals ($P < 0.001$).

Entropy Between the Groups During Wake Stage and Different Sleep Stages

The results revealed that, compared with the healthy control group, the AD group exhibited significantly lower entropy (En) during wakefulness but higher En during the N3 sleep stage (all $P < 0.001$; see [Figure 1](#) and [Table 3](#)).

Individual-Scale Wavelet Entropy During Wake Stage and Different Sleep Stages Between Two Groups

Wavelet entropy analysis was conducted on EEG signals at individual scales to explore the variations in scale-specific wavelet entropy between the AD group and HC group during wakefulness and distinct sleep stages. The results are illustrated in [Figure 2](#) (A: wake stage, B: N2 stage, C: N3 stage, D: REM stage), with detailed statistical values provided in [Supplementary Tables 2–5](#) for each corresponding stage.

Since no significant differences in total entropy during the N1 stage were observed between the AD and HC groups, the scale-specific entropy was not discussed in this context. Wavelet entropy analysis was conducted on EEG signals at individual scales to explore the variations in scale-specific wavelet entropy between the AD group and the HC group during wakefulness and distinct sleep stages. The results revealed that during wakefulness ([Figure 2A](#)), the AD group

Table 2 Demographic and Clinical and Demographic Data in Healthy Control Subjects and Alzheimer's Disease Patients

Group	HC	AD	ANOVA p-value
Total number	15	15	NS
Male/Female	7/8	8/7	NS
Age (range) years	68.73 $\pm$ 5.56	69.93 $\pm$ 4.86	NS
MMSE	29.27 $\pm$ 0.80	17.53 $\pm$ 3.92	<0.001

Note: Data are presented as mean $\pm$ standard deviation.

Abbreviations: AD, Alzheimer's disease patients; HC, Healthy controls; MMSE, Mini-Mental State Examination; NS, not significant;

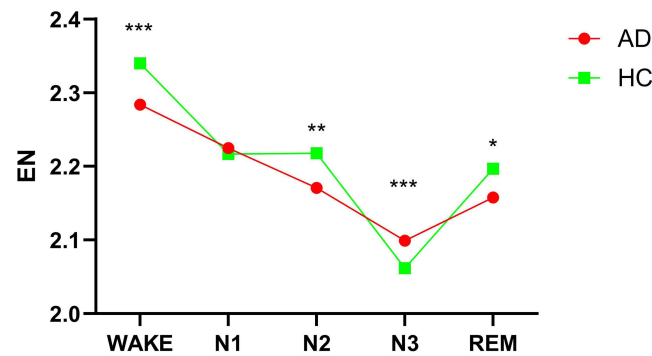


Figure 1 Differences in the integral wavelet entropy during wake and different sleep stages between the AD and healthy control groups.
Notes: *Represents $P < 0.05$, **Represents $P < 0.01$, ***Represents $P < 0.001$. Wavelet entropy (EN) is a dimensionless parameter representing the complexity of EEG signals.
Abbreviations: AD, Alzheimer's disease patients; HC, Healthy controls.

exhibited lower En (3–10) wavelet entropy at the 3–10 scales compared to the HC group, whereas higher entropy was observed at the 12–16 scales in the AD group. In the N2 stage (Figure 2B), the HC group displayed elevated wavelet entropy at the 6–9 scales relative to the AD group, while the AD group showed increased entropy at the 13–16 scales. During the N3 stage (Figure 2C), the AD group demonstrated higher wavelet entropy at the 4–12 scales compared to the HC group, but lower entropy at the 14–16 scales. Finally, in REM sleep (Figure 2D), the AD group exhibited greater En (4–8) wavelet entropy at the 4–8 and 11–12 scales than the HC group, whereas the HC group showed higher entropy at the 14–16 scales.

Individual-Scale Wavelet Entropy Was Compared Between Groups Across EEG Frequency Bands During Wake Stage and N3 Sleep

The En(a) was assessed across canonical EEG frequency bands, including β , α , θ , and δ . Each scale corresponded to a distinct EEG frequency band, with scales 7, 9, 12, and 15 mapped to the β , α , θ , and δ bands, respectively. In the wake stage (Figure 3), AD group exhibited significantly lower En(a) values in the β band compared to the HC group, particularly over the FP1, FP2, F4, C3, C4, P3, P4, O1, O2, and T6 electrodes ($P < 0.05$, Figure 3). In the α -band, AD group also showed reduced En(a) relative to the NC group, with pronounced differences observed in the O1 and O2 electrodes ($P < 0.05$). Conversely, in the θ and δ bands, AD group demonstrated higher En(a) values than the NC group, most notably in the O1 and O2 electrodes ($P < 0.05$). Specific statistical details are provided in [Supplementary Tables 6–9](#).

During the N3 stage (Figure 4), AD group exhibited significantly higher mean En(a) values in the β , α , and θ bands compared to HC, with pronounced elevations observed at the T3 electrode (β band) and O1 electrode (α and θ bands) ($P < 0.05$, Figure 4). Additionally, the AD group demonstrated overall elevated En(a) values in the δ band relative to the HC group. Specific statistical details are provided in [Supplementary Tables 10–13](#).

Table 3 The Comparison of Integral Wavelet Entropy During Wake and Different Sleep Stages Between the Alzheimer's Disease Patients and Healthy Control Groups

	Wake	N1	N2	N3	REM
HC (mean±SD)	2.340±0.012	2.217±0.028	2.218±0.027	2.062±0.008	2.197±0.015
AD (mean±SD)	2.284±0.017	2.225±0.031	2.171±0.016	2.099±0.021	2.158±0.009
ANOVA p-value	<0.001	0.600	0.001	<0.001	0.046

Note: Data are presented as mean ± standard deviation.
Abbreviations: HC, Healthy control groups; AD, Alzheimer's Dementia group.

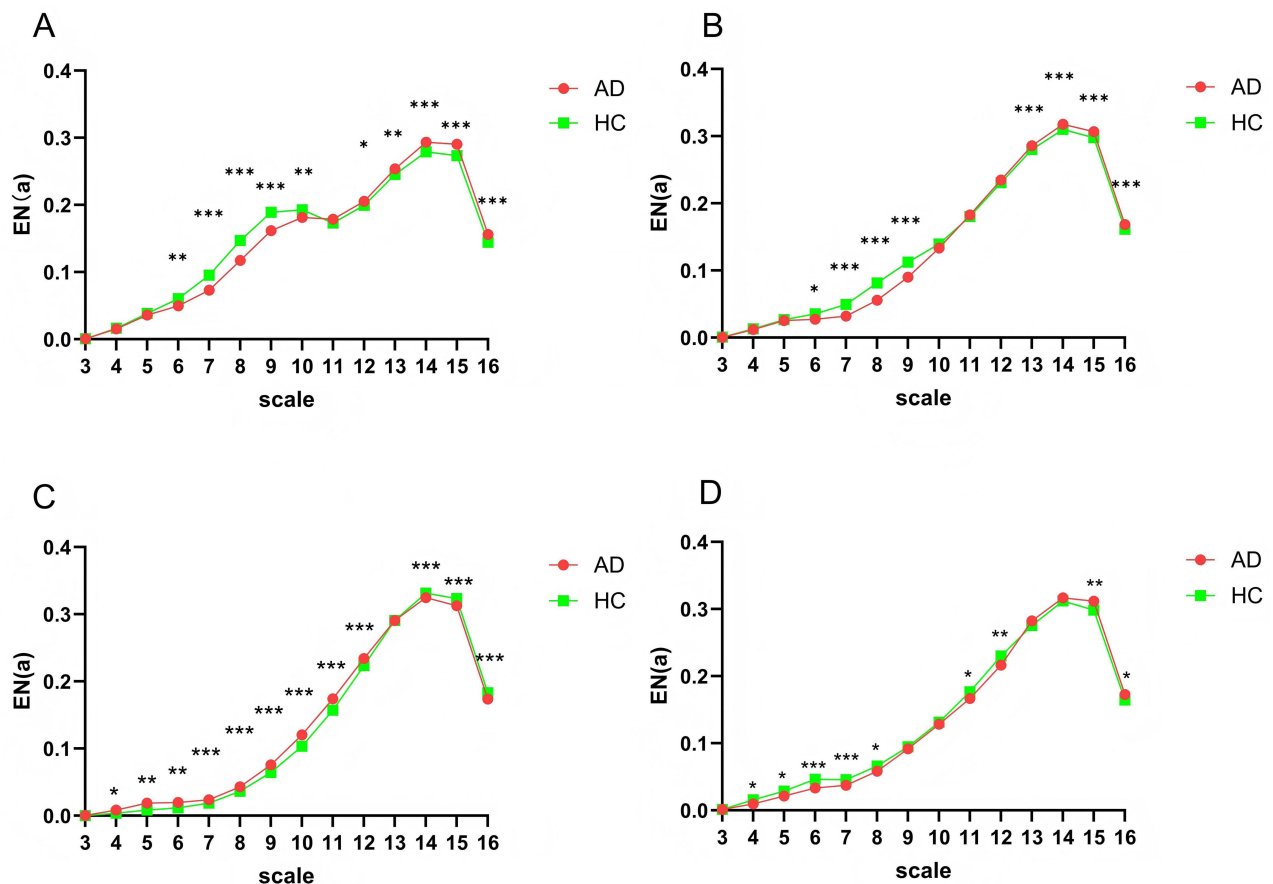


Figure 2 The differences at the individual-scale wavelet entropy during wake and different sleep stages between the AD and healthy control groups.

Notes: *Represents $P < 0.05$, **Represents $P < 0.01$, ***Represents $P < 0.001$. A: wake stage, B: N2 stage, C: N3 stage, D: REM stage. Specific statistical details are provided in [Supplementary Tables 2–5](#).

Abbreviations: AD, Alzheimer's disease patients; HC, Healthy controls.

Discussion

To our knowledge, this is the first study applying wavelet entropy analysis to characterize EEG complexity across full sleep architecture in AD patients. In present study, we found the alternation of wavelet entropy in AD individuals compared with HC. Three key findings emerge: (1) AD patients exhibited significantly reduced global entropy during wakefulness but paradoxically elevated entropy in the N3 sleep stage compared to HC; (2) Individual-scale analysis revealed spatially heterogeneous entropy changes in specific frequency bands, particularly in prefrontal and occipital regions; (3) These entropy abnormalities demonstrate stage-dependent correlations with AD pathophysiology, offering new electrophysiological perspectives on disease progression. The results provide valuable insights into the neurophysiological changes associated with AD. Overall, these findings partially support our hypothesis that patients with Alzheimer's disease exhibit altered EEG complexity across wakefulness and sleep stages compared with healthy controls.

While previous studies have established links between AD progression and sleep macroarchitecture deterioration (eg. sleep fragmentation, reduced slow-wave sleep duration),^{21,22} the scrutiny of sleep EEG in AD has garnered relatively limited attention. Despite this, in NREM sleep, numerous studies have delineated AD-associated alterations in sleep spindles, K-complexes,²³ slow wave activity, and spindle-slow wave coupling, several of which exhibit correlations with the accrual of amyloid and/or tau pathology, or with perturbations in cognitive function.^{4,24–27} Cognition and higher-order perception, which deteriorate in AD, originate from the collective, concerted activity of a substantial number of neurons within intricate cortical circuits and across the brain's intricate large-scale systems.^{8,28} Nonlinear dynamical approaches rooted in information theory allow modeling of large-scale brain activity. Specifically, entropy-based methods facilitate the integration of experimental data derived from diverse modalities into a comprehensive, collective framework. It has been unequivocally

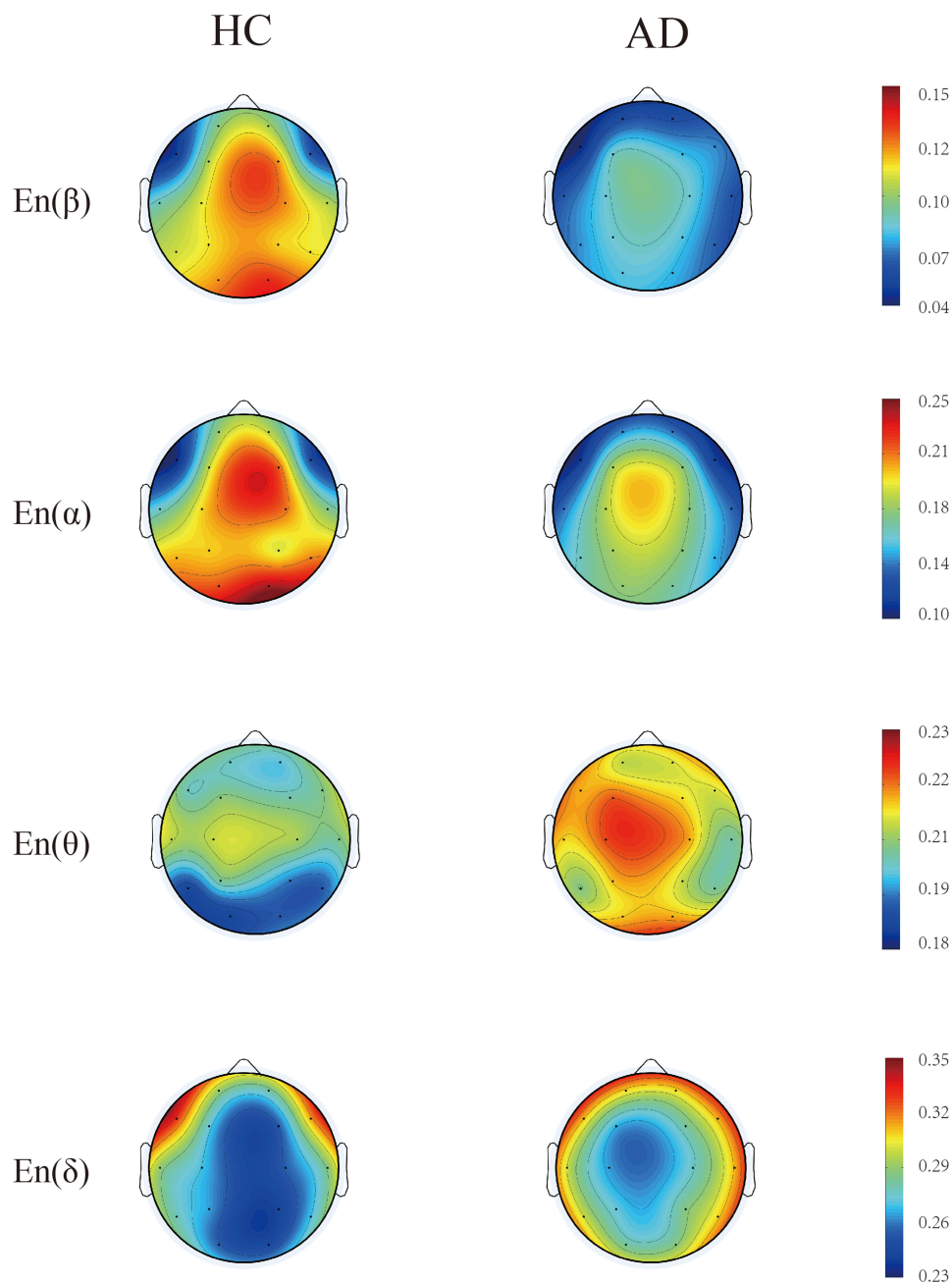


Figure 3 Topographic maps depicted EEG frequency band distributions in HC and AD groups during wake stage. $En(\beta)$, spectral entropy in the beta band; $En(\alpha)$, spectral entropy in the alpha band; $En(\theta)$, spectral entropy in the theta band; $En(\delta)$, spectral entropy in the delta band; Specific statistical details are provided in [Supplementary Tables 6–9](#).
Abbreviations: AD, Alzheimer's disease patients; HC, Healthy controls.

established that collective, nonlinear dynamics constitute the foundation of adaptive cortical activity and are intricately linked to numerous brain disorders.^{8,29}

In recent years, the concept of entropy has been rigorously implemented in the examination of sleep-wake states.^{10,30,31} Wavelet entropy reflects how EEG signal energy is distributed across time and frequency scales. Lower wavelet entropy generally indicates a more regular and synchronized oscillatory pattern, whereas higher wavelet entropy reflects greater irregularity and reduced neural synchronization. From a physiological perspective, it can therefore be interpreted as an index of the degree of organization of large-scale neuronal activity across brain states. Previous study showed that older adults had significantly higher beta-to-theta entropy ratios than young individuals.³² During wakefulness, the brain typically exhibits more complex and variable neural activity, which is associated with higher entropy. In

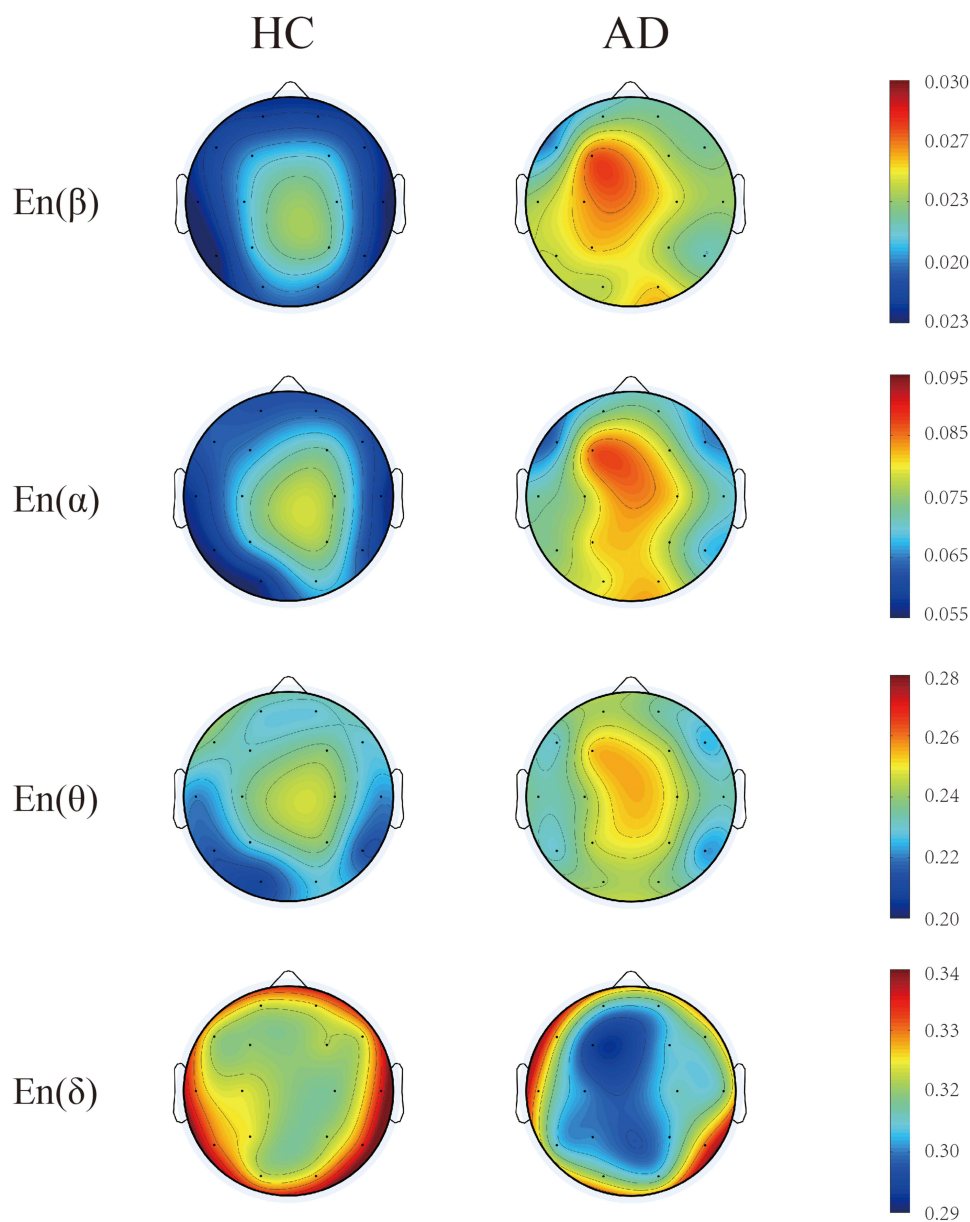


Figure 4 Topographic maps depicted EEG frequency band distributions in HC and AD groups during N3 stage. $En(\beta)$, spectral entropy in the beta band; $En(\alpha)$, spectral entropy in the alpha band; $En(\theta)$, spectral entropy in the theta band; $En(\delta)$, spectral entropy in the delta band; Specific statistical details are provided in [Supplementary Tables 10–13](#).

Abbreviations: AD, Alzheimer's disease patients; HC, Healthy controls.

contrast, deeper NREM sleep, especially N3, is characterized by more synchronized oscillatory activity and therefore lower entropy. A prior research endeavor explored the fluctuations in sample entropy as subjects transitioned from wakefulness to sleep, encompassing both adult and pediatric subjects. The findings revealed a comparable pattern in the variation of sample entropy between these age groups, adhering to the sequence of Wake>REM>N2>N3.³³ Specifically, the entropy of EEG signals in healthy adults was observed to augment during wakefulness and REM sleep, whereas it declined during slow wave sleep.¹¹ Our results indicated that entropy attained its peak during wakefulness and its nadir during the N3 stage in the HC group. This pattern is consistent with the physiological characteristics of healthy sleep. In healthy individuals, including both younger and older adults, N3 sleep is generally expected to show lower entropy than wakefulness and lighter sleep stages because it is dominated by highly synchronized slow-wave activity. Although aging may slightly reduce the degree of synchronization during deep sleep, N3 in healthy older adults still typically represents a relatively low-entropy state.³⁴ The individual-scale wavelet entropy of EEG

signals measures the complexity of the information contained in the components of EEG signals at an individual scale.³⁵ In present study, during wake stage, the AD group exhibited significantly lower En(a) values in the β band compared to the HC group. This reduced β band entropy suggests decreased neural activity in the higher frequency range, which is associated with cognitive functions such as attention and executive control. A recent PET-fMRI study observed β band entropy reduction during wakefulness may reflect A β -mediated synaptic depletion in prefrontal circuits.³⁶

In the α band, the AD group also showed reduced En(a) values, particularly over the O1 and O2 electrodes. This finding indicates reduced neural activity in the occipital regions, which are involved in visual processing and other cognitive functions. Conversely, the AD group demonstrated higher En(a) values in the θ and δ bands, most notably in the O1 and O2 electrodes. Elevated θ and δ band entropy might reflect increased neural activity in lower frequency bands, potentially related to cognitive decline and pathological processes.

During the N3 sleep stage, the AD group exhibited significantly higher En(a) values in the β (T3), α (O1), θ (O1), and δ bands compared to HC. Because N3 sleep normally reflects a highly synchronized cortical state, elevated wavelet entropy during this stage in AD likely indicates impaired neural synchronization and a loss of normal slow-wave organization. This elevated entropy may reflect pathological processes related to impaired synaptic downscaling or other disruptions in slow-wave sleep regulation, coinciding with prior observations of reduced slow-wave activity (SWA) in AD³⁷—a change linked to impaired memory consolidation and synaptic integrity. Additionally, AD-related sleep spindle reduction³⁸ (critical for thalamocortical communication and memory integration) may contribute to these N3 entropy alterations. This, combined with the known SWA reduction in AD, suggests that wavelet entropy may provide a useful marker of AD-related neurophysiological alterations.

Cognitive functions arise in neural networks interconnected by distant brain regions, thereby reflecting their neural activity as manifestations of long-range neuronal interactions.³⁹ These interactions entail a significant level of information integration. Numerous studies have documented that elderly individuals with impaired cognitive function exhibit reduced temporal complexity in their brain activity.⁷

The significantly lower En in AD patients during wakefulness suggests a diminished capacity for neural synchronization and information processing, likely due to the widespread neuronal loss, synaptic dysfunction, and disrupted connectivity characteristic of AD. This is consistent with previous studies showing that AD is associated with reduced functional connectivity and altered neural dynamics in higher frequency bands (eg., β and α), which are critical for cognitive processing.^{5,8,28} The lower En(a) values in the β and α bands observed in our study further support this interpretation, as these frequency bands are closely linked to attention and executive functions, which are impaired in AD.

In contrast, the elevated En during the N3 sleep stage in AD patients may reflect compensatory mechanisms or pathological disruptions in slow-wave sleep regulation. N3 sleep, characterized by slow-wave activity (SWA), is crucial for memory consolidation and synaptic homeostasis. The increased En(a) in the β , α , and θ bands during N3 sleep in AD patients suggests heightened neural activity in these frequency ranges, which may indicate a failure to properly synchronize neural activity during deep sleep. This could be related to the accumulation of A β and tau pathology, which has been shown to disrupt SWA and impair memory consolidation.^{25,26} Specifically, A β deposition is known to interfere with the generation and propagation of slow waves, while tau pathology is associated with synaptic dysfunction and neuronal hyperexcitability, both of which could contribute to the observed increase in entropy during N3 sleep.^{24,25} The elevated δ -band entropy in AD patients during N3 sleep further supports the idea of disrupted slow-wave activity, as δ waves are a hallmark of deep sleep and are critical for restorative processes. These findings suggest that wavelet entropy abnormalities in AD patients are not only stage-dependent but also closely linked to the disease's underlying pathophysiology. This result is consistent with previous findings on nonlinear EEG dynamics in Alzheimer's disease. Jeong⁴⁰ and Maturana-Candelas et al⁴¹ reported that Approximate Entropy and Sample Entropy tend to be reduced in AD patients, indicating diminished neural spontaneity and impaired cortical regulation. The reduced entropy during wakefulness may reflect impaired neural synchronization and cognitive decline, while the increased entropy during N3 sleep may indicate disrupted slow-wave activity and synaptic dysfunction, potentially driven by A β and tau pathology. Future studies should explore the direct relationship between wavelet entropy changes and AD markers (eg., A β and tau levels) to further elucidate these mechanisms and validate the utility of wavelet entropy as a diagnostic tool for AD. Compared to traditional EEG-based markers, which often focus on spectral power or sleep spindle density, wavelet entropy provides a dynamic and multiscale assessment of EEG complexity. This enables

more sensitive detection of subtle neurophysiological changes, particularly during different sleep stages—an area where existing markers may lack resolution. Thus, the proposed method not only complements existing techniques but may offer additional diagnostic value.

In summary, our findings demonstrated wavelet entropy's utility in quantifying EEG complexity across sleep-wake states. Compared to controls, AD patients exhibited reduced entropy during wakefulness and elevated entropy in NREM3 sleep stage. These findings position wavelet entropy as a novel tool for mapping neurophysiological dysfunction in AD, particularly in sleep-wake cycle fragmentation and cortical hyperexcitability during slow wave sleep. These promising results also suggest the potential of wavelet entropy as a component in future EEG-based diagnostic systems for AD. Although the current sample size is limited, individual-level patterns in entropy variability hint at possible differentiation across disease stages. With validation in larger cohorts, this approach could contribute to a scalable, non-invasive framework for both disease detection and monitoring.

One limitation of this study is the inability to obtain full sleep macrostructure variables (such as TIB, TST, WASO, and sleep stage percentages). This study used a dataset acquired for dynamic EEG analysis rather than full polysomnography (PSG). Therefore, standard PSG components like EOG and EMG were not available. As a result, traditional sleep macrostructure parameters, such as TIB, WASO, and sleep efficiency, could not be reliably derived. Future studies can incorporate PSG data to explore the relationship between EEG complexity and traditional sleep parameters. This will help improve our understanding of sleep in Alzheimer's disease and provide more information for clinical diagnosis. Another limitation is the small sample size, with only 15 AD patients. A small sample size may affect the generalizability and statistical significance of the results. Therefore, this study should be considered a pilot study. Future research will increase the sample size to validate our findings and improve the reliability of the results. With a larger sample size, we can better capture the differences in EEG complexity and sleep patterns in AD patients at different clinical stages, further clarifying the potential and application of wavelet entropy in AD research. Additionally, this study could not fully exclude the influence of medication. Although participants refrained from using medications that may affect sleep or brain activity, potential medication effects may still exist. Future studies should consider the impact of medication on EEG. Finally, due to the cross-sectional design and relatively small sample size, the stability of wavelet entropy in AD remains to be validated in larger cohorts with longitudinal or multi-night EEG recordings.

Conclusion

In summary, wavelet entropy may capture dynamic alterations in EEG complexity across wakefulness and sleep stages. Patients with AD exhibited reduced wavelet entropy (En) during wakefulness compared to healthy controls, suggesting diminished arousal levels, while elevated En during N3 sleep implied impaired slow-wave sleep regulation. These findings are consistent with our hypothesis that EEG complexity across wakefulness and sleep stages is altered in individuals with Alzheimer's disease. Wavelet entropy may therefore provide a useful approach for characterizing EEG alterations in AD and may offers additional insights into the relationship between sleep-wake dynamics and neurodegenerative processes.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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