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Original Article

Investigating Cortical Complexity in Mixed Dementia through Nonlinear Dynamic Analyses: A Resting-State EEG Study

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Abstract

Objective: Dementia is a broad term referring to a decline in problem-solving abilities, language skills, memory, and other cognitive functions to a degree that it significantly disrupts everyday activities. The underlying cause of dementia is the impairment or loss of nerve cells and their connections within the brain. The particular symptoms experienced are contingent upon specific regions of the brain affected by this damage. In this research, we aimed to investigate the nonlinear dynamics of the mixed demented brain compared to healthy subjects using electroencephalogram (EEG) analysis.
Method: For this purpose, EEG was recorded from 66 patients with mixed dementia and 65 healthy subjects during rest. After signal preprocessing, sample entropy and Katz fractal dimension analyses were applied to the preprocessed EEG data. Analysis of variance with repeated measures was utilized to compare the nonlinear dynamics of brain activity between dementia and healthy states and partial correlation analysis was employed to explore the relationship between EEG complexity measures and cognitive and neuropsychiatric symptoms of patients.
Results: Based on repeated measures ANOVA, there was a significant main effect between groups for both Katz fractal dimension ($F = 4.10$, $P = 0.01$) and sample entropy ($F = 4.81$, $P = 0.009$) measures. Post hoc comparisons revealed that EEG complexity was significantly reduced in dementia mainly in the occipitoparietal and temporal areas ($P < 0.05$). MMSE scores were positively correlated with EEG complexity measures, while NPI scores were negatively correlated with EEG complexity measures, mainly in the occipitoparietal and temporal areas ($P < 0.05$). Moreover, using a KNN classifier, all significant complexity measures yielded the best classification performance with an accuracy of 98.05%, sensitivity of 97.03% and specificity of 99.16% in detecting dementia.
Conclusion: This study demonstrated a unique dynamic system within the brain impacted by dementia that results in more predictable patterns of cortical activity mainly in the occipitoparietal and temporal areas. These abnormal patterns were associated with patients' cognitive capacity and neuropsychiatric symptoms.

Key words: *Cognition; Complexity Analysis; Dementi; Diagnosis; Electroencephalography*

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Dementia is a progressive and complex neurological disorder that impairs cognitive function and memory, affecting an individual's ability to execute daily activities. It is characterized by a decline in cognitive function beyond what might be expected from normal aging (1). Dementia is a prevalent condition worldwide, with an increasing number of cases as the global population ages. Based on the World Health Organization (WHO), around 50 million people were living with dementia in 2020, and this number is expected to triple by 2050 (2). The pathology of dementia involves the cumulating of irregular protein deposits in the brain, causing nerve cell damage and disrupting communication between brain cells (3). Two most prevalent types of dementia are Alzheimer's disease, characterized by the buildup of tau tangles and amyloid plaques in the brain, and vascular dementia, caused by decreased blood flow to the brain leading to cell damage (4). Other types of dementia, such as Lewy body dementia and frontotemporal dementia, have distinct pathological features (5). Understanding the underlying pathology of dementia is crucial for developing effective treatments and interventions to control the condition and enhance the quality of life for people affected by this challenging disorder (6).

As mentioned, vascular dementia and Alzheimer's disease are two prevalent types of dementia that pose significant challenges to the aging population worldwide. Alzheimer's disease is the most prevalent form of dementia, accounting for around 60-70% of all cases (7), while vascular dementia ranks as the second most common type (8). Neuropathologically, Alzheimer's disease primarily affects the hippocampus and cerebral cortex, whereas vascular dementia is associated with small and large vessel disease, impacting various brain regions depending on the location of vascular damage (9). Despite their distinct etiologies, vascular dementia and Alzheimer's disease share some common symptoms such as memory loss, executive dysfunction, and impaired cognitive abilities (10). Both conditions can exhibit behavioral changes, language difficulties, and challenges in daily functioning, making accurate differential diagnosis crucial for appropriate management and care planning (11). Early detection and intervention are vital in enhancing outcomes and quality of life for individuals affected by these debilitating neurodegenerative disorders (12).

Understanding and analyzing electroencephalogram (EEG) oscillations is paramount in unraveling the complexities of neurological disorders, particularly dementia (13-16). These brainwave patterns provide valuable information regarding the functional connectivity and activity of various brain regions (17), shedding light on how neural circuits are affected in conditions such as dementia (18). By examining the specific frequency bands and coherence of EEG oscillations, researchers can uncover disruptions in neural synchrony and communication that are characteristic of neurodegenerative diseases (19). In dementia, alterations in EEG oscillations, such as disruptions in alpha and beta band activities, have been associated with cognitive decline and memory impairments (20). Detecting and interpreting these aberrant oscillatory patterns can aid in the early diagnosis and monitoring of dementia progression, enabling clinicians to implement timely interventions and personalized treatment strategies (21, 22). Utilizing EEG oscillations as biomarkers not only enhances our understanding of the underlying pathophysiology of neurological disorders (23, 24) but also holds promise for improving diagnostic accuracy and developing targeted therapies for effectively managing conditions like dementia (25, 26). Meanwhile, EEG complexity is a measure that quantifies the intricate structure and dynamics of brain activity captured in electroencephalogram recordings (27). It provides insights into the richness and diversity of neuronal interactions occurring in the brain during different cognitive states and tasks (28). High EEG complexity indicates a more diverse and flexible neural network, capable of rapid information processing and integration, while low complexity may suggest a more rigid or compromised brain function (19). Al-Nuaimi *et al.* (29) utilized three different complexity measures including lempel-ziv, Tsallis entropy, and fractal dimension to quantify EEG changes in Alzheimer's disease. They revealed a significant reduction in the complexity of EEG subbands among patients. Hogan and colleagues showed that people with dementia had lower EEG entropy values (30). Houmani *et al.* found that EEG entropy values were slightly lower in Alzheimer's patients compared to healthy individuals (31). Recent review articles also confirm the findings of these studies (13, 32, 33). However, small sample sizes, imbalance between the studied groups, uncertainty surrounding the EEG analysis method, and the use of entropy measures alone are among the limitations of most of these studies.

Although previous studies have analyzed EEG complexity in dementia and have generally shown reduced EEG complexity in different brain regions in dementia (13, 32, 33), they face important limitations. Almost all previous studies have used only one measure of complexity, and some of them have not met the prerequisites for using these measures, such as the length of the EEG signal under analysis, which could confound the validity of the findings. Also, some studies have examined a limited sample size. Others have not investigated the cognitive correlates of brain complexity. Therefore, in this study, we try to conduct a comprehensive study with a sufficient sample size, using several nonlinear dynamic analysis methods, and measuring possible correlations between these nonlinear measures and cognitive performance of patients with mixed dementia.

Materials and Methods

The study was done following the ethical guidelines outlined in the Declaration of Helsinki (1996) and adhering to the current Good Clinical Practice guidelines. Anonymized subject data was used exclusively for the purpose of the research project. This study was approved by the Academic Council and Bioethics Committee of Pirogov Russian National Research Medical University (Protocol number 10 of 2023-06-28). All subjects (the patients and their guardians) signed written informed consent forms for entering the research project, and the utilization of medical data, and publications of the results.

Participants

Between September 2021 and October 2023, we performed a retrospective review of the records of patients in two private neurology clinics who underwent EEG measurements with the same EEG device (Nihon Kohden, Neurofax EEG-1200) under similar conditions (a quiet room, with the patients seated by experienced operators). Our study focused on individuals referred to the clinic during that period. We included EEG signals of patients with dementia who met the established criteria for diagnosis of mixed dementia (vascular dementia and another neurodegenerative disease especially Alzheimer's disease), as evaluated by skilled neurosurgeons. Out of the initial pool of 113 EEGs from patients with mixed dementia who had recorded EEG data, 47 patients with mixed dementia were excluded due to poor EEG recordings, and overlapping or probable diagnoses. Therefore, we included EEG signals from 66 patients with mixed dementia (average age of 76.54 ± 10.72 years, ~69% male) in the study. In addition, healthy subjects in the same age range were invited to participate in this research through advertisements in local newspapers and also referrals from the acquaintances of the patients. Their physical and mental health conditions were confirmed through clinical interviews conducted by both a neurologist and a psychiatrist. Hence, 65 healthy aging controls (75.05 ± 9.91 years old, ~75% Male) were also recruited in our study.

EEG Recording and Preprocessing

EEG was captured through 19 Ag/AgCl disc scalp electrodes placed according to the international 10-20 system (Fp2, Fp1, T5, Fz, C3, F3, P3, F4, F7, T6, F8, Cz, C4, Pz, T4, P4, T3, O1, and O2). Two additional electrodes A1 and A2 were placed on the earlobes as references. Electrode impedance was kept below 5 kΩ during signal recording. A band-pass filter was set at 0.5-70 Hz during the EEG recording and the sampling frequency was set at 512 Hz. The EEG data were captured continuously for 10 minutes while the individuals rested comfortably in a dimly lit, silent room, with their eyes open. The first minute of EEG signals was removed due to the adaptation of the subject to the environment.

While collecting EEG signals, they can become unintentionally corrupted by various forms of noise and artifacts. These unwanted disturbances stem from a range of sources, both biological and non-biological in nature. Examples include movements and eye blinks, heartbeat, muscular activities, channel noise, and power line interference. Consequently, the recorded EEG signals may not accurately reflect the genuine neural activity occurring within the brain. To address this issue and prevent misleading analysis, it is crucial to incorporate an EEG signal preprocessing phase. This preprocessing stage aims to attenuate noise and eliminate disruptive artifacts, ensuring that the resulting signals primarily represent the pure brainwave activity for subsequent accurate analysis. To process the EEG signals in this study, a proposed pipeline for preprocessing was utilized, employing the EEGLAB toolbox found in the MATLAB software. Initially, the EEG data were re-referenced to the average of A1 and A2 channels as reference points. Subsequently, all the aligned EEG signals underwent a high-pass filtering process with a cutoff frequency of 1 Hz, followed by low-pass filtering with a cutoff frequency of 50 Hz. This particular approach effectively mitigates muscular activity and power line interference, as these artifacts typically tend to exhibit higher frequency power. To address other forms of artifacts, the filtered signals were subjected to a careful visual inspection by skilled neurologists. Finally, a 60-second clean EEG was selected for each subject for further analysis.

Nonlinear Dynamic Analyses

In this study, to verify the findings regarding EEG complexity in patients with dementia, two different complexity measures were extracted from all 19 preprocessed channels: Katz fractal dimension and sample entropy. In the following, these measures and how they are calculated are explained.

Katz fractal dimension. It is an algorithm for calculating the complexity of a signal. This feature is computed through calculating the distance between points along the signal and then calculating the ratio of the logarithm of the total distance to the logarithm of the number of points. The Katz fractal dimension feature can be computed through the following relation (34):

$$D = \frac{\log(N)}{\log(N) + \log(L/L_0)} \qquad (1)$$

D denotes the Katz fractal dimension feature; N indicates the count of samples in the signal; L denotes the total length of the signal, and L_0 is the maximum distance between the initial sample and other samples. The Katz fractal dimension is a useful tool in signal processing and can be utilized for a range of applications, including image processing, speech recognition, and biomedical signal analysis. Higher values of D indicate a more complex signal with a higher

degree of irregularity or roughness, while lower values of D show a simpler signal with less irregularity or roughness.

Sample entropy. It is an index of the irregularity of a signal based on the idea of comparing the similarity between all pairs of subsequences of a given length m in a time series. It is calculated using the following equation (35):

$$SE(m.r) = -\log\left(\frac{C(m.r+1)}{C(m.r)}\right) \qquad (2)$$

where m represents the embedding dimension; r is the tolerance or similarity criterion, and $C^m(r)$ denotes the number of pairs of subsequences that have a distance less than or equal to r. The Euclidean distance criterion was used to calculate the distance. According to previous EEG studies (36, 37), m = 2 and r = 0.2×SD were set, where SD represents the standard deviation of the signal. A higher value of SE indicates a more irregular or complex time series with a higher degree of entropy, while a lower value of SE demonstrates a smoother time series with less entropy.

Clinical and Cognitive Evaluation

The mini-mental state examination (MMSE) was utilized for cognitive evaluation of the patients. It has 19 items with 11 domains covering recall, attention/calculation, repetition, orientation, naming, registration, verbal and written comprehension, construction and writing. The MMSE is a very common tool to evaluate cognitive states in patients with dementia (38). Various studies have confirmed the reliability and validity of the MMSE for the evaluation of cognitive states in dementia patients and the diagnosis of dementia. A meta-analysis study showed that in memory clinical settings, the sensitivity, specificity, and positive predictive value of the MMSE were 79.8%, 81.3% and 86.3%, respectively (39). Moreover, psychological and behavioral symptoms of the patients were assessed through the Neuropsychiatric Inventory (NPI). This tool supplies quantitative evaluation for 12 domains, including dysphoria, euphoria, apathy, hallucination, delusion, anxiety, aggression, irritability, disinhibition, appetite change, aberrant motor activities, and sleep change (40).

Statistical Analysis

SPSS version 21 was utilized for statistical analyses. After calculating the nonlinear measures, two-way repeated measures analysis of variance (ANOVA) with Huynh-Feldt correction for sphericity was employed to compare brain complexity between dementia patients and healthy controls across the EEG channels. An independent t-test was utilized to investigate between-group differences for demographic and complexity measures between the healthy and patient groups. The relationships between the EEG complexity measures and the MMSE and NPI scores were investigated through partial correlation analysis, controlling for age. Statistical significance needed a P-value < 0.05.

Furthermore, a classification model was developed through K-nearest-neighbors (KNN) to classify dementia patients and healthy controls. KNN is a non-parametric classification algorithm that is commonly utilized in machine learning. The algorithm is based on the idea that samples that are close to each other in the feature space are likely to belong to the same class. Given a new data point, the KNN technique searches for the K nearest neighbors in the training set and assigns the class label that is most common among them. Mathematically, this can be expressed as Equation 3 (41):

$$\hat{y} = arg\max_{y_i} \sum_{i=1}^{K} [y_i = y] \qquad (3)$$

where $\hat{y}$ is the predicted class label; y_i indicates the class label of the i-th nearest neighbor, and K denotes the count of neighbors taken into account. The separation between the samples is measured through the Euclidean rule:

$$d(x_i.x_j) = \sqrt{\sum_{k=1}^{n} (x_{ik} - x_{jk})^2} \qquad (4)$$

where x_{ik} and x_{jk} are the k-th feature values of the i-th and j-th data points, respectively. The choice of K is a hyperparameter that can be tuned using cross-validation. Small values of K can result in overfitting, while a large value of K can lead to underfitting. The KNN algorithm is simple and easy to implement, but it may be computationally overpriced for large datasets. In this work, K = 3 was considered.

Results

Baseline and clinical features of the subjects are reported in Table 1. As shown, the groups did not differ in gender, age, and education ($P > 0.05$). Subjects with dementia had significantly lower total MMSE scores than healthy subjects ($P < 0.001$).

Table 1. Baseline and Clinical Characteristics of Patients with Dementia and Healthy Controls.

Characteristics	Dementia group (n = 66)	Healthy group (n = 65)	P-value
Age (year)	76.54 ± 10.72	75.05 ± 9.91	0.410
Gender (% male)	69.70%	75.38%	0.622
Education (year)	11.89 ± 4.16	12.36 ± 4.95	0.557
Duration of illness (year)	2.54 ± 1.45		
MMSE total score	18.21 ± 4.29	29.30 ± 1.09	< 0.001
NPI total score	13.89 ± 7.58		
NPI-dysphoria	1.64 ± 1.89		
NPI-euphoria	0.22 ± 0.37		
NPI-apathy	0.25 ± 0.40		
NPI-hallucination	0.46 ± 0.97		
NPI-delusion	0.85 ± 1.20		
NPI-anxiety	1.29 ± 1.32		
NPI-aggression	1.14 ± 1.56		
NPI-irritability	1.48 ± 0.96		
NPI-disinhibition	0.87 ± 1.17		
NPI-appetite change	2.00 ± 1.75		
NPI-aberrant motor activities	0.92 ± 1.23		
NPI-sleep change	1.91 ± 1.84		

Based on the repeated measures ANOVA, there was a significant main effect between groups for both Katz fractal dimension ($F = 4.10$, $P = 0.01$) and sample entropy ($F = 4.81$, $P = 0.009$) measures. All channels had significant within-subject effects and the interaction between group and electrodes was significant for both Katz fractal dimension ($F = 4.05$, $P = 0.02$) and sample entropy ($F = 5.23$, $P = 0.002$) measures. Post hoc comparisons revealed that dementia patients had significantly lower values of Katz fractal dimension at P3, O1, P4, O2 and Pz channels ($P < 0.05$), and lower values of sample entropy at F4, P3, T5, Fz, T6, O2, P4, O1, Cz and Pz channels ($P < 0.05$), as displayed in Figure 1. Furthermore, Table 1 shows the relationship between EEG complexity measures and cognitive and clinical scales (i.e., MMSE and NPI total scores). It should be noted that only statistically significant correlation coefficients are summarized in this table. As shown, MMSE scores were positively correlated with EEG complexity measures, whereas NPI scores were negatively correlated with EEG complexity measures mainly in the occipitoparietal and temporal areas ($P < 0.05$).

Table 2. Significant Correlations between EEG Channels and Mini-Mental State Examination (MMSE) Scores and Neuropsychiatric Inventory (NPI) Scores (P < 0.05) Controlled for Age

	Sample entropy						
	T5	T6	P3	P4	O1	O2	Pz
MMSE score	0.42	0.41	0.48	0.49	0.50	0.47	0.48
NPI score	-0.38	-0.40	-0.36	-0.39	-0.35	-0.37	-0.38
	Katz fractal dimension						
	T4	C4	T6	P4	O1	O2	Pz
MMSE score	0.41	0.38	0.51	0.55	0.62	0.64	0.58
NPI score	-0.46	-0.40	-0.53	-0.56	-0.55	-0.54	-0.55

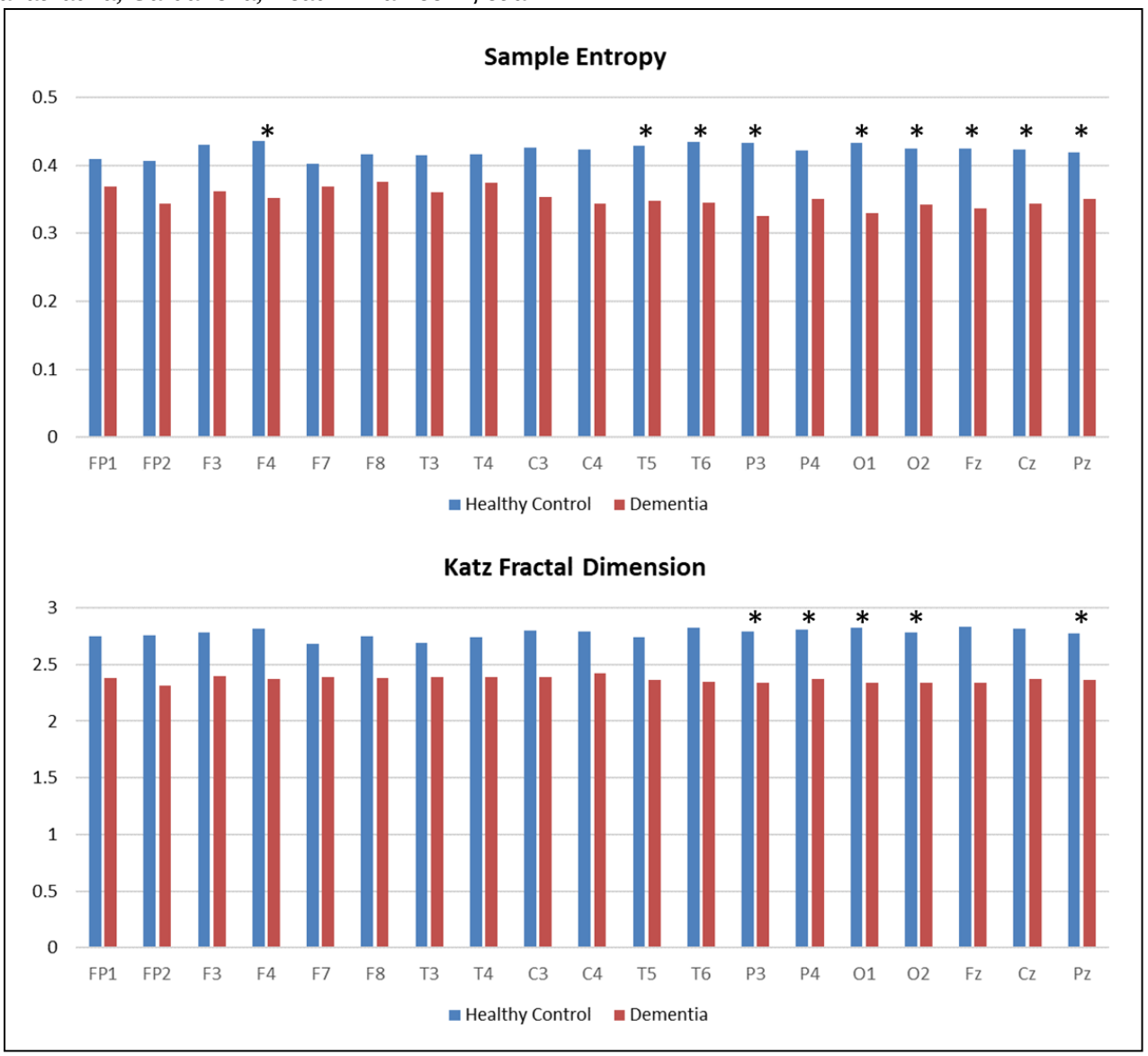

Figure 1. Comparison of Averaged Values of Sample Entropy and Katz Fractal Dimension Measures between Patients with Dementia and Healthy Subjects. The Asterisks Show Statistically Significant Differences.

Table 3 shows the classification accuracies obtained through the KNN model for dementia diagnosis using EEG complexity measures. For classification, complexity data from all the individuals were utilized to build and test various classification models. To this end, 75% of the EEG features were randomly allocated to classification modeling (training), and the remaining 25% of the features were reserved for model validation (testing). The outputs of the 20-time running of the KNN were averaged to determine the final classification results. To prevent data leakage from testing data to the training process, finding significant features were conducted separately in the training data of each run. According to Table 3, all complexity measures yielded an accuracy of 92.13% in detecting dementia with 87.36% sensitivity and 96.81% specificity. However, significant features led to better classification performance (95.78% accuracy for significant entropy measures and 96.44% accuracy for significant fractal measures). However, all significant complexity measures yielded the best classification performance with an accuracy of 98.05%, sensitivity of 97.03% and specificity of 99.16% in detecting dementia.

Table 3. Classification Accuracies between Dementia and Healthy Groups Obtained by the K-Nearest-Neighbors (KNN) Model

Features	Accuracy (%)	Sensitivity (%)	Specificity (%)
All data	92.13 ± 4.28	87.36 ± 4.11	96.81 ± 4.57
Significant entropy features	95.78 ± 2.49	93.90 ± 2.97	97.52 ± 2.85
Significant fractal features	96.44 ± 3.05	95.25 ± 3.00	97.60 ± 2.98
All significant features (entropy + fractal)	98.05 ± 2.34	97.03 ± 2.16	99.16 ± 2.20

Discussion

The link between the EEG variables, especially those related to slow activity levels, and the severity of dementia is widely recognized (42, 43). This research examines two different EEG complexity measures derived from different nonlinear analytical techniques, aiming to comparing them to identify the most effective parameter for potential use in clinical settings. Our findings showed that the EEG complexity was significantly reduced in dementia mainly in the occipitoparietal and temporal areas, which is consistent with previous findings (13, 19, 44). Seker *et al*. compared the permutation entropy of EEGs recorded from 85 Alzheimer's patients and 85 healthy controls and found that EEG complexity is reduced in patients (19). Yang *et al*. compared the multiscale entropy of EEGs recorded from 15 Alzheimer's patients and 15 healthy controls and found that EEG complexity is reduced in patients on short-time scales (45). Labate *et al*. (46) and McBride *et al*. (47) also reported similar results comparing Alzheimer's patients and healthy subjects with a low sample size (15 subjects per group) using sample entropy and Lempel-Ziv complexity. However, it should be noted that the previous findings were mainly observed on the population of Alzheimer's patients and other types of dementia, such as frontotemporal dementia, while mixed dementia has received less attention in research studies. This significant finding suggests the existence of unique dynamic systems within the brain impacted by dementia, lending support to the disconnectivity theory that forms the basis of dementia neuropathology (48, 49). It also offers additional understanding of the atypical neural connectivity present in this condition. Actually, reduced EEG complexity in individuals with dementia could signify a shift in brain activity towards more predictable patterns (45). Our findings indicated a significant correlation between complexity measures in occipitoparietal EEG electrodes with MMSE scores. This result aligns with previous studies that linked EEG alterations in the posterior brain areas to cognitive deterioration in individuals with Alzheimer's disease (45, 50, 51). Indeed, EEG complexity was positively correlated with patients' cognitive capacity and negatively correlated with patients' neuropsychiatric symptoms. Previous studies showed that the decrease in complexity was found to be associated with cognitive dysfunction, particularly affecting language and memory abilities, in individuals diagnosed with frontotemporal dementia (52). Understanding the neuropsychiatric connections of EEG complexity could offer understanding on how brain function in distinct areas influences the behavioral and psychological manifestations of dementia. These discoveries might impact the application of EEG complexity examination as an uncomplicated clinical method to evaluate the intensity of neuropsychiatric symptoms among individuals with dementia.

Limited research has investigated the nonlinear characteristics of EEG signals in individuals with dementia. Traditional EEG power assessments in these patients commonly reveal a slowing EEG pattern characterized by elevated delta band power and diminished alpha activity (42). The extracted nonlinear EEG features using the KNN classifier could achieve an average accuracy of 98% in dementia diagnosis, which is much higher than previous studies that utilized linear features (53, 54). According to the obtained results, nonlinear features of EEG signals emerged as a promising approach for detecting dementia. EEG is a technique that captures the electrical activity of the brain. The signals obtained from EEG are intricate and nonlinear, making it difficult to explore them through traditional linear approaches (55). Nonlinear analysis of EEG signals involves the use of mathematical techniques that can capture the complex and dynamic nature of the brain's electrical activity. Nonlinear features extracted from EEG signals can provide valuable information about the brain's functional connectivity, complexity, and synchronization, which are not easily detectable using linear methods (56). Overall, the nonlinear nature of EEG signals provides a unique opportunity for researchers and clinicians to gain a deeper understanding of the brain's complex dynamics and develop more effective strategies for diagnosis and monitoring of dementia (57).

Limitation

Despite the strengths of the current study, including a relatively suitable sample size, investigating the relationship between nonlinear EEG indicators and the cognitive and clinical level of patients, and achieving a high accuracy in diagnosing dementia through EEG analysis, there are also limitations that should be pointed

out. First, this is a cross-sectional study and therefore the findings cannot be considered definitive. Longitudinal studies with appropriate design are needed to confirm the findings of this study. Second, at the time that the EEG tests were performed, the dementia patients were taking medications that may have affected the pattern of their brain signals, thereby influencing the study's findings. Third, we investigated mixed dementia in this study, while other types of dementia are also common and should be further investigated in future studies.

Conclusion

In summary, this study demonstrated a unique dynamic system within the brain impacted by dementia that results in more predictable patterns of cortical activity mainly in the occipitoparietal and temporal areas. These abnormal patterns were associated with patients' cognitive capacity and neuropsychiatric symptoms. Our machine learning model could achieve a high accuracy of 98% for dementia diagnosis using these abnormalities, which demonstrates the importance of EEG complexity analysis for studying brain activity in patients with mixed dementia. Overall, evaluating the complexity of EEG signals using nonlinear approaches of entropy and fractal dimension could serve as a straightforward and dynamic indicator to gauge the cognitive and neuropsychiatric impact of dementia. The potential creation of a convenient EEG monitoring tool, possibly utilizing dry EEG electrodes, could enable real-time monitoring of brain activity in superficial brain regions. This tool could offer valuable clinical insights for the precise evaluation of neuropsychiatric manifestations in individuals with dementia. Future longitudinal studies with large populations of patients with different types of dementia should be conducted to confirm the findings of the present study.

Conflict of Interest

None.

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