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ORIGINAL RESEARCH

Prolonged Disease Course Leads to Impaired Brain Function in Anxiety Disorder: A Resting State EEG Study

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Objective: Anxiety disorder (AD) is a common disabling disease. The prolonged disease course may lead to impaired cognitive performance, brain function, and a bad prognosis. Few studies have examined the effect of disease course on brain function by electroencephalogram (EEG).

Methods: Resting-state EEG analysis was performed in 34 AD patients. The 34 patients with AD were divided into two groups according to the duration of their illness: anxious state (AS) and generalized anxiety disorder (GAD). Then, EEG features, including univariate power spectral density (PSD), fuzzy entropy (FE), and multivariable functional connectivity (FC), were extracted and compared between AS and GAD. These features were evaluated by three previously validated machine learning methods to test the accuracy of classification in AS and GAD.

Results: Significant decreased PSD and FE in GAD were detected compared with AS, especially in the Alpha 2 band. In addition, FC analysis indicated that GAD patients' connection between the left and right hemispheres decreased. Based on machine learning, AS and GAD are classified on a six-month criterion with the highest classification accuracy of up to 0.99 ± 0.0015.

Conclusion: The brain function of patients is more severely impaired in AD patients with longer illness duration. Resting-state EEG demonstrated to be a promising examination in the classification in GAD and AS using machine learning methods with better classification accuracy.

Keywords: electroencephalogram, EEG, disease course, anxiety disorder, brain function, machine learning

Introduction

Anxiety disorder (AD) is one of the most common mental health disorders, putting a heavy burden on patients themselves, their relatives and society,[1] with data from 2015 showing a lifelong incidence rate of anxiety disturbance ranging from 16% to 34%.[2] Generalized anxiety disorder (GAD) is the most common type of anxiety disorder. GAD is characterized by excessive worry, apprehensive expectations, and persistent anxiety. Previous studies have shown that the prevalence of GAD increases from age 40 to 55[3] and then declines.[4,5] However, due to traditional diagnostic conception, GAD is often marginalized and ignored; researchers and clinicians have long debated its taxonomic and neurobiological uniqueness.[6] Therefore, early identification of risk factors for anxiety disorder is important. According to the DSM-V diagnostic criteria, GAD can be diagnosed for more than six months if the criteria of symptoms and severity are met. If the disease lasts less than six months, it is diagnosed as an anxiety state (AS), which is also referred to in studies by Hans-Peter et al as subthreshold anxiety or subsyndromal anxiety.[7] The study provided a systematic overview of the definitions of subthreshold anxiety and subsyndromal anxiety. For example, the definition of subthreshold anxiety used by Maier et al is as follows: all ICD-10 GAD symptom criteria, but relaxed time criterion (<1 versus 1–6 months of duration).[8] A study by Wittchen et al

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suggested that subthreshold GAD should meet the following conditions: full DSM-IV GAD but of 1–6 months of duration.[9] When the patient comes to the clinic, the time of the illness can only be obtained through the patient's supervisor's memories, and there is no relevant laboratory examination. In recent decades, in-depth studies have improved the understanding of GAD towards precise diagnosis.[10] Clinical manifestations of GAD may vary with age and prolonged course, which can make it difficult for a doctor to diagnose.[11] People who have been sick for a long time are not able to get effective treatment in a timely manner. Delayed treatment can lead to worse clinical outcomes is often seen in certain psychiatric disorders, such as major depression disorder[12] and panic attacks.[13] It has also been shown that the shorter the duration of GAD, the better the response to the first-line treatment-selective serotonin reuptake inhibitors.[14] In other words, delaying treatment may lead to worse treatment outcomes. From the social-psychological level, it can also negatively impact the long-course of GAD. In addition, symptom severity, duration, and comorbidities were the best predictors of persistent anxiety disorders.[15] However, few published researches have reported potential outcome and predictors of disease course in GAD. Therefore, it is important for diagnosis and prognosis to be clear about the time of the disease, and further research is needed on the effect of the duration on the brain function of the patient. Early recognition and treatment of GAD is the priority we need to pay attention to.

Brain imaging technology has been widely used in the diagnosis of mental disorders. Previous studies have shown that emotional processing is mediated by lateralization of the frontal cortex.[16] In recent years, electroencephalogram (EEG) has been increasingly used to predict and diagnose mental disorders. For example, reliable correlational indicator of frontal lobe activity is the frontal electroencephalogram Alpha asymmetry, reflected in the Alpha band as measured by EEG.[17] Recent evidence suggested an inverse relationship between activity in the Alpha range and cortical processing. For example, Alpha decreased when the underlying cortical system was active.[18] We speculate that people with mood disorders have specific EEG Alpha wave changes. Compared with linear dynamics analysis, nonlinear dynamics analysis can track changes in brain functional activities and convey information about neural networks.[19,20] It is noteworthy that power spectral density (PSD) analysis with typical cerebral electrocardiogram characteristic rhythms revealed associated deformities of anxiety disorder, which researchers may be associated with negative emotions.[21] Furthermore, functional connected (FC) analysis provides a unique quantitative approach to the neural mechanisms that analyze anxiety disorders from the perspective of the whole brain's functional network. In brain neuroscience, FC represents the correlation of simultaneous activity between different brain anatomical regions. According to the theory of the global working space of neurons, the brain, even if it performs very simple tasks, relies on multiple brain functional regions, and changes in brain function will inevitably be mapped to the FC between the entire brain functional regions.[22] In addition, although nonlinear EEG analysis of AD has been poorly reported, it has been suggested for further study of the relationship between cortical function and generalized anxiety and is considered a complementary tool for detecting dysfunctions in AD. The advantages of brain-based electrodes with high time resolution are that they can be used as a prospective non-invasive biological marker.

Machine learning technology can help deal with multiple variables of asymmetric distribution,[23] using a paradigm transformation to predict diagnosis using complex computational algorithms provided by big data sets.[24] One of the advantages of machine learning is that it is suitable for the analysis of large amounts of data. Machine learning algorithms are able to automatically learn from data and extract useful features and information. In addition, the emergent habit algorithm has the ability to adjust and optimize the model to achieve the best performance on a given task. By using different optimization algorithms and parameter adjustment methods, the accuracy of the model can be further improved. There are studies using machine learning to assess the importance and effectiveness of clinical data in predicting MDD and GAD. Identify significant predictors of GAD and MDD to aid in early detection of MDD and GAD.[12] Therefore, machine learning was chosen in this study to define the length of the disease, and then explore the relationship between the length of the disease and brain function.

In this study, we have combined multidimensional EEG characteristics and machine learning methods with the ultimate goal of increasing our understanding of the potential abnormal neural mechanisms of AD. This article aims to compare the brain functional changes of AD patients with different disease durations using EEG nonlinear dynamic analysis and to evaluate the effect of anxiety severity on cortical functional activity. It is also hoped to propose a reliable AD identification method to better machine learning classification performance.

Methods

Participants

Thirty-four patients who met the following conditions: Hamilton Anxiety Scale (HAMA) scores ≥14; 17-item Hamilton Depression Scale (HAM-D_{17}) scores <17; first time sick; no drugs used; met the DSM-V diagnostic criteria for anxiety disorders were recruited from Huzhou Third Municipal Hospital. Based on the DSM-V diagnostic criteria, GAD requires symptoms to last for at least 6 months. Therefore, according to the duration of the illness, the 34 patients were divided into two groups. With a six-month time limit, the AS group is for patients who have had less than six months of illness. The GAD group has had more than or equal to six months. Exclusion criteria were as follows: 1) comorbidity of other psychiatric disorders (such as dementia, schizophrenia, bipolar disorder); 2) anti-inflammatory or immunosuppressive use over the past year; 3) infectious diseases over the last two weeks; 4) accompanying immune system diseases such as rheumatoid arthritis, systemic sclerosis; 5) serious physical diseases (such as hypertension, diabetes); 6) pregnancy and lactation history; 7) alcohol or other psychotropic abuse. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Huzhou Third Municipal Hospital. Informed consent was obtained from all subjects involved in the study. Thirty-four patients were divided into AS and GAD patients, with demographic and clinical characteristics in Table 1.

EEG Data Acquisition and Preprocessing

Sixteen-channel EEG data, Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, and P8, were collected by an EEG apparatus (Nicolet EEG TS215605) according to the international 10–20 system, and referenced to the average of the left and right mastoids, with 250Hz sampling rate and the electrode impedance controlled below 5000Ω. Each participant was required to close the eyes, be awake and relaxed for ten minutes to collect EEG data. The whole experiment was conducted in a professional EEG lab in Huzhou Third People's Hospital.

As for the preprocessing procedure, the raw EEG data were down sampled from 250Hz to 125Hz and filtered between 4Hz and 30Hz by a digital fourth-order Butterworth band pass filter firstly. Secondly, fast ICA was utilized for artifact removal (such as eye blinks, slow eye movements and so on). Then, the EEG was segmented with four seconds as a fragment, and the overlap rate was 50% to obtain 4330 GAD data samples and 4124 AS data samples. Finally, EEG rhythms of Theta (4–8 Hz), Alpha1 (8–10 Hz), Alpha2 (10–13 Hz), and Beta (13–30 Hz) was extracted for every EEG samples by the same band pass filter.

EEG Features Extraction

In the present study, three widely used types of EEG feature extraction strategies, that is, power spectrum density analysis, nonlinear dynamic analysis, and functional connectivity analysis were conducted. Specifically, the power spectral density (PSD), fuzzy entropy (FE), and phase lag index (PLI) are calculated for each EEG samples. EEG power calculation, fuzzy entropy calculation and PLI calculation can be referred to Shen's study.[25]

Table 1 Demographic and Clinical Characteristics of the Participants

Characteristics	AS (n=18)	GAD (n=16)	t/Z	*p*-value
Age (year)[a]	45.94±12.30	45.81±8.06	0.036	0.971
Gender: male/female[b]	5/13	3/13	–	0.693
BMI[a]	22.28±2.92	23.37±3.03	−1.061	0.297
Education (year)[c]	16.00 (6.00, 13.00)	8.69 (6.00, 16.00)	−1.256	0.209
Duration of illness (month)[c]	1.00 (1.00, 3.25)	36.00 (15.00, 60.00)	−5.066	<0.001
HAMA[a]	21.50±4.23	23.75±5,63	−1.325	0.195
HAM-D_{17}[c]	13.50 (11.75, 15.00)	14.50 (12.50, 15.00)	−1.395	0.163

Notes: [a]Independent sample *t*-test [Mean (SD)]. [b]Fisher's exact test. [c]Mann–Whitney *U*-test [M (P_{25}, P_{75})]. *p*-value: *p*-value obtained after comparison using Mann Whitney's *U*-test or a separate sample of *t*-test; $p < 0.05$ is considered statistically significant.

PSD Calculation

For the given EEG signal $x(i)$ (i=1, 2, 3, ..., N; N is the number point of $x(i)$), its frequency spectrum $X(f)$ can be estimated by fast Fourier transform (FFT), and then the power spectrum $P_x(f)$ was gained with equation (1). The relative power of $PSD(h)$ for each EEG rhythm can be computed through equation (2). In equation (2), h represents the EEG rhythms of Theta, Alpha1, Alpha2, and Beta, f_m and f_n are the upper and lower frequencies of the EEG signal with four rhythms, while f_h and f_l are the upper and lower frequencies of h rhythm, respectively.

$$P_x(f) = \frac{1}{N}|X(f)|^2 \tag{1}$$

$$PSD(h) = \frac{\int_{f_l}^{f_h} P_x(f)df}{\int_{f_n}^{f_m} P_x(f)df} \times \frac{f_m - f_n}{f_h - f_l} \tag{2}$$

FE Calculation

For the given EEG signal $x(i)$ (i=1, 2, 3, …, N), it can be reconstructed into a set of m-dimensional vectors X_i^m shown in equation (3), where m is the embedding dimension, and $x_0(i)$ represents the mean value shown in equation (4). The distance d_{ij}^m between X_i^m and X_j^m is calculated by equation (5). Then, the similarity D_{ij}^m between X_I^m and X_j^m is defined as equation (6). The $O^m(r)$ is calculated by equation (7). The FE[26] of the EEG signal $x(i)$ could then be estimated as equation (8).

$$X_i^m = \{x(i), x(i+1), \cdots, x(i+m-1)\} - x_0(i), (i = 1, 2, \cdots, N-m+1) \tag{3}$$

$$x_0(i) = \frac{1}{m}\sum_{j=0}^{m-1} u(i+j) \tag{4}$$

$$d_{ij}^m = \max_{k\in(1,m)} \{|(u(i+k) - u_0(i)) - (u(j+k) - u_0(j))|\}, (i \neq j) \tag{5}$$

$$D_{ij}^m = \exp\left(-\ln(2) \cdot \left(\frac{d_{ij}^m}{r}\right)^2\right) \tag{6}$$

$$O^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m}\left(\frac{1}{N-m-1}\sum_{j=1, j\neq i}^{N-m} D_{ij}^m\right) \tag{7}$$

$$FE(m, r, N) = \ln O^m(r) - \ln O^{m+1}(r) \tag{8}$$

In the current study, a typical value for the embedding dimension m is set as 2, and the value r is determined by $k \times \delta$, N is the length of the EEG signal $x(i)$ under observation (N = *1000*). Additionally, k is the constant value set as 0.2 (usually the value range is between 0.10 and 0.25), and δ is the standard deviation of the EEG signal $x(i)$.

PLI Calculation

For the given EEG time series $x_i(t)$, it can be expressed as $z_i(t)$ by Hilbert transform[27] shown in equation (9):

$$z_i(t) = Z_i(t)e^{j\varphi_i(t)} \tag{9}$$

where Z_i and φ_i are the instantaneous amplitude and phase of $x_i(t)$, respectively. Then the PLI[28] of two EEG time series $x_k(t)$ and $x_l(t)$ can be estimated by equation (10):

$$PLI_{k,l} = |<sign(\varphi_k(t) - \varphi_l(t))>| \tag{10}$$

where *sign* is sign function, <•> means the average value, and |•| denotes the absolute value. The PLI value ranges between 0 and 1. PLI = 0 represents the case where there is no phase synchronization, while PLI = 1 indicates the perfect phase locking between two EEG time series.

Machine Learning for Classification

In the present study, four kinds of popular machine learning models, namely support vector machine (SVM), K-Nearest Neighbor (KNN), random forest (RF) and ensemble learning of back propagation neural network based on bagging strategy (BP_Bagging), all adopted 5-fold cross validation, that is, training set and test set were divided according to 8:2. The number of training set samples was 8454*0.8 = 6763. The number of test set samples was 1691. The number of base classifier is 10, 20% of the data is used for testing, and the other 80% is used for training. The training set constructs feature disturbances and sample disturbances according to the 80% ratio and reservation method, that is, the input features of each base classifier are 608*80% = 486. The number of samples was 8454*80%*80% = 5410. The characteristics of each base classifier were different from the samples. The remaining 20% training set samples were used as the base classifier of the test set to evaluate the performance of the base learner, and the first 91% base classifier was selected according to the accuracy rate for the final vote to get the classification accuracy.

Statistical Analysis

Descriptive statistical analysis was carried out using statistical software SPSS (version 25.0) to describe demographic information and general characteristics of AS and GAD patients. Fisher's exact test was used to analyze the ratio differences of classified variables. Prior to the statistical analysis of continuous variables, the Shapiro–Wilk test was used to testing normality of the data; the independent *t*-test was used to assess the differences of the consecutive variables with mean and standard differences; and the Mann–Whitney *U*-test was used to evaluate the irregular distribution of the continuous data with intermediate and quadratic spacing. One-way ANOVA was performed on the power, fuzzy entropy, and functional connectivity between AS group and GAD group to determine the significant statistical differences of EEG characteristics. The statistical differences were considered significant at 0.05 threshold ($p < 0.05$). Statistical analysis of brain electrical characteristics was carried out using MATLAB 2019b software.

Results

PSD Value Difference

Figure 1A–D demonstrated the results of PSD analysis between the AS group and the GAD group. Figure 1A and 1B suggested that slow EEG rhythms' (Theta and Alpha1) PSD values of 16 channels had no significant difference between the two groups, $p > 0.05$. While Alpha2 PSD values had significant difference between the two groups on channel C4, P3, O1, O2 and T5, $p < 0.05$, especially on channel P4 and T6, $p < 0.01$ (see Figure 1C). Beta PSD values had significant difference between the two groups on channel FP1, F8 and T4, $p < 0.05$, especially on channel F7, $p < 0.01$ (see Figure 1D).

Nonlinear Dynamics Analysis (Fuzzy Entropy) Results

Nonlinear dynamics analysis was conducted using fuzzy entropy analysis. There was no statistical significance of Theta FE values of 16 channels between the two groups (Figure 2A). Among the 16 channels, Alpha1 FE values of channel O2 had significant difference between the two groups, $p < 0.05$ (Figure 2B). Alpha2 FE values of channel FP2, F3, F4, C4, P3, P4, T4, and T5 had significant difference between the two groups, $p < 0.05$, especially of channel O1, O2 and T6, $p < 0.01$ (Figure 2C). There was statistical significance of Beta FE values on channel F7 and F8 between the two groups, $p < 0.01$, $p < 0.05$, respectively (Figure 2D).

Functional Connection Analysis (PLI) Results

We analyzed the functional connectivity (FC) of 16 channels using Phase lag index (PLI). Figure 3A–D showed the degree of functional connectivity between different channels in the AS group compared to the GAD group. The analysis of Theta rhythm showed that four functional connections were significantly different in the AS group compared with the GAD group. Three of the functional connections were lower in the AS (Figure 3A). For Alpha1 rhythm, there was just one significant stronger connection of GAD between two channels (Figure 3B). As for Alpha2 rhythm, as showed in Figure 3C, there were a lot of blue lines without red lines, indicating that the AS group had stronger connectivity between left hemisphere and right hemisphere

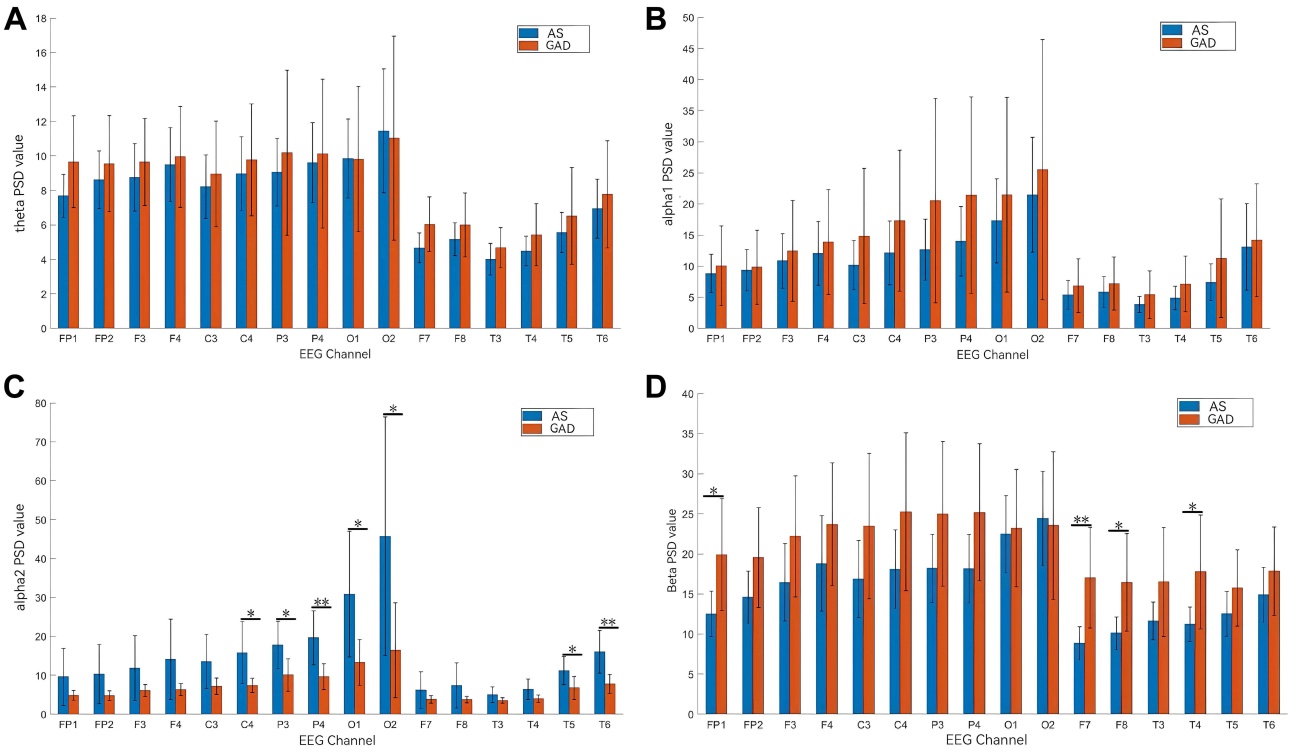

Figure 1 (**A**–**D**) Four rhythms, Theta (**A**), Alpha1 (**B**), Alpha2 (**C**), Beta (**D**) PSD values of 16 EEG channels of the AS group and the GAD group respectively. Each value is the average of all subjects. PSD refers to power spectral density.
Notes: *$p < 0.05$; **$p < 0.01$.

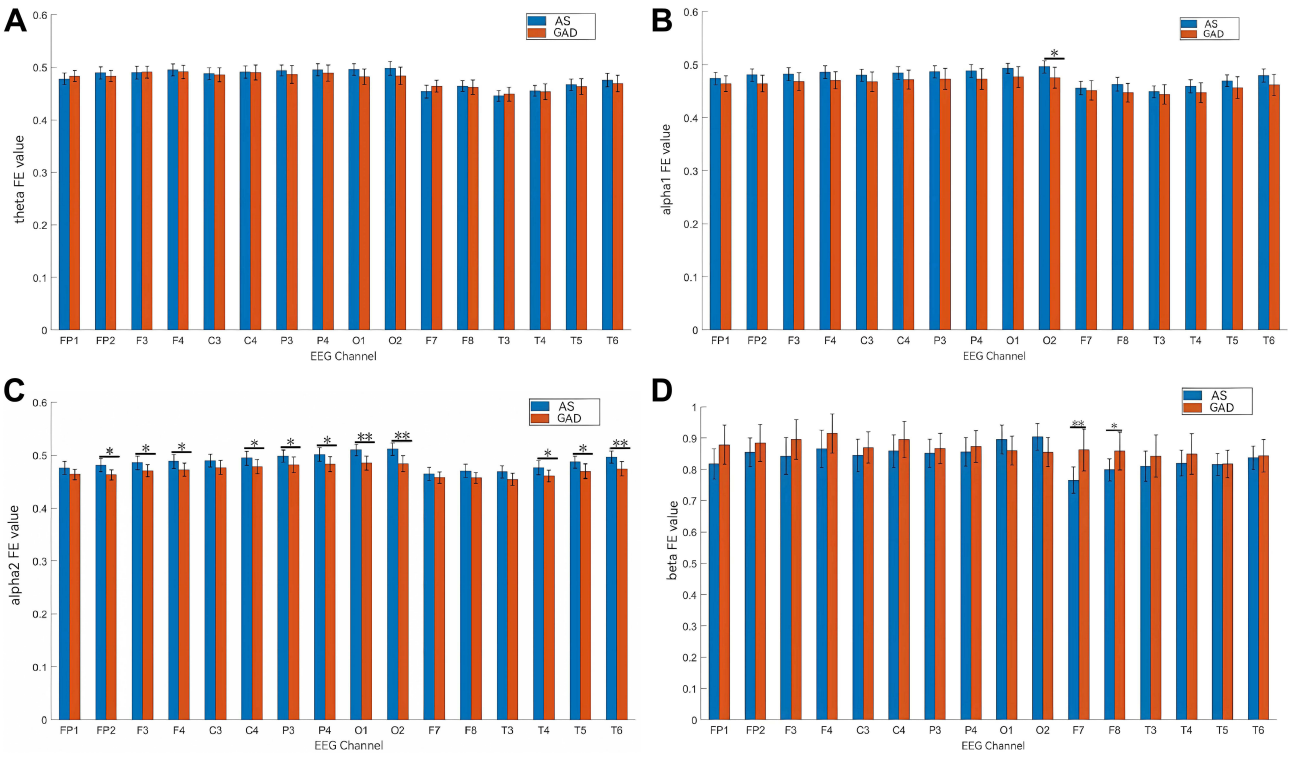

Figure 2 (**A**–**D**) Four rhythms, Theta (**A**), Alpha1 (**B**), Alpha2 (**C**), Beta (**D**) FE values of 16 EEG channels of the AS group and the GAD group respectively. Each value is the average of all subjects. FE refers to fuzzy entropy.
Notes: *$p < 0.05$; **$p < 0.01$.

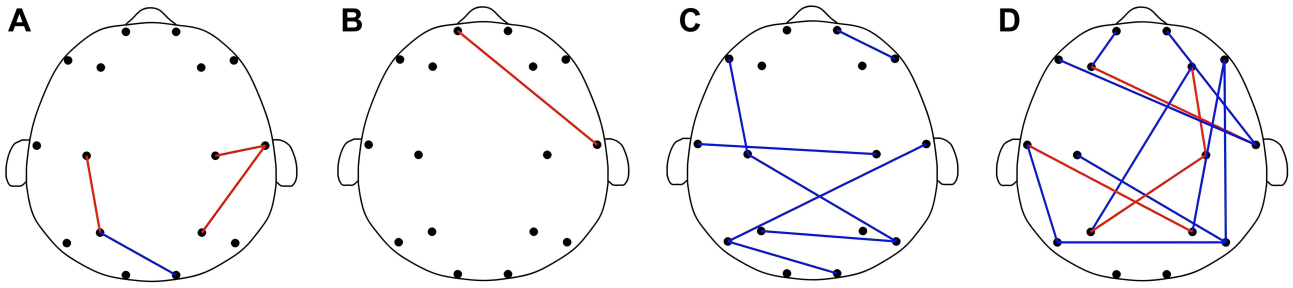

Figure 3 (**A**–**D**) Brain functional network of Theta (**A**), Alpha1 (**B**), Alpha2 (**C**), Beta (**D**) rhythms of 16 EEG channels of the AS group and the GAD group respectively. The line indicates that the PLI between the two channels is significantly different between the two groups. Blue lines indicate that the PLI values of AS group are higher than the GAD group, and red lines indicate that the PLI values of GAD group are higher than the AS group.

than the GAD group. For Beta rhythm, the AS group seemed to have wider and farther connectivity between the channels, although the GAD group did have 4 significant stronger connections (Figure 3D).

Figure 3A–D indicated that compared to slow rhythms (Theta and Alpha1), there were more significant connectivity differences of fast rhythms (Alpha2 and Beta) between the two groups. Interestingly, 67% of the existed FCs (1/4 for Theta, 0/1 for Alpha1, 7/7 for Alpha2, and 8/12 for Beta) have higher values in the AS group compared to the GAD group. The topological distributions of the brain networks of fast rhythms indicate that the FCs are mainly between the left hemisphere and the right hemisphere. Specifically, the ratio of the FCs between the two hemispheres is 63% in total and 5/7, 7/12 for Alpha2 and Beta rhythms, respectively.

Machine Learning for Classification

According to the preprocessing of the EEG data, there were 4124* (4*120+16*8) samples for AS group and 4330* (4*120+16*8) samples for GAD group. Four machine learning methods were used to verify if the criterion of 6 months was the reasonable length of course to divide AS and GAD, classification accuracy of each approach is shown in Table 2. A fivefold cross validation (fourfold samples for training and onefold sample for testing) was used in this study with 10 repetitions to verify the generalization ability of the model. The final evaluation result was the average of all test results. According to the results, classification accuracy was quite high (all equal or above 0.97) no matter using which machine learning approach, which indicated that the criterion of 6 months was appropriate to distinguish the severity of anxiety disorders.

Discussion

In this resting-state EEG study, we used EEG-based connectomics and feature extraction strategies to examine illness duration and brain function in AD. The significant findings are as follows: first, compared to GAD patients, PSD and FE values were significantly increased in AS patients, especially in the Alpha2 frequency range. Second, the two groups' functional connections of the brain's hemispheres were distinct. In all frequency bands, more connectivity and more activity in the bilateral cerebral hemispheres of the brain can be observed in AS patients. This phenomenon is evident in the Beta-frequency band, which is thought to be associated with cognitive function. Third, we used machine learning to detect the classification accuracy of multidimensional EEG characteristics, finding more accurate classification effects.

Our most important result is that both groups' PSD and FE in the Alpha2 band differed significantly. According to a 2019 literature review, the Alpha band has been extensively studied.[29] In the study of mood disorders, Alpha is often thought to be associated with changes in emotional responses.[30] The Alpha frequency is the dominant EEG rhythm in healthy adults at rest and is associated with a state of calm and relaxation.[31] Previous studies have found that increased

Table 2 Classification Accuracies of Four Machine Learning Approaches

Machine Learning Approaches	SVM	KNN	RF	BP_Bagging
Classification Accuracy	0.99±0.0015	0.99±0.0015	0.97±0.0083	0.98±0.0043

Alpha may indicate decreased alertness.[32] Some evidence suggests that reduced Alpha activity is associated with anxiety.[33] These findings suggest that Alpha frequency activity is associated with anxiety disorders. Power values for PSD reflect the complexity of brain activity. A similar study, based on relevant dimensional analysis, also indicated an increased complexity of brain electrical characteristics in patients with GAD.[34] This phenomenon may be explained by an increase in the internal cognitive processing of GAD patients in the process of non-specific information processing in the form of diffuse negative bias.[35] Alpha band is usually associated with calm and relaxation. If there is excessive stress or concentration, Alpha band would be suppressed. Previous studies have shown significant changes in the complexity of EEG features in GAD patients, which may be related to the internal cognition of GAD patients with negative bias. Our results showed that in the Alpha2 band, PSD and FE were lower in the GAD group. This suggests that patients with GAD were overstressed and unable to relax. Previous research has shown that in the presence of anxiety, the current density (a measure of brain activity) of the brain in the prefrontal lobe decreases.[36] This could support our findings. The complexity of entropy is also associated with the quantity of "information" that the signal carries.[37] Higher entropy levels have been associated with a healthy state in which the nervous system can respond and adapt to dynamic changes. However, lower entropy values are closely related to pathological conditions and forfeit the ability to respond to nervous system changes.[38] This suggested that in the Alpha2 band, there were abnormal changes in brain activity on more channels in GAD patients. In addition, the decrease in the relative power of the slow-wave frequency band and the significant increase in the electromagnetic power of the fast-wave frequencies reflect the activation of negative emotions in the brain.[15] The Beta band is generally thought to be associated with cognition. Higher power values and fuzzy entropy of GAD in the Beta band suggested the activation of negative emotions in the brain.[15] One possible explanation is that in the processing of non-specific information, GAD patients are concerned about increased cognitive processing manifested by dispersive negative biases and mental fluctuations.[35] The core symptoms of GAD patients are persistent excessive worry and anxiety about the things around them, and the prolonged disease process can be seen to disrupt the work of the brain, which suggests the nervous mechanisms of the GAD disease. There is still a shortage of research on the length and duration of anxiety disorder, and our research has filled this gap. Significant differences in EEG rhythms between AS and GAD provide a theoretical basis for further exploration of the development of AD in brain imaging.

This paper evaluates the weakness of brain functional connections by calculating the PLI in two groups of AD patients, with the advantage of overcoming the volume-transmitted problems in the process of cerebroelectric collection.[39] Our previous analysis of the GAD and the cerebro-electric characteristics of healthy people showed a decrease in the functional connection between the GAD area and other regions of the brain.[25] Lower FCs are associated with higher characteristic anxiety,[40] and researchers have observed Alpha connectivity disorders.[41] Instead, in resting brain electromagnetic studies, increased Theta rhythm fluctuation consistency compared to HC indicates higher connectivity of social anxiety disorder.[42] In this study, we found that the functional connectivity of the left brain is significantly lower in GAD patients, who has been sick longer, especially in the Beta frequency. Varieties of psychiatric, cognitive, and behavioral phenotypes have been related to brain functional connectivity. Coherent intrinsic brain activity is significant for healthy brain function. FC of the sensory system was reduced in highly anxious individuals.[43] Another significant result is that the functional connectivity in the four-band rhythms is more complex in AS ones, and it runs through the left and right hemispheres. Functional connections between the left and right cerebral hemispheres increased more in AS patients than those with GAD. It does not mean any functional connections between the brain and the body in GAD patients. However, as the disease progressed, functional connections weakened. This result revealed that after controlling for age and Hamilton Anxiety Scale score, patterns of EEG functional connectivity decrease as the disease progresses if untreated, which is consistent with the results of Carmen Andreescu, MD et al 's study on functional connectivity of GAD in the whole life cycle.[44] There is now increasing evidence to support the view that anxiety disorder is associated with abnormal communication between brain regions. Our research shows that the decreased connectivity between the left and right hemispheres of the brain may be seen in untreated patients with a long course of GAD. It indicates that the brain function of GAD patients is impaired.

The onset of illness can often be hard to be detected for patients in clinical practice. However, anxiety disorders are treated differently based on their disease course,[14] so the time when the illness began is crucial. Machine learning can extract information based on a certain amount of data and predict diagnosis through complex algorithms.[23] So far, machine learning has been used to diagnose schizophrenia,[45] major depression,[46] and bipolar disorder.[24] GAD is

characterized by persistent and excessive anxiety for at least 6 months. Four machine learning methods have proven the accuracy of the classification criteria and achieved excellent classification performance, and the results showed that the 6-month classification of the course of disease showed a good accuracy (all equal or above 0.97) in machine learning. This indicates that six months later, the brain function of AD patients was impaired. Therefore, it is necessary and correct to classify patients with AD using cerebrospinal characteristics for the duration of their illness while demonstrating the advantages of machine learning in classifying diseases.

Overall, based on machine learning methods, we divided AD patients into two groups on the basis of whether the course of the disease had reached six months and obtained a higher classification accuracy. By analyzing the results of brain electrodes and calculating machine learning accuracy, we found that the power spectrum and fuzzy entropy in AS patients, especially in the Alpha2 band, were significantly higher than those with GAD. In addition, the functional connectivity between the left and right hemispheres of the GAD patients was significantly weakened compared with that of the AS group, that is, the connectivity between the left and right hemispheres was decreased. This indicates that the structure and function of the brain are increasingly affected as the duration of the disease is prolonged. Therefore, the DSM-V diagnostic criteria set the course criteria for GAD to meet the duration of six months of illness is reasonable and important for further treatment. In the future, studies of prolonged course of disease that lead to impaired brain function in patients with anxiety disorder deserve more attention.

Limitations and Future Research

Some limitations in this study must be considered. First, the sample sizes were so relatively small that future research is needed to test whether these patterns replicate in larger samples. It would have been better to analyze the results in subgroups (sex and age). Samples well-matched in age and sex would be ideal for subsequent studies. Second, our experiment only collected 16 channels of EEG data, and more channels can be applied in future studies to get more detailed and precise results and can try to find relationships to brain sites. Disease duration was obtained from participants' reports, a retrospective bias-weighted approach. The study lacked healthy controls, so we had no way of knowing trends from healthy people to sick people.

Conclusion

In this study, we extracted the brain function changes of AD patients with different durations by analyzing resting state EEG characteristics. Combined with multidimensional EEG characteristics and statistical analysis, we found that the Alpha2 band power and fuzzy entropy were lower in GAD patients compared with the AS group. It reflects that the prolonged course of the disease causes more pronounced abnormal changes in brain activity. The results of functional connectivity found that PLI between the brains of the GAD group was weakened at high-frequency bands, indicating a decrease in functional connectivity. This suggests that prolonged illness may be associated with impaired brain function, which is crucial for early diagnosis and treatment. In addition, we achieved the highest classification performance by differentiating the duration of disease at a 6-month interval. All four machine learning methods achieved classification accuracy of more than 97%. In conclusion, this study used machine learning to reveal the neural mechanism of GAD from the perspective of multi-dimensional features based on EEG. The electrophysiological findings reported in this paper have potential applications in the neural mechanisms and diagnosis of anxiety disorder.

Data Sharing Statement

Data sets generated during the period and/or analyzed in this study can be obtained from the corresponding author upon reasonable request.

Ethics Statement

Huzhou Third Municipal Hospital's Ethics Committee approved human participant studies. We provide patients with informed consent to participate in this study. The publication of any potentially identifiable images or data contained in this paper requires their written and informed permission. We confirm that all methods were performed in accordance with the relevant guidelines and regulations including the statement in the methods section.

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This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-3510763/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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