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Research

A Study of the Relationship between Brain Structure and Cognitive Function in Epileptic Patients based on VBM

Ling Huang[1#*], Zhaomin Meng[1#], Ziwei Huang[1], Deyou Huang[2], Li Su[1],Caimei Yang[1], Qiujie Xiao[1]

[1]*Department of neurology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.*

[2]*Deparment of Radiology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.*

Abstract **Objective:** This study utilizes voxel-based morphometry (VBM) in conjunction with neuropsychological scales and event-related potentials (ERP) to explore the relationship between structural brain changes and cognitive function in patients with epilepsy. The aim is to provide a theoretical basis for understanding cognitive dysfunction in epileptic patients. Methods: (1) A total of 32 epileptic patients were enrolled as the case group, including 17 patients with cognitive impairment (CIE group) and 15 without cognitive impairment (non-CIE group). Seventeen healthy subjects were selected as the control group. All participants underwent conventional MRI scanning, and whole-brain sagittal 3D T1-weighted imaging (3D T1WI BRAVO) was performed. (2) Both the case and control groups were assessed using neuropsychological scales and ERP measurements. (3) VBM was employed to analyze the differences in brain regions between the groups. The regions showing significant differences were defined as regions of interest (ROIs), from which gray matter volumes were extracted. Partial correlation analyses were conducted to evaluate the relationships between gray matter volumes in the ROIs, neuropsychological scale scores, and ERP indices.

Results: Compared to the non-CIE group, the CIE group showed a significant reduction in gray matter volumes in the right cerebellar lobules 8 and 6, right inferior temporal gyrus, and left orbital middle frontal gyrus ($P<0.001$). No significant increases were observed ($P>0.001$). The gray matter volumes of the right inferior temporal gyrus and left orbital middle frontal gyrus positively correlated with MoCA scores ($P<0.05$) and negatively correlated with P300 latency ($P<0.05$). There were no significant correlations between the gray matter volumes of the right cerebellar lobules 8 and 6 and either MoCA scores or P300 latency ($P>0.05$). Compared to the control group, the CIE group exhibited a significant reduction in gray matter volumes in bilateral cerebellar lobule 9, left cerebellar lobule 7b, left parahippocampal gyrus, right hippocampus, left hippocampus, left middle temporal gyrus, right cuneus, right supramarginal gyrus, left angular gyrus, and right superior parietal lobule ($P<0.001$). No significant increases were observed ($P>0.001$). The gray matter volumes of the right cuneus, left angular gyrus, and right superior parietal lobule positively correlated with MoCA scores ($P<0.05$) and negatively correlated with P300 latency ($P<0.05$). The gray matter volume of the left cerebellar lobule 9 positively correlated with MoCA scores ($P<0.05$) but showed no significant correlation with P300 latency ($P>0.05$). There were no significant correlations between the gray matter volumes of the left parahippocampal gyrus, right hippocampus, and left hippocampus with MoCA scores ($P>0.05$), though these regions negatively correlated with P300 latency ($P<0.05$). In the non-CIE group, compared to the control group, an increase in gray matter volume was observed in the left lingual gyrus, right insula, and right superior parietal lobule ($P<0.001$), while a reduction was noted in the left middle temporal gyrus ($P<0.001$).

Conclusion: (1) The right inferior temporal gyrus and left orbital middle frontal gyrus may be involved in the mechanisms underlying cognitive dysfunction in epilepsy patients. (2) The brain regions exhibiting gray matter atrophy are more extensive in the CIE group compared to the non-CIE group. (3) The structural changes observed in the brains of non-CIE

*Correspondence:Ling Huang, Department of neurology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.Email: hl13737682991@163.com.

epilepsy patients might be related to compensatory mechanisms within the body.

Keywords: Epilepsy; Cognitive Function; Magnetic Resonance Imaging; VBM; Event-Related Potentials; P300

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1 Introduction

Epilepsy is a common central nervous system disorder, affecting approximately 70 million people worldwide, with over 9 million cases in China alone. The incidence is highest among infants and the elderly【1】. Epilepsy is caused by various factors, leading to abnormal brain function due to abnormal neuronal discharges. The clinical manifestations are complex, and while pharmacological treatment is the primary approach, some patients do not respond effectively【2】. About 50% of adult epilepsy patients have comorbid conditions such as sleep disorders and depression【3-5】, and over 80% experience cognitive dysfunction【6】. The frequency and duration of seizures are directly related to neuronal damage, which in turn affects cognitive function, significantly impacting the quality of life of these patients. The underlying mechanisms of this relationship have increasingly become the focus of research attention.

The brain is the central organ responsible for advanced neural functions, with structural changes in various brain tissues and neural networks regulating cognitive function. The regions affected by epileptic seizures and the extent of the damage differ, leading to varying degrees of cognitive decline across different domains. Temporal lobe epilepsy primarily impairs language and memory; frontal lobe epilepsy affects emotions and executive functions【7】; parietal lobe epilepsy disrupts interlobar connections, affecting executive function and attention【8】; occipital lobe epilepsy impairs visual processing-related functions【9】. Seizures are triggered by abnormal neuronal discharges, with complex mechanisms involving genetic mutations, infections, immune responses, and neurotransmitter imbalances that further influence brain structure and cognitive function【10,11】. Normal brain function relies on stable brain waves, and epileptic discharges can alter neuronal structure and information transmission. Related studies have shown that interictal spikes are associated with cognitive impairment【12,13】.

Voxel-based morphometry (VBM) is a fully automated technique for analyzing in vivo brain structure via magnetic resonance imaging (MRI). It allows for quantitative analysis of gray matter and white matter density and volume abnormalities, reflecting subtle changes in brain tissue. VBM is characterized by being non-invasive, comprehensive, objective, simple, reproducible, and accurate【14】. It has been widely applied in the study of various neurological diseases, including cerebral infarction, Parkinson's disease, schizophrenia, Alzheimer's disease, and obstructive sleep apnea【15-19】. Traditional VBM involves spatial normalization, image segmentation, smoothing, and statistical analysis, but it is limited by potential segmentation errors and dependency on image quality. An optimized VBM method improves segmentation accuracy by performing segmentation before normalization【20】.

Currently, the evaluation of cognitive dysfunction primarily relies on neuropsychological assessment scales, such as the Hasegawa Dementia Scale, Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and Wechsler Adult Intelligence Scale. However,

*Correspondence:Ling Huang, Department of neurology, Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, Guangxi Zhuang Autonomous Region, China.Email: hl13737682991@163.com.

these scales are susceptible to subjective influences from both the examiner and the patient, as well as factors such as educational level, social environment, and age. This introduces limitations due to high subjectivity and numerous influencing factors. The MMSE focuses on assessing memory and language functions, while MoCA includes additional tests such as the trail-making, clock-drawing, and digit span tasks, offering a broader evaluation. Although MoCA is slightly less specific than MMSE, it is more sensitive【21】.

Event-related potentials (ERPs) are studied using classic experimental paradigms, including Stroop, Oddball, Go/No-Go, and Flanker tasks. ERPs are brain potentials generated in response to specific stimuli while the patient is awake, reflecting the brain's processing of information 【22】. The primary endogenous components are N200 and P300. N200 is a negative wave with a latency of approximately 200 ms, reflecting the speed of conflict detection; P300 is a positive wave with a latency of approximately 300 ms, representing the process from stimulus reception to response, indicating brain response speed and processing capacity. The amplitude of the P300 wave reflects the subject's response to information and can be used to assess cognitive function. P300 is not affected by the physical properties of the stimulus, making it objective, non-invasive, and sensitive【23】.

This study employs VBM, combined with neuropsychological scales and ERP, to analyze structural brain changes and their relationship with cognitive function in epileptic patients. The goal is to explore the underlying mechanisms, providing new insights and a theoretical basis for the study of cognitive dysfunction in epilepsy.

2 Research Subjects and Methods

2.1 Research Subjects

We collected data from epilepsy patients who sought treatment at the Affiliated Hospital of Youjiang Medical University for Nationalities between November 2021 and February 2023. The control group consisted of healthy subjects matched with the case group in terms of gender, age, and education level. All participants were over 15 years old and right-handed. The study was approved by the Ethics Committee of Youjiang Medical University for Nationalities. The inclusion criteria for each group are as follows:

2.1.1 Epilepsy with Cognitive Dysfunction Group

Inclusion Criteria:

(1) Patients who meet the diagnostic criteria for epilepsy as outlined in the "Clinical Diagnosis and Treatment Guidelines for Epilepsy" established by the China Association Against Epilepsy.

(2) Patients with a clear diagnosis based on clinical symptomatology and electroencephalogram (EEG) results.

(3) Subjects aged between 15 and 65 years.

(4) Subjects who can cooperate well with cranial MRI examination.

(5) Subjects who voluntarily participate and sign the informed consent form.

(6) Subjects who can adequately complete the Mini-Mental State Examination (MMSE), with a score of less than 27, indicating cognitive dysfunction.

Exclusion Criteria:

(1) Patients with severe familial genetic disorders or other serious psychiatric or neurological diseases.

(2) Patients with other severe organic brain lesions or systemic diseases.

(3) Individuals with a history of chronic severe alcohol abuse, drug misuse, or substance abuse.

(4) Patients unable to cooperate with cranial MRI examination.

2.1.2 Epilepsy without Cognitive Dysfunction Group

Inclusion Criteria:

Subjects who can adequately complete the Mini-Mental State Examination (MMSE) with a score of 27 or higher, indicating no cognitive dysfunction.

Other inclusion criteria are the same as those for the epilepsy with cognitive dysfunction group (criteria 1, 2, 3, 4, and 5).

Exclusion Criteria:

The exclusion criteria are the same as those for the epilepsy with cognitive dysfunction group.

2.1.3 Normal Control Group

Healthy right-handed subjects matched for age, gender, and education level with the epilepsy patient group are selected. The selection criteria include:

(1) Subjects who voluntarily participate in the study.

(2) Healthy individuals aged 15 to 65 years.

(3) Individuals without a history of chronic severe alcohol abuse, drug misuse, or substance abuse.

(4) Individuals without a family history of epilepsy, severe central nervous system diseases, or systemic diseases.

(5) Subjects who can adequately complete the Mini-Mental State Examination (MMSE) with a score of 27 or higher, indicating no cognitive dysfunction.

2.2 Research Methods

2.2.1 Data Collection

Data collected include clinical information from both the case and control groups, such as name, gender, age, number of participants, years of education, age of onset, duration of disease, neuropsychological test scores, and history of antiepileptic drug treatment.

2.2.2 Cranial Magnetic Resonance Imaging (MRI) Data Acquisition

All participants undergo whole-brain MRI scanning in the Department of Imaging at the Affiliated Hospital of Youjiang Medical University for Nationalities, using a Discovery MR 750 3.0T scanner (GE Healthcare, USA). The MRI procedure is explained to the subjects, and fixed sponges are used to minimize artifacts. Subjects are asked to remain quiet in a supine position to avoid head movements. Routine head scans, including T1-weighted, T2-weighted, and FLAIR sequences, are performed first to exclude severe intracranial lesions. Subsequently, sagittal whole-brain three-dimensional T1-weighted imaging (3D T1WI) is conducted with parameters as follows: field of view (FOV) of 240 mm × 240 mm, 164 slices, slice thickness of 1 mm, repetition time (TR) of 8.5 ms, echo time (TE) of 3.3 ms, matrix size of 256 × 256, number of excitations (NEX) of 1, and scanning time of 4 minutes and 27 seconds.

2.2.3 Cognitive Function Assessment

Neuropsychological assessments, including the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), are conducted by clinicians in a quiet environment for all subjects. The MMSE is widely used for its simplicity and rapid assessment of cognitive function, covering orientation in time and place, language, memory, visuospatial abilities, attention, and calculation, with a total score of 30 points; a score of less than 27 indicates cognitive dysfunction. The MoCA is used for rapid screening of mild cognitive impairment in clinical settings, covering eight cognitive domains with a total score of 30 points; a score of less than 26 indicates cognitive dysfunction.

2.2.4 Event-Related Potential (ERP) Detection

Event-related potentials are measured by clinicians using the MEB-2306C electromyography evoked potential device in a quiet environment. Electrode placement follows the international 10/20 system, and the impedance between electrodes and skin is kept below 5 kΩ. The experiment employs the oddball paradigm, where the auditory stimuli include a target stimulus of 80 dB sound intensity at 2 kHz frequency, with a 20% probability of occurrence, and a non-target stimulus of 60 dB sound intensity at 1 kHz frequency, with an 80% probability of occurrence. The procedure is explained to the participants, who are instructed to respond to the target stimulus and the number of occurrences is recorded. Detection metrics include the latency and amplitude of N200 and P300 waves. Latency is defined as the horizontal distance from the onset of the stimulus to the peak of the wave, and amplitude is defined as the vertical distance from the peak of the potential wave to the baseline.

2.2.5 Magnetic Resonance Imaging Data Processing

Voxel-based morphometry (VBM) analysis and processing of the 3D T1-weighted images are conducted using the CAT12 toolbox running on MATLAB 2018b. The preprocessing steps for the images are as follows:

(1) Image Data Format Conversion:

The MRIcron software package is used to convert the 3D T1WI structural MRI images from DICOM format to NIFTI format using the dcm2niigui tool.

(2) Image Segmentation:

The New Segment tool in CAT12 is applied to segment the 3D T1WI structural MRI images into three components: gray matter, white matter, and cerebrospinal fluid.

(3) Spatial Normalization:

All images are registered to the standard Montreal Neurological Institute (MNI) space.

(4) Quality Check:

A quality check of the segmented gray matter images is performed using CAT12.

(5) Homogeneity Check:

Homogeneity of the segmented gray matter images is assessed using CAT12.

(6) Image Smoothing:

The smoothed images are processed with an 8 mm × 8 mm × 8 mm full-width at half-maximum (FWHM) Gaussian kernel using the Smooth tool in SPM12 to improve the signal-to-noise ratio and enhance data validity for subsequent statistical analysis.

(7) Total Intracranial Volume Calculation:

The Total Intracranial Volume (TIV) for each subject is calculated using the Estimate TIV function in CAT12, and TIV is included as a covariate in subsequent statistical analyses to control for inter-subject variability in intracranial volume.

2.3 Data Analysis and Processing

2.3.1 Clinical Data Analysis

Statistical analysis of the clinical data from the epilepsy groups with and without cognitive dysfunction, as well as the normal control group, is performed using SPSS 26.0. Continuous variables are presented as mean ± standard deviation or median and interquartile range, depending on the distribution. For data that follow a normal distribution, one-way analysis of variance (ANOVA) is employed, with post-hoc comparisons conducted for significant differences. Non-normally distributed data are analyzed using non-parametric tests. Gender differences are assessed using the chi-square test. The significance level is set at $\alpha = 0.05$, and $P < 0.05$ is considered statistically significant.

For the analysis of magnetic resonance data, intracranial

volume, gray matter volume, and white matter volume are evaluated using one-way ANOVA. The preprocessed VBM data are statistically analyzed using SPM12, with $P < 0.001$ deemed statistically significant, and a cluster size of ≥2 voxels. The results are visualized using xjView.

In the correlation analysis, regions with significant differences are selected as regions of interest (ROIs). Gray matter volume is extracted using DPABI 6.0, and partial correlation analysis is performed in SPSS 26.0, with age, gender, years of education, and total intracranial volume included as covariates.

3 Results

3.1 Comparison of Clinical Data

A total of 44 patients with epilepsy were recruited from the Affiliated Hospital of Youjiang Medical University for Nationalities between November 2021 and February 2023. Based on the inclusion and exclusion criteria, 12 patients were excluded, resulting in 32 patients being included in the study as the case group. Among them, 17 patients were classified into the epilepsy with cognitive dysfunction group, and 15 patients were classified into the epilepsy without cognitive dysfunction group. For the control group, 17 healthy right-handed individuals matched with the case group for gender, age, and education level were selected, making a total of 49 participants.

In the epilepsy with cognitive dysfunction group, there were 17 patients (7 males and 10 females) with a mean age of 33.64 ± 14.19 years and a mean education level of 8.41 ± 4.31 years. In the epilepsy without cognitive dysfunction group, there were 15 patients (9 males and 6 females) with a mean age of 28.20 ± 12.02 years and a mean education level of 10.60 ± 3.50 years. In the control group, there were 17 participants (8 males and 9 females) with a mean age of 37.23 ± 13.57 years and a mean education level of 9.82 ± 4.53 years.

The three groups are well-matched in terms of age, gender, and education level, with no statistically significant differences observed (all $P > 0.05$). Additionally, no statistically significant differences are found between the epilepsy with cognitive dysfunction group and the epilepsy without cognitive dysfunction group in terms of age of onset and duration of illness ($P > 0.05$). The detailed results are presented in Table 2-1.

Table 2-1 Comparison of clinical data among the three groups

Group	Epilepsy with Cognitive Dysfunction (n = 17)	Epilepsy without Cognitive Dysfunction (n = 15)	Control (n = 17)	*P*-value
Age (years)	33.64±14.19	28.20±12.02	37.23±13.57	0.171
Gender (Male/Female)	7/10	9/6	8/9	0.558
Years of Education	8.41±4.31	10.60±3.50	9.82±4.53	0.326
Age of Onset (years)	21.84±14.43	23.33±12.97	-	0.759
Duration of Illness (months)	60 (12, 270)	36 (11, 72)	-	0.226

3.2 Comparison of Neuropsychological Test Scores

There is a significant difference in the total scores of the Montreal Cognitive Assessment (MoCA) among the three groups ($P < 0.05$). Further post-hoc analysis indicates that there is a significant difference in the MoCA total scores between the group with epilepsy and cognitive dysfunction (21.00 ± 3.92) and both the group with epilepsy without cognitive dysfunction (25.80 ± 3.02) and the control group (25.64 ± 3.10) ($P < 0.05$). However, no significant difference is observed between the epilepsy without cognitive dysfunction group and the control group ($P > 0.05$). The results are presented in Table 2-2.

Table 2-2 Comparison of neuropsychological scale scores among the three groups

Group	Patients with Epilepsy and Cognitive Dysfunction (n=17)	Patients with Epilepsy without Cognitive Dysfunction (n=15)	Control Group (n=17)	*P*-value
Montreal Cognitive Assessment (MoCA)	21.00±3.92	25.80±3.02	25.64±3.10	<0.001[a,b,c]

a. Comparison between the group with epilepsy and cognitive dysfunction and the group with epilepsy without cognitive dysfunction, P < 0.05.
b. Comparison between the group with epilepsy and cognitive dysfunction and the control group, P < 0.05.
c. Comparison between the group with epilepsy without cognitive dysfunction and the control group, P > 0.05.

3.3 Comparison of Event-Related Potential Data

There are no significant differences in the N200 latency or P300 amplitude among the three groups (P > 0.05). However, the P300 latency shows significant differences (P < 0.05). Further post-hoc analysis indicates significant differences between the group with epilepsy and cognitive dysfunction and both the group with epilepsy without cognitive dysfunction and the control group (P < 0.05). In contrast, there are no significant differences between the group with epilepsy without cognitive dysfunction and the control group (P > 0.05). The results are detailed in Table 2-3.

Table 2-3 Comparison of event-related potential data among three

	Epilepsy with Cognitive Dysfunction (n=17)	Epilepsy without Cognitive Dysfunction (n=15)	Control Group (n=17)	*P*-value
P300 Latency (ms)	380.47±52.28	341.13±36.07	309.11±46.73	<0.001[a,b,c]
P300 Amplitude (μV)	6.16±5.11	10.35±7.40	8.53±5.07	0.142
N200 Latency (ms)	233.23±36.01	229.46±33.05	215.94±32.79	0.309

a: Significant difference between the epilepsy with cognitive dysfunction group and the epilepsy without cognitive dysfunction group, P < 0.05.
b: Significant difference between the epilepsy with cognitive dysfunction group and the control group, P < 0.05.
c: No significant difference between the epilepsy without cognitive dysfunction group and the control group, P > 0.05.

3.4.2 Comparison between the Epilepsy with Cognitive Dysfunction Group and the Epilepsy without Cognitive Dysfunction Group

When comparing the epilepsy with cognitive dysfunction group to the epilepsy without cognitive dysfunction group, regions with reduced gray matter volume (P < 0.001) are identified. The areas showing significant differences are primarily located in the right cerebellar lobule VIII, right cerebellar lobule VI, right inferior temporal gyrus, and left orbital part of the middle frontal gyrus. No regions with increased gray matter volume are found (P > 0.001). The detailed results are presented in Table 2-5 and illustrated in Figure 2-1.

Table 2-5 Differences in brain regions between epilepsy with cognitive impairment and epilepsy without cognitive impairment

Group Comparison	Brain Region	Peak MNI Coordinates			Voxel Value	Peak Intensity
		x	y	z		
Epilepsy with Cognitive Impairment < Epilepsy without Cognitive Impairment	Right Cerebellar Lobule VIII	16.5	-54	-63	61	3.9838
	Right Cerebellar Lobule VI	36	-31.5	-33	11	3.6555
	Right Inferior Temporal Gyrus	61.5	-37.5	-25.5	4	3.4975
	Left Orbital Part of the Middle Frontal Gyrus	-19.5	61.5	-13.5	2	3.4549

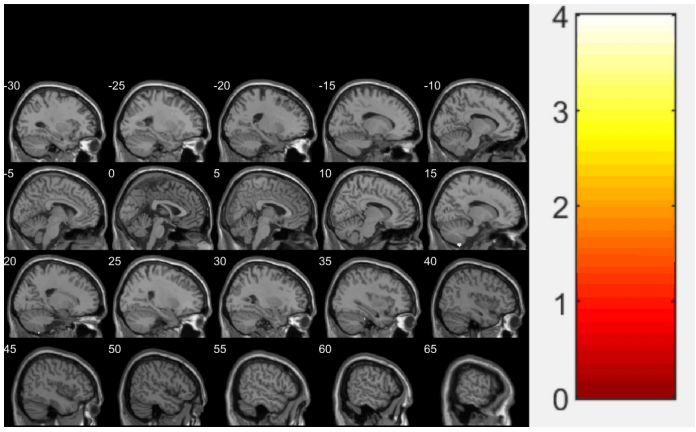

Figure2-1 The brain regions of epilepsy with cognitive impairment were different from those of epilepsy without cognitive impairment

3.4.3 Comparison between the Epilepsy with Cognitive Impairment Group and the Normal Control Group

When comparing the epilepsy with cognitive impairment group to the normal control group, regions with a significant reduction in gray matter volume are identified (P<0.001). The primary areas showing decreased gray

matter volume include the left cerebellar lobule IX, right cerebellar lobule IX, left cerebellar lobule VIIb, left parahippocampal gyrus, right hippocampus, left hippocampus, right cuneus, left middle temporal gyrus, right supramarginal gyrus, left angular gyrus, and right superior parietal lobule. No regions with an increase in gray matter volume are detected (P>0.001). These results are detailed in Table 2-6 and Figure 2-2.

Table 2-6 The brain regions of epilepsy with cognitive impairment were different from those of the normal group

Intergroup Comparison	Brain Region	Peak MNI Coordinates			Voxel Value	Peak Intensity
		x	y	z		
Epilepsy with Cognitive Impairment Group < Normal Group	Left Cerebellar Lobule IX	-10.5	-55.5	-60	148	3.8233
	Right Cerebellar Lobule IX	16.5	-52.5	-54	487	4.536
	Left Cerebellar Lobule VIIb	-39	-63	-54	29	3.4785
	Left Parahippocampal Gyrus	-24	-9	-30	148	3.9519
	Right Hippocampus	33	-10.5	-16.5	7	3.5223
	Left Hippocampus	-19.5	-34.5	-3	26	3.5035
	Left Middle Temporal Gyrus	-66	-21	0	142	4.7302
	Right Cuneus	21	-93	12	5	3.4679
	Right Supramarginal Gyrus	64.5	-42	30	9	3.522
	Left Angular Gyrus	-40.5	-40.5	49.5	3	3.471
	Right Superior Parietal Lobule	19.5	-66	64.5	73	3.987

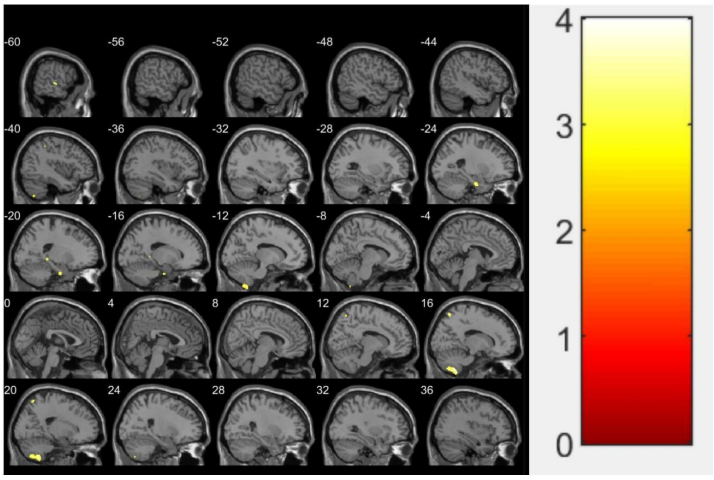

Figure2-2 The brain regions of epilepsy with cognitive impairment were different from those of the normal group

3.4.4 Comparison between Epileptic Patients without Cognitive Impairment and the Control Group

The regions where the gray matter volume is increased in the epilepsy without cognitive impairment group compared to the control group include the left lingual gyrus, the right insula, and the right superior parietal lobule (P < 0.001). Conversely, the gray matter volume is decreased in the left middle temporal gyrus in this group compared to the control group (P < 0.001). These results are presented in Table 2-7 and Figures 2-3.

Table 2-7 Different brain regions in epilepsy without cognitive impairment compared with normal group

Comparison	Brain Region	Peak MNI Coordinates			Voxel Value	Peak Intensity
		x	y	z		
Epilepsy without Cognitive Impairment > Control Group	Right Insula	42	3	-6	39	3.8462
	Left Lingual Gyrus	-15	-79.5	0	67	4.3204
	Right Superior Parietal Lobule	39	-57	60	3	3.6465
Epilepsy without Cognitive Impairment < Control Group	Left Middle Temporal Gyrus	-69	-21	3	44	-3.8394

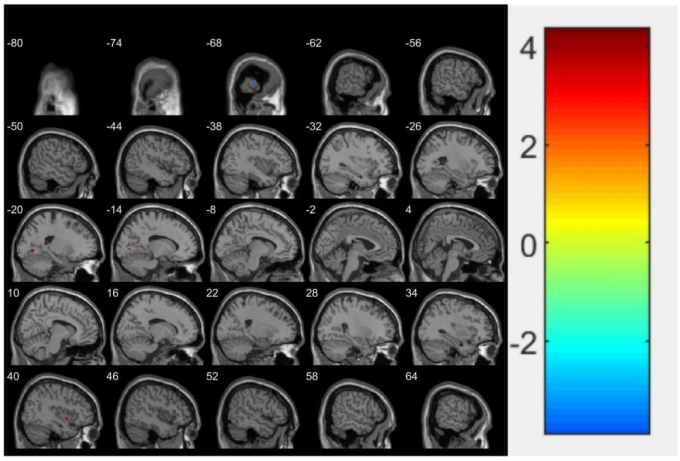

Figure 2-3 Different brain regions in the epilepsy group without cognitive impairment compared with the normal group

3.5.1 Correlation Between Gray Matter Volume in Brain Regions with Inter-group Differences and MoCA Scores, P300 Latency

(1) Epilepsy with Cognitive Impairment Group and Epilepsy without Cognitive Impairment Group

In this analysis, we selected the brain regions with significant differences between the epilepsy with cognitive impairment group and the epilepsy without cognitive impairment group as regions of interest (ROIs). The gray matter volume within these ROIs was extracted for each participant. Partial correlation analysis was then conducted between the gray matter volume and both the total MoCA

score and P300 latency, controlling for age, gender, years of education, and total intracranial volume (TIV).

The results show that the gray matter volume of the right inferior temporal gyrus is positively correlated with the total MoCA score (r = 0.463, P = 0.013) and negatively correlated with P300 latency (r = -0.498, P = 0.007). Similarly, the gray matter volume of the left orbital part of the middle frontal gyrus is positively correlated with the total MoCA score (r = 0.395, P = 0.037) and negatively correlated with P300 latency (r = -0.443, P = 0.018). No significant correlation is observed between the gray matter volumes of the right cerebellar lobule VIII and right cerebellar lobule VI with either the total MoCA score or P300 latency. The detailed results are presented in Table 2-8.

Table 2-8 Correlation analysis of grey matter volume, total MoCA score and P300 latency between epilepsy with and without cognitive impairment

Region	MoCA		P300 Latency	
	r	P	r	P
Right Cerebellum 8	0.170	0.388	-0.118	0.549
Right Cerebellum 6	0.352	0.066	-0.158	0.423
Right Temporal Gyrus	0.463	0.013	-0.498	0.007
Left Orbitofrontal Gyrus	0.395	0.037	-0.443	0.018

(2) Comparison between Epileptic Patients with Cognitive Impairment and Normal Controls

Brain regions showing significant differences between the group of epileptic patients with cognitive impairment and the normal control group are selected as regions of interest (ROIs). Gray matter volumes of these ROIs are extracted for each subject, and partial correlation analyses are conducted between gray matter volumes and MoCA total scores as well as P300 latency. Age, sex, years of education, and total intracranial volume (TIV) are controlled for in these analyses.

Table 2-9 Correlation analysis of grey matter volume, total MoCA score and P300 latency between epileptic with cognitive impairment and normal groups

	MoCA		P300 Latency	
	r	*P*	*r*	*P*
Left Cerebellum 9	0.387	0.035	-0.357	0.053
Right Cerebellum 9	0.247	0.188	-0.320	0.085
Left Cerebellum 7b	0.245	0.192	-0.331	0.074
Left Parahippocampal Gyrus	0.259	0.167	-0.470	0.009
Right Hippocampus	0.310	0.096	-0.398	0.029
Left Hippocampus	0.131	0.489	-0.501	0.005
Left Middle Temporal Gyrus	0.205	0.277	-0.322	0.083
Right Cuneus	0.458	0.011	-0.499	0.005
Right Supramarginal Gyrus	0.278	0.137	-0.349	0.059
Left Inferior Parietal Lobule	0.477	0.008	-0.402	0.028
Right Superior Parietal Lobule	0.530	0.003	-0.418	0.021

4 Discussion

Epileptic patients often experience cognitive impairments. By employing voxel-based morphometry (VBM) for quantitative analysis of brain structure, subtle changes that are not visible to the naked eye can be detected. This study utilizes VBM to explore brain structural changes and their relationship with cognitive function in three groups: 17 epileptic patients with cognitive impairment, 15 epileptic patients without cognitive impairment, and 17 healthy controls. The findings provide clinical insights and research clues for understanding the underlying mechanisms of cognitive impairments in epileptic patients.

4.1 Comparison between Epileptic Patients with and without Cognitive Impairment

This study finds that the gray matter volume in certain brain regions is significantly reduced in epileptic patients with cognitive impairment, particularly in the right cerebellum lobule VIII, right cerebellum lobule VI, left

orbital frontal gyrus, and right inferior temporal gyrus, with no observed increase in gray matter volume in these regions. This reduction may be related to abnormal electrical activity caused by seizures, leading to neuronal ischemia and hypoxia. There are no significant differences in age at onset or disease duration between the two groups; however, the differences in brain regions might be related to factors such as medication use and treatment duration. After controlling for factors such as years of education, age, sex, and total intracranial volume (TIV), some brain regions' gray matter volumes show a correlation with cognitive function, suggesting a potential impact on cognitive impairment in epileptic patients.

Damage to the temporal lobe can lead to cognitive impairments including memory, attention, language, and executive functions. This study finds that gray matter volume in the right inferior temporal gyrus negatively correlates with P300 latency and positively correlates with MoCA scores, indicating a link between the inferior temporal gyrus and cognitive function. The temporal lobe's involvement with cognitive function in epileptic patients might contribute to cognitive impairments. Research shows that white matter is often damaged in epilepsy, with patients having lower mean kurtosis (MK) values in the temporal lobe compared to healthy controls, and even lower MK values in those with cognitive impairment, suggesting that seizures can cause damage to white matter fibers. The inferior temporal gyrus connects with other brain regions through multiple white matter tracts, and reduced gray matter volume may affect the connectivity of neural networks, thereby impacting cognitive function.

The frontal lobe, a crucial part of brain development, influences higher neural functions and is divided into dorsolateral, medial, and orbital regions. Frontal lobe damage can result in cognitive impairments such as executive function and memory issues. The frontal lobe forms neural circuits with other brain regions through fiber bundles, and damage can lead to executive function deficits. Studies show that the medial frontal regions are associated with selection and decision-making, emotional disorders; the dorsolateral regions are related to decision-making; and the ventral regions are linked to cognitive and emotional regulation. This study finds that gray matter volume in the left orbital frontal gyrus positively correlates with MoCA scores and negatively correlates with P300 latency, indicating its relevance to cognitive function and potential impact on cognitive impairment in epileptic patients. The orbital frontal gyrus, part of the frontal lobe, has extensive connections with the limbic system and cerebral cortex and is involved in sensory information processing and emotion generation. Additionally, patients who underwent resection of the left orbital frontal gyrus may experience minor memory impairments, supporting its role in information processing and cognitive regulation. Therefore, reduced gray matter volume in the orbital frontal gyrus may be one of the pathological mechanisms for cognitive impairment in epileptic patients.

Compared to epileptic patients without cognitive impairment, those with cognitive impairment show significant reductions in gray matter volume in the right cerebellum lobule VIII and right cerebellum lobule VI. Changes in cerebellar volume are caused by various complex mechanisms. In this study, the relationship between cerebellar substructural changes and cognitive function in epileptic patients is not significant. Additionally, the use of antiepileptic drugs and disease progression may also affect cerebellar morphology. Future research should further explore cerebellar substructural changes and

integrate clinical data for a more comprehensive evaluation to reveal more detailed information.

4.2 Comparison between Epileptic Patients with Cognitive Impairment and Normal Controls

The gray matter volume in patients with epilepsy and cognitive impairment is significantly reduced in several regions, including the left and right cerebellum lobule IX, left cerebellum lobule VIIb, bilateral hippocampi, bilateral cuneus, bilateral middle temporal gyri, bilateral supramarginal gyri, bilateral angular gyri, and the right superior parietal gyrus. No regions exhibit increased gray matter volume. Compared to the group without cognitive impairment, the group with cognitive impairment shows a more extensive reduction in gray matter volume, with the left middle temporal gyrus being the only region showing a reduction in the non-cognitive impairment group. Changes in these brain regions may be related to long-term electrical damage from seizures or differences in cognitive function. After controlling for age, sex, years of education, and TIV, some brain regions' gray matter volumes correlate with cognitive function, though the specific effects require further investigation.

The study finds that compared to normal controls, patients with epilepsy and cognitive impairment show reduced gray matter volume in the left parahippocampal gyrus, bilateral hippocampi, and the right cuneus. Pengcheng Ma's research also reports reduced gray matter volume in the left hippocampus and cuneus in patients with temporal lobe epilepsy and cognitive impairment[27], consistent with our findings. The parahippocampal gyrus, a primary cortical input to the hippocampus, is involved in episodic memory, visuospatial processing, and emotional processing, making it a critical center for memory processing[28]. The hippocampus plays a role in spatial navigation and the storage and conversion of long-term memory; damage to the hippocampus can lead to memory deficits and cognitive decline[29]. Additionally, the study reveals that reduced gray matter volume in the hippocampus correlates negatively with P300 latency, indicating the hippocampus's significance for cognitive function. Although less correlated with MoCA scores, P300 latency is a more objective measure of cognitive function. Given the hippocampus's role as a primary epileptic focus, its reduced gray matter volume in the cognitive impairment group may result from epilepsy.

The study also finds that reduced gray matter volume in the right cuneus in patients with epilepsy and cognitive impairment is positively correlated with MoCA scores and negatively correlated with P300 latency, suggesting a potential association with cognitive function. The cuneus, located in the medial occipital lobe, participates in visual processing; lesions can impair delayed visual recall and affect cognitive function[30]. Moreover, the gray matter volume in the parietal lobe's internal regions is reduced in the epilepsy group. The parietal cortex is responsible for sensory impulse analysis and judgment; damage can lead to reading, writing disorders, and attention problems[31]. The right supramarginal gyrus does not show a clear correlation with cognitive function, whereas the gray matter volumes in the left angular gyrus and right superior parietal gyrus are negatively correlated with P300 latency and positively correlated with MoCA scores, suggesting their involvement in the default mode network and executive function.

In comparisons between the epilepsy with cognitive impairment group and normal controls, several cerebellar substructures show atrophy, indicating that changes in cerebellar structure might interact with epilepsy, potentially

as both a result and a cause of seizures. The study finds reduced gray matter volume in the left cerebellum lobule IX, positively correlated with MoCA scores. Schmahmann's cerebellar cognitive affective syndrome (CCAS) challenges the traditional view of the cerebellum's role in motor control alone, highlighting its involvement in cognitive, attentional, emotional, and language functions, manifesting as spatial cognitive deficits, executive function impairments, personality changes, and speech difficulties. Additionally, cerebellar lesions are related to network connections with the frontal, temporal, parietal, and limbic lobes[32]. Katanoda's fMRI research shows that the right cerebellar hemisphere is activated during right-handed writing, participating in the writing process[33]. Currently, there is limited research on cerebellar structure in epilepsy patients, and future studies should include prospective, large-sample investigations.

4.3 Comparison between Epileptic Patients without Cognitive Impairment and Normal Controls

In the group of epileptic patients without cognitive impairment, significant increases in gray matter volume are observed in the right superior parietal gyrus, left lingual gyrus, and right insula, while a reduction is noted in the left middle temporal gyrus. There are no significant differences between the two groups in terms of MoCA total scores and P300 latency. Research indicates that epilepsy is a network disorder of the brain, where abnormal discharges in epileptic foci affect not only the local area but also involve multiple brain regions[34]. The lingual gyrus is associated with the visual network and memory, while the insula reflects the propagation of epileptic activity[35]. The increased gray matter volumes in the right superior parietal gyrus, left lingual gyrus, and right insula may be a result of cellular compensation, whereas the reduction in the left middle temporal gyrus may be related to the disease progression. Further investigation is required to explore the relationship between these structural changes and cognitive function.

5 Conclusion

1.The right inferior temporal gyrus and left orbital frontal gyrus may be involved in the mechanisms of cognitive impairment in epileptic patients.

2.The extent of gray matter atrophy is more widespread in the group with epilepsy and cognitive impairment compared to the group with epilepsy but without cognitive impairment.

3.The structural changes observed in epileptic patients without cognitive impairment may be related to compensatory mechanisms in the body.

Conflict of Interest

None.

Author Contributions

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