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Regional gray matter atrophy and neuropsychologcal problems in relapsing-remitting multiple sclerosis

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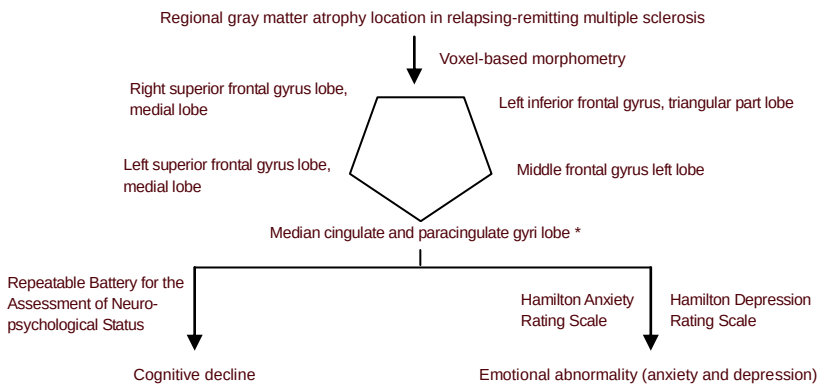
Graphical Abstract



*represents the region with the greatest gray matter atrophy.

Abstract

In multiple sclerosis, gray matter atrophy is extensive, and cognitive deficits and mood disorders are frequently encountered. It has been conjectured that focal atrophy is associated with emotional decline. However, conventional MRI has revealed that the pathological characteristics cannot fully account for the mood disorders. Moreover, there is no correlation between cognitive disorders and MRI results in clinically isolated syndromes or in cases of definite multiple sclerosis. In this case-control study, voxel-based morphometric analysis was performed on 11 subjects with relapsing-remitting multiple sclerosis, and the results show that these patients exhibit gray matter atrophy. Moreover, the gray matter atrophy in the superior and middle gyri of the right frontal lobe in patients with multiple sclerosis was correlated with scores from the Hamilton Anxiety Rating Scale. The scores obtained with the Repeatable Battery for the Assessment of Neuropsychological Status were associated with gray matter atrophy in the middle gyrus of the left frontal lobe, the superior and middle gyrus of the right frontal lobe, the middle gyrus of the left cingulate, the superior and middle gyri of the left frontal lobe, and the triangular area of the left frontal lobe. However, there was no statistical significance. These findings suggest that the cingulate and frontal cortices of the nant hemisphere are the most severely atrophic regions of the brain, and this atrophy is correlated with cognitive decline and emotional abnormalities.

Aiyu Lin and Fuyong Chen contributed equally to this work.

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Author contributions: Yu T and Lin AY was responsible for study design, writing and validation. Chen FY and Liu F took part in study design. Li ZW provided research guidance. Liu Y was responsible for MR technical support. Lin SF, Wang XY and Zhu JT conducted the Repeatable Battery for the Assessment of Neuropsychological Status scale, Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale tests. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Ethical approval: The study was approved by the Ethics Committee of Fujian Medical University in China and was in accordance with the *Declaration of Helsinki*. All participants provided informed written consent.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application disputations.

Key Words

neural regeneration; neurodegeneration; MRI; relapsing-remitting multiple sclerosis; gray matter atrophy; cognitive; mood; voxel-based morphometry; neuroregeneration

INTRODUCTION

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. It is widespread in western populations, but China is a low-incidence country[1]. The clinical and genetic features of multiple sclerosis are heterogeneous in the Eastern and Western populations. Focal cortical gray matter atrophy is present in all disease phenotypes, including progressive multiple sclerosis, “benign” multiple sclerosis and clinically isolated syndromes suggestive of multiple sclerosis[2-5]. Although cognitive deficits are frequently encountered in multiple sclerosis[2], they have a complex and multifactorial etiology that cannot be adequately explained by pathological features recorded on conventional MRI[6], and no significant association has been found between cognitive impairment and routine MRI measurements in clinically isolated syndromes or newly diagnosed multiple sclerosis patients[7-8]. Patients with low cognitive status exhibit a unique distribution of gray matter atrophy[3, 9], which is most prominent in the frontal and temporal areas of the brain[10]. Mood disorders are often accompanied with multiple sclerosis[11-12]. Evidence indicates that the early focal atrophy may be associated with clinical progression and neuropsychological decline[13].

The effects of focal cortical gray matter atrophy on clinical presentation, including cognitive and emotional scores, have not yet been fully established. Therefore, additional research is required to clarify the relationship between them. Furthermore, there are very few reports examining whether gray matter atrophy is present in Chinese multiple sclerosis patients, and it is unclear whether it is extensive or focal. In recent years, the assessment of brain atrophy by MRI has been given great importance by foreign researchers interested in understanding the pathogenesis of the disease. The development of voxel-based morphometry has made it possible to accurately measure cerebral atrophy. This method has proven to be the most reliable and effective means of assessing gray matter atrophy.

For many years, motor and sensory disorders received widespread attention because they are easily identified[14-15]. However, non-motor deficits, such as cognitive impairment and abnormal emotion, are not only very common, but also seriously affect the patient’s quality of life[16]. Therefore, it is not sufficient to evaluate the disability status of patients with multiple sclerosis using only the Expanded Disability Status Scale. Clinicians should also focus on the value of cognitive function in the understanding of multiple sclerosis. Indeed, greater attention has been given to cognitive function in recent years. Effective and active measures should be taken to lessen the cognitive functional decline. Early drug intervention and treatment in the progression of the disease have great potential in preventing or delaying the onset of cognitive impairment and emotional disorders[17].

In this study, we used the voxel-based morphometry method to accurately measure gray matter atrophy in eleven Chinese patients with multiple sclerosis to better understand the characteristics of gray matter atrophy. Furthermore, our study is the first to apply the Repeatable Battery for the Assessment of Neuropsychological Status scale in Chinese patients with relapsing-remitting multiple sclerosis to evaluate cognitive function. This study should provide insight into the relationship between gray matter atrophy and cognition and emotion impairments in relapsing-remitting multiple sclerosis.

RESULTS

Quantitative analysis of subjects

A total of 11 patients with relapsing-remitting multiple sclerosis and 11 healthy controls were enrolled and entered into the final analysis. Demographic and clinical data are displayed in Table 1.

Table 1 Clinical data for the multiple sclerosis and healthy control groups

Clinical data	Multiple sclerosis group (*n* = 11)	Healthy control group (*n* = 11)	*P* (Mann-Whitney *U* test)
Age (mean ± SD, year)	38.5±12.2	39.5±13.2	
Gender (female/male, *n*)	7/4	7/4	
Education received (mean ± SD, year)	12.3±4.7	12.6±4.4	
Time of onset (mean ± SD, year)	8.0±6.7	NA	0.855 9
Duration (mean ± SD, year)	30.5±11.1	NA	0.853 1
The total recurrence times	4.2±1.6	NA	
Dominant hemisphere (Left/right, *n*)	11/0	11/0	
EDSS score (mean ± SD)	3.4±2.3	NA	

EDSS: Expanded Disability Status Scale; NA: not applicable.

Gray matter atrophy in relapsing-remitting multiple sclerosis patients

Voxel-based morphometric analysis showed that the volume of the gray matter in the multiple sclerosis group was significantly reduced compared with that in the healthy control group, most significantly in the cingulate and frontal cortices of the dominant hemisphere. The atrophic brain regions in the automated anatomical labeling template included the median cingulate and paracingulate gyri, the superior frontal gyrus, the medial inferior frontal gyrus, the triangular part, and the middle frontal gyrus (Figure 1, Table 2).

Cognitive decline and emotional abnormality in relapsing-remitting multiple sclerosis patients

A statistically significant lower Repeatable Battery for the Assessment of Neuropsychological Status score was observed in the multiple sclerosis group compared with the healthy control group (Mann-Whitney *U* test, *P* = 0.001). The analysis of the items of the Repeatable Battery for the Assessment of Neuropsychological Status revealed that the multiple sclerosis patients had deficits in immediate memory, visuospatial skills and attention (Table 3). The existence of mood disorders in the multiple sclerosis patients was suggested by the higher scores in the Hamilton Anxiety Rating Scale (*P* = 0.050) and the Hamilton Depression Rating Scale (*P* = 0.035) compared with the healthy control group (Table 4).

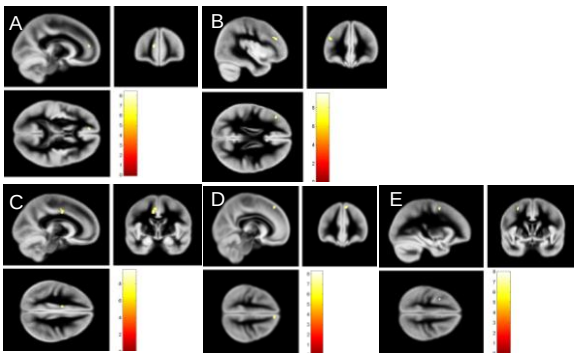

Figure 1 Gray matter atrophy in relapsing-remitting multiple sclerosis patients by MRI.

Voxel-based morphometric analysis showed that the volume of the gray matter in the multiple sclerosis group was significantly reduced compared with the healthy control group. Map of yellow dots represents significant parts of gray matter atrophy. The atrophy was most significant in the cingulate and frontal cortices of the dominant hemisphere. The atrophic brain regions in the automated anatomical labeling template included the following lobes: Cingulum_Mid_L (A): Median cingulate and paracingulate gyri left; Frontal_Sup_Medial_R (B): Superior frontal gyrus, medial right; Frontal_Inf_Tri_L (C): Inferior frontal gyrus, triangular part left; Frontal_Mid_L (D): Middle frontal gyrus left, and Frontal_Sup_Medial _L (E): Superior frontal gyrus, medial left.

Table 2 Gray matter volume reduction in voxel-based morphometry based on T1 (False Discovery Rate correction *q*-value = 0.01)

Brain region	Voxel number	Peak Montreal Neurological Institute coordinate (mm)			Peak intensity (*t*-score)
		x	*y*	*z*	
Cingulum_Mid_L	369	–10	–5	40	–9.614 3
Frontal_Sup_Medial_R	156	8	36	51	–8.269 8
Frontal_Inf_Tri_L	132	–40	35	24	–9.513 4
Frontal_Sup_	102	–11	48	13	–8.397 0
Medial_L	65	–29	2	53	–7.949 5

Results were reported according to the automated anatomical labeling software package and digital atlas of the human brain. Cingulum_Mid_L: Median cingulate and paracingulate gyri left; Frontal_Sup_Medial_R: superior frontal gyrus, medial right; Frontal_Inf_Tri_L: inferior frontal gyrus, triangular part left; Frontal_Sup_Medial_L: superior frontal gyrus, medial left.

Correlation between regional gray matter atrophy and cognitive decline/emotional abnormalities in patients with relapsing-remitting multiple sclerosis

There was a significant association between gray matter

atrophy in the superior frontal gyrus, medial right, and the scores in the Hamilton Anxiety Rating Scale (P = 0.033 5, Pearson correlation). Cognitive testing also revealed a trend towards a correlation between the Repeatable Battery for the Assessment of Neuropsychological Status items and regional atrophy of the gray matter, especially in the frontal medial left, frontal superior medial right, cingulum medial left, frontal superior medial left, and frontal inferior triangular left lobes, but without statistical significance (P = 0.06–0.65; Table 5).

Table 3 Cognitive data from the Repeatable Battery for the Assessment of Neuropsychological Status items in multiple sclerosis patients and healthy controls

Cognitive function and test	Multiple sclerosis group (n = 11)	Healthy control group (n = 11)	P
Repeatable Battery for the Assessment of Neuropsychological Status	79.1±17.9	104.8±8.2	0.001 3
Immediate memory	72.5±21.1	97.5±10.6	0.007 4
Visuospatial	81.6±30.5	108.3±8.9	0.005 1
Language	81.8±21.4	96.5±7.5	0.035 1
Attention	91.3±9.4	112.5±14.3	0.002 0
Delayed memory	81.8±24.5	103.7±8.5	0.030 2

Data were expressed as mean ± SD. The comparisons between the multiple sclerosis and healthy control groups were performed using the Mann-Whitney U test. Contents of the Repeatable Battery for the Assessment of Neuropsychological Status included immediate memory, visuospatial, language attention and delayed memory.

Table 4 Psychological data for multiple sclerosis patients and healthy controls

Psychological test	Multiple sclerosis group (n = 11)	Healthy control group (n = 11)	P
Hamilton Depression Rating Scale	8.9±10.3	2.0±2.4	0.050 0
Hamilton Anxiety Rating Scale	11.0±8.2	4.3±3.3	0.035 0

Data were expressed as mean ± SD. The comparisons between the multiple sclerosis and healthy control groups were done using the Mann-Whitney U test.

DISCUSSION

Previous reports have conclusively established that there is a relationship between regional gray matter atrophy and cognitive impairment[2, 8-9]. However, relapsing-remitting multiple sclerosis has been less investigated as it has the lowest rate of gray matter atrophy of all multiple sclerosis types. The results of this study not only confirm the presence of gray matter atrophy in relapsing-remitting multiple sclerosis, but suggest, for the first time, that the cingulate and frontal cortices of the dominant hemisphere are the most severely atrophied regions of the brain. Earlier research on gray matter atrophy in multiple sclerosis only included the frontal and temporal lobes and several deep gray matter foci[9, 18-19]. Moreover, the present study demonstrates that gray matter atrophy in the cingulate and frontal cortices of the dominant hemisphere correlates with cognitive decline and emotional abnormalities. Previous studies have also shown a relationship between mood disorders and gray matter atrophy. Koolschijn's study of early-onset depression suggested that prefrontal and limbic system atrophy is a neural hallmark of senile depression[20]. The medial temporal lobe, prefrontal cortex and anterior cingulate cortex participate in emotional regulation[21].

Table 5 Correlation between cognitive/emotional scores and gray matter atrophy in multiple sclerosis patients

Rating scale	Regions of gray matter atrophy in the automated anatomical labeling template	Pearson correlation	
		r	P
Repeatable Battery for the Assessment of Neuro-psychological Status	Frontal_Mid_L	0.409 0	0.240 5
	Frontal_Sup_Medial_R	0.225 8	0.530 5
	Cingulum_Mid_L	0.161 7	0.656 4
	Frontal_Sup_Medial_L	–0.464 2	0.176 6
	Frontal_Inf_Tri_L	–0.122 1	0.736 9
Hamilton Anxiety Rating Scale	Frontal_Mid_L	–0.456 5	0.184 8
	Frontal_Sup_Medial_R	–0.671 5	0.033 5
	Cingulum_Mid_L	–0.570 3	0.085 2
	Frontal_Sup_Medial_L	–0.593 3	0.070 6
	Frontal_Inf_Tri_L	–0.603 9	0.064 5
Hamilton Depression Rating Scale	Frontal_Mid_L	0.013 2	0.971 0
	Frontal_Sup_Medial_R	–0.292 6	0.412 0
	Cingulum_Mid_L	0.016 1	0.964 8
	Frontal_Sup_Medial_L	–0.186 6	0.605 8
	Frontal_Inf_Tri_L	–0.053 1	0.884 2

Statistical analysis was performed using Pearson correlation. Frontal_Mid_L: Frontal medial left; Frontal_Sup_Medial_R: frontal superior medial right; Cingulum_Mid_L: cingulum medial left; Frontal_Sup_Medial_L: frontal superior medial left; Frontal_Inf_Tri_L: frontal inferior triangular left.

In the present study, we found that there is no relationship between selective gray matter atrophy and loss of motor function in relapsing-remitting multiple sclerosis, suggesting that gray matter atrophy is not correlated with atrophy of critical white matter tracts or functional damage[20-24]. Longitudinal studies are now warranted to determine how white matter and gray matter atrophy evolve and to clarify their relationship with the progression of the disease[20-24]. Although white matter and gray matter atrophy can both occur in the forebrain and deep nuclei, the gray matter atrophy spectrum analysis showed that gray matter loss affects mainly the anterior portions of the brain, whereas white matter atrophy is also present in

the brainstem and cerebellum, where gray matter loss is not seen[8-9, 25]. The demonstration of a discrepancy between gray matter and white matter loss in infratentorial regions of patients with relapsing-remitting multiple sclerosis is in line with the pathological findings in these patients, which reveals relative axonal and neuronal preservation in the affected cerebellar cortical regions[26].

Previous studies show that multiple sclerosis patients exhibit deficits in memory, attention, information processing and executive function[27], but that memory recall and language comprehension are preserved[28]. This suggests that cognitive impairment in multiple sclerosis is not uniform and that the etiology is complex. Previous studies have suggested that diffuse subtle brain damage results in overall cognitive decline, whereas focal lesions are responsible for the specific cognitive impairments. Among the various types of multiple sclerosis, relapsing- remitting multiple sclerosis presents with the mildest cognitive decline, suggesting that its anatomical basis differs from the progressive forms of the disease. Our study suggests that the selective frontal and cingulate atrophic changes in the dominant hemisphere are likely the anatomical basis of the cognitive decline and emotional deficits in relapsing-remitting multiple sclerosis. In comparison, greater diffuse gray matter damage could be involved in primary progressive and secondary progressive multiple sclerosis. However, whether unique regional distribution patterns can be used to identify different clinical types of multiple sclerosis and neuromyelitis optica remains unclear. The present study also shows that there is no correlation between gray matter atrophy and disease course or the frequency of relapses. Gray matter atrophy may be present during the entire course of the disease, even at the early stage. This observation indicates the importance of early intervention for cognitive impairment in multiple sclerosis. As suggested by previous studies, treatment with donepezil and selective serotonin reuptake inhibitors[29-31], immunotherapeutic approaches[32-33] and disease-modifying drugs[28] seem to be advisable for preventing or delaying the development of cognitive and emotional impairment in multiple sclerosis.

Although gray matter atrophy is widespread in multiple sclerosis, conventional MRI techniques are not sensitive enough to detect mild or early gray matter atrophy. The voxel-based morphometry technology quantitatively detects the density differences of the brain tissue and allows the dynamic monitoring of gray matter atrophy during the course of the disease. In addition, the voxel-based morphometry method uses the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra algorithm, which improves data registration and provides an accurate localization of the structural damage[34]. It also encompasses an automated lesion-filling technique, which minimizes the effect of focal lesions on tissue segmentation[8, 35]. Because brain atrophy detected by voxel-based morphometric analysis may be associated with manifestations of multiple sclerosis, the method may be used as a tool for assisting early prediction of the clinical features and prognosis of the disease.

Because of the limited number of cases and differences in some parameters between the healthy control and multiple sclerosis groups, the correlations between regional gray matter atrophy and cognitive decline did not exhibit statistical significance. Nonetheless, obvious trends towards correlations were observed. However, the pathophysiological basis of gray matter atrophy in multiple sclerosis remains unclear. Further studies with larger sample sizes are required to unravel the mechanisms underlying the selective gray matter atrophy in relapsing- remitting multiple sclerosis.

In conclusion, the present study provides important neuroimaging evidence for regional gray matter atrophy in relapsing-remitting multiple sclerosis patients, which is associated with cognitive and emotional abnormalities, even at the early stage of the disease. These findings also suggest that monitoring the evolution of gray matter damage is important for the prediction of disease course, response to therapy and prognosis in multiple sclerosis.

SUBJECTS AND METHODS

Design

A case-control imaging study.

Time and setting

The study was performed in the Department of Neurology and Imaging, the First Affiliated Hospital of Fujian Medical University in China from January to June 2011.

Subjects

We recruited patients and volunteers by word of mouth, and then they signed informed consent. Multiple sclerosis patients were enrolled from the Outpatient Department of the First Affiliated Hospital of Fujian Medical University in China from 2010 to 2011. Normal controls were the local residents. Study participants included eleven healthy volunteers and eleven relapsing-remitting multiple sclerosis patients. They were matched for sex,

age and years of education. Inclusion criteria for patients were a diagnosis of relapsing-remitting multiple sclerosis (McDonald criteria 2010 revised)[36], aged 21–59 years and a disease duration of 2–24 years. Exclusion criteria included poor cooperativity and abnormal lesions on the T2WI in the control group. Subjects underwent regular follow-up visits, and would undergo detailed clinical and neuropsychological testing and a comprehensive MRI examination with a 3.0T magnet. Demographic and clinical data recorded included age, gender, age at disease onset, disease duration, and treatment. Disability was measured with the Expanded Disability Status Scale. In patients with relapsing-remitting multiple sclerosis, we also assessed the annualized relapse rate as a measure of clinical disease activity. Relapses were defined as the appearance or reappearance of at least one neurological symptom or the worsening of an old symptom attributed to multiple sclerosis that lasted for at least 24 hours and that was preceded by a relatively stable or improving neurological state of at least 30 days[36]. All patients with multiple sclerosis received therapy consisting of high-dose methylprednisolone of 1 000 mg daily for 3 days in the relapse phase, then the dosage was gradually reduced to a full stop in the following month. Two of the patients received a treatment course with interferon beta-1a (Rebif) therapy (44 μg injected subcutaneously three times a week; Merck Serono, Geneva, Switzerland) for 12–34 months in the stable phase of the disease. None of the patients received neuropsychological therapy.

Methods

Neuropsychological testing

All subjects underwent neuropsychological assessment and Expanded Disability Status Scale scoring[37] within a time frame of 1 month. Each subject underwent (1) 3T MRI screening to rule out the presence of active lesions or incidental abnormal findings in the healthy volunteers; (2) Evaluation of cognitive function with the Repeatable Battery for the Assessment of Neuropsychological Status[38] scale and evaluation of emotional status with the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale[39-40].

The Repeatable Battery for the Assessment of Neuropsychological Status, which is a brief neurocognitive battery with four alternate forms measuring immediate and delayed memory, attention, language and visuospatial skills, was administered to each subject. The testing session lasted approximately 25 minutes. Technically, the Repeatable Battery for the Assessment of Neuropsychological Status is a “pencil-and-paper” test, with only a stimulus booklet and record form being necessary for its administration and scoring. It is broadly used for clinical diagnostic purposes and is increasingly employed as an endpoint in clinical trials of medication that may affect neurocognitive status. The Chinese translated and validated Repeatable Battery for the Assessment of Neuropsychological Status, Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale tests were conducted by two neurologists. A quiet, sunny room was provided, and a neat desk was placed for testing. The Repeatable Battery for the Assessment of Neuropsychological Status test was carried out according to the instructions. The whole evaluation process took 25–30 minutes. The majority of participants completed the test in one session. The Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale were used to assess the anxiety and depression status of the subjects by the two neurologists.

MRI data acquisition

MRI data were collected using a Siemens Verio 3T system (Siemens Healthcare, Erlangen, Germany). Sagittal T1-weighted images (repetition time/echo time = 2 000 ms/2.98 ms, flip angle = 9°, matrix = 240 × 256, field of view = 24 × 24 cm^2, slice thickness/gap = 1 mm/0 mm, 176 slices covered the whole brain) were acquired.

Data preprocessing

Data preprocessing was partly carried out using the statistical parametric mapping software (SPM8, http://www.fil.ion.ucl.ac.uk/spm). Each 3D T1-weighted image was segmented using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra SPM 8 toolbox[41]. The T1-weighted images were first segmented into gray matter, white matter and cerebrospinal fluid. The gray and white matter images were then imported into Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra space for preprocessing. The segmented gray matter images of each participant were used to create a study-specific template for warping and normalization. The images underwent a non-linear transformation using a diffeomorphic registration algorithm[41] and were then transformed into Montreal Neurological Institute stereotactic space using the default International Consortium for Brain Mapping template. Prior to the statistical computations, the images were smoothed with an 8 mm full width at half maximum Gaussian filter to minimize individual anatomical variability and reduce the chance of false positives[42]. All images were reviewed before statistical analysis to ensure the quality of the segmentation process. The preprocessed images were used for voxel-wise statistical comparison.

Data analysis

The differences between multiple sclerosis patients and healthy controls in gray matter were evaluated using voxel-level random-effects analysis (two-sample *t*-tests controlling potentially confounding variables, such as age, gender, white matter and cerebrospinal fluid). Each parametric map was statistically assessed at a threshold *P* value < 0.01 with a threshold extent of 20 voxels and with false discovery rate corrected for multiple comparisons. The Mann-Whitney *U* test was used to assess whether two independent samples of observations have equally large values. Pearson correlation was used to analyze the correlation between the parameters.

Research background: Cognitive dysfunction and emotional abnormalities appear during the early stages of multiple sclerosis. They may be used for disease surveillance and prognostic assessment, but the underlying mechanisms are unclear. Numerous international studies have suggested that gray matter atrophy may be involved in the development of cognitive and emotional impairment. The atrophic regions include the frontal lobe, temporal lobe and deep nuclei.

Research frontiers: This study examined the presence of gray matter atrophy and the relationship between neuropsychological and clinical characteristics in Chinese relapsing-remitting multiple sclerosis patients. It is the first study to use the Repeatable Battery for the Assessment of Neuropsychological Status scale to evaluate cognitive status in relapsing-remitting multiple sclerosis. Voxel-based morphometric analysis was performed to evaluate gray matter atrophy. The findings indicate that the regions with the greatest gray matter atrophy are the cingulate and frontal cortices of the dominant hemisphere. Furthermore, the regional gray matter atrophy was significantly associated with emotional abnormalities.

Clinical significance: This study examines gray matter atrophy in patients with relapsing-remitting multiple sclerosis to provide insight into the relationship between the cognitive and affective disorders and the neuroanatomical lesions, and to further our understanding of the neuropathological basis of the deficits.

Academic terminology: Voxel-based morphometry is a comprehensive, objective, unbiased brain structural imaging analysis technique, which can quantitatively analyze small changes in brain structure and find occult brain structural damage. It has been widely used in clinical research into brain damage, including the relationship between gray matter volume reduction and intelligence quotient in heart failure patients, brain structural research in Parkinson disease, cerebellar volume asymmetry in handedness, age and gender effects on brain anatomy, brain structure in multiple system atrophy and brain structural research in amyotrophic lateral sclerosis.

Peer review: The magnetic resonance imaging analysis and neuropsychological assessment demonstrate that regional gray matter atrophy is present in relapsing-remitting multiple sclerosis, and that it is significantly correlated with emotional disorder. This study has strong clinical significance.

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