Altered degree centrality in patients with non-neuropsychiatric systemic lupus erythematosus: a resting-state fMRI study

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ABSTRACT

This study used a voxel-wise degree centrality (DC) method to evaluate differences in brain activity between patients with non-neuropsychiatric systemic lupus erythematosus (non-NP-SLE) and healthy controls (HCs) and to assess the relationship of DC values with clinical and neuropsychological data. Thirty-two female patients with non-NP-SLE and 28 well-matched HCs were recruited and underwent resting-state functional MRI. Differences in spontaneous brain activity between the two groups were evaluated using a DC method. Correlations between the altered DC values of specific brain regions and clinical and neuropsychological data were explored using Spearman correlation analysis. Receiver operating characteristics curve analysis was applied to differences in DC values in specific brain regions to determine their value in distinguishing patients with non-NP-SLE from HCs. Compared with HCs, DC values in patients with non-NP-SLE were significantly lower in the bilateral postcentral gyrus and the orbital part of the left superior frontal gyrus (LFMO). DC values in some specific brain regions such as the bilateral postcentral gyrus and the LFMO correlated with Mini-Mental State Examination scores in both subject groups. In patients with non-NP-SLE, DC values of the right postcentral gyrus were positively correlated with IgA levels, and DC values of the LFMO were positively correlated with Systemic Lupus Erythematosus Disease Activity Index 2000 scores, as well as IgA levels. Receiver operating characteristics curve analysis revealed that the DC values of specific brain regions can be used to differentiate patients with non-NP-SLE from HCs.

Significance of this study

What is already known about this subject?

- Patients with non-neuropsychiatric systemic lupus erythematosus (non-NP-SLE) may have mild cognitive dysfunction; however, the diagnosis of cognitive dysfunction is challenging and there are no validated non-invasive biomarkers to assess the cognitive status of patients with non-NP-SLE.
- In recent years, with the development of resting-state functional MRI, the degree centrality method has been widely used to evaluate alterations in brain activity and explore possible neuropathological mechanisms in many diseases.
- Few studies have applied the degree centrality method to patients with non-NP-SLE.

What are the new findings?

- Compared with healthy controls, the degree centrality values of the bilateral postcentral gyrus were higher in patients with non-NP-SLE, while values in the orbital part of the left superior frontal gyrus (LFMO) were lower.
- Correlation analysis revealed correlations between altered degree centrality values of specific brain regions and Mini-Mental State Examination scores in the two subject groups.
- In patients with non-NP-SLE, degree centrality values of the LFMO positively correlated with Systemic Lupus Erythematosus Disease Activity Index 2000 scores and IgA levels, and degree centrality values of the right postcentral gyrus were positively correlated with IgA levels.
- Degree centrality values of specific brain regions could be useful in distinguishing patients with non-NP-SLE from healthy controls.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disease involving multiple organs; it can affect both the central and the peripheral nervous systems, leading to neuropsychiatric SLE (NP-SLE).[1] NP-SLE is diagnosed according to the American College of Rheumatology (ACR) guidelines, which involve 19 typical neuropsychiatric symptoms.[2] Among patients with SLE, the incidence rate of NP-SLE is as high as 75%, and it is an important cause of morbidity and mortality.[3] Recently, many studies have shown that even patients without neuropsychiatric symptoms (defined as non-NP-SLE) may have mild cognitive dysfunction,[4] mainly presenting as impairments to attention, speed

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Significance of this study

How might these results change the focus of research or clinical practice?

- In this study, we investigated brain activity changes in patients with non-NP-SLE via a voxel-wise degree centrality method.
- Our findings shed light on the neural and pathophysiological mechanisms in non-NP-SLE and suggest potential imaging features for identifying non-NP-SLE.

of information processing, visuospatial ability, and working memory.[5] Furthermore, such impairments may be precursors to more severe cognitive dysfunction.[6] Studies have found that appropriate disease management can control or even reverse cognitive dysfunction in SLE,[4 7] and that early detection and intervention are key to improving patients' prognoses. However, the diagnosis of cognitive dysfunction is still challenging, and the underlying mechanisms by which SLE causes abnormal symptoms have not been fully elucidated.

In recent years, researchers have used brain imaging techniques to attempt to find new biomarkers for the diagnosis of SLE. Mackay *et al*[8] found that decreased fractional anisotropy in the parahippocampus correlated with increased neurotoxic autoantibody levels and reflected the spatial memory of patients with non-NP-SLE. They pointed out that differences in fractional anisotropy values may be a potential imaging biomarker for autoantibody-induced cognitive damage. Cao *et al*[9] found that functional connectivity values between the right putamen and lobule VI of the vermis were abnormal, and that altered functional connectivity values between the two regions may be used as a neuroimaging marker to detect cognitive decline in patients with SLE. Zhang *et al*[10] found that analysis with functional connectivity density and amplitude of low-frequency fluctuation revealed abnormal activity of the hippocampus and parahippocampus in patients with non-NP-SLE. They suggested that abnormal activity in these areas might be used to detect brain dysfunction in patients with non-NP-SLE.[10]

As a non-invasive method, resting-state functional MRI (fMRI) reflects spontaneous neural activity by measuring fluctuations in blood oxygen level-dependent signal while the subject is at rest, and is the preferred imaging modality for assessment of central nervous system involvement in disease.[11] Degree centrality (DC), which can quantify the importance of each node in a brain network at the voxel level by calculating the number of direct connections of a given node, is an important method for evaluating changes in brain network activity.[12 13] Voxel-wise DC methods have been used to explore the neuropathological mechanisms of many diseases, including Parkinson's disease[14] and type 2 diabetes[15]; however, few studies have applied the DC method to patients with non-NP-SLE. Therefore, in this study, we used the DC method to investigate differences in brain activity between patients with non-NP-SLE and normal controls, then correlated these differences with clinical and neuropsychological data.

MATERIALS AND METHODS

Subjects

Female patients diagnosed with SLE according to the ACR criteria atthe Department of Rheumatology from October 2019 to December 2020 were recruited. The inclusion criteria were as follows: (1) 18–60 years of age; (2) right-handed; (3) SLE without neuropsychiatric symptoms as defined by the 1999 revised ACR criteria; and (4) ability to cooperate with MRI and neuropsychological examinations. The exclusion criteria were as follows: (1) obvious neuropsychiatric symptoms, epilepsy, or persistent headache; (2) history of psychiatric/neurological disorders, brain surgery, or substance or alcohol abuse; (3) intracranial lesions such as cerebrovascular disease, brain trauma, and obvious brain atrophy; (4) other autoimmune diseases, arterial hypertension, diabetes, and malignant tumors; and (5) any contraindication to MRI.

Well-matched healthy volunteers from the community near the hospital were recruited and served as healthy controls (HCs). The inclusion criteria for the HCs were as follows: (1) 18–60 years of age; (2) right-handed; and (3) ability to cooperate with MRI and neuropsychological examinations. The exclusion criteria were the same as those for the patients. According to the above-mentioned inclusion and exclusion criteria, 32 female patients with non-NP-SLE and 28 HCs were included in this study.

Demographics of the patients and HCs, such as name, age, and years of education, were collected by two trained psychiatric graduate students. Patients' laboratory test results (levels of immunological parameters, complement protein 3 (C3), C4, IgA, and IgM) within 5 days before and after the MRI scan were obtained from the hospital information system. Disease activity was measured according to the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K). Before the MRI scan, all subjects underwent a series of neuropsychological tests: the Fatigue Scale for Motor and Cognitive Functions (FSMC), including FSMC-M and FSMC-C, which can detect motor and cognitive fatigue, respectively; the Hospital Anxiety and Depression Scale (HADS), consisting of an anxiety subscale (HADS-A) and a depression subscale (HADS-D), which can assess the anxiety and depression status of subjects, respectively; and the Mini-Mental State Examination (MMSE), which assesses cognitive abilities.

Written informed consent was obtained from all subjects enrolled in this study.

MRI acquisition

MRI scanning procedures were performed by the same radiologist. All imaging data were acquired on a 3 T Siemens Skyra scanner with a four-channel head coil. All subjects were instructed to close their eyes, stay awake, and keep their heads stable. First, conventional T1-weighted images and T2-weighted fluid-attenuation inversion recovery images were acquired and assessed by two experienced radiologists to exclude organic lesions in the brain. Then, fMRI data were obtained using an echo planar imaging (EPI) sequence with the following parameters: repetition time (TR)=2160 ms, echo time (TE)=30.0 ms, flip angle (FA)=90°, thickness=3 mm, field of view (FOV)=256 mm × 256 mm, time point=240, slices=40, total scan time=526 s, and voxel size 4×4×3 mm.

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Image preprocessing and analysis

Image preprocessing was performed using Matlab software (V.R2013b). The procedures included (1) format conversion; (2) discarding of the first five volumes to remove signal equilibration effects and allow the subjects to adapt to the scanning environment; (3) slice timing correction; (4) head motion correction (four patients and one HC who demonstrated excessive head motion, ie, translation >2 mm or rotation in any direction >2°, were excluded); (5) spatial normalization to the standard Montreal Neurological Institute EPI template (resampling voxel size=3×3×3 mm); (6) linear detrending; (7) band-pass time-series filtering (0.01–0.08 Hz); and (8) regressing out of nuisance covariates (ie, the six motion correction parameters, and white matter and cerebrospinal fluid signals).

DC value calculation

DC values were calculated using the Restplus V.1.2 package. Pearson's correlation coefficients (r) were calculated for every possible pairing of voxels within a default whole-brain mask, and a threshold of r>0.25 was taken to indicate significant functional connectivity. The weighted DC of a node was calculated as the sum of weights of significant connections between a given node and all other nodes. The DC values of each node were then converted to z scores (an entire brain map of z values was created using Fisher's z transformation)[14] and used for subsequent statistical analysis.

Statistical analysis

The demographic data of patients with non-NP-SLE and HCs were analyzed using SPSS V.25.0 software. Two-sample t-tests were performed if the demographic data conformed to a normal distribution; otherwise Mann-Whitney U test was used.

Imaging data were analyzed using SPM V.12, with two-sample t-tests being used to analyze between-group differences in DC values, with educational level used as a covariate. The analysis was restricted to voxels within an explicit mask (eg, AAL_binary_msk_nocerebellum). The AlphaSim correction was performed for multiple comparisons (voxel p<0.01 and cluster p<0.05). The DC values in regions showing significant group differences were extracted using Restplus V.1.2 software. Spearman correlation analysis was used to explore correlations between spontaneous brain activity and clinical and neuropsychological data. P<0.05 was considered statistically significant.

To assess whether the DC values could be useful in discriminating patients from HCs, receiver operating characteristics (ROC) analysis was performed, with the extracted zDC values of brain regions showing between-group differences being used as the test variable, and having or not having the disease being considered as the state variable. The areas under the curve (AUCs) were then calculated from the ROC curves.

RESULTS

Demographic characteristics

Mann-Whitney U test was used to analyze the differences in demographic data between the subject groups because the data did not conform to a normal distribution. No significant difference was found in age, but educational level, MMSE scores, and HADS-A and HADS-D scores were significantly different between the two groups (p<0.05; table 1).

Differences in DC values between the two groups

Compared with HCs, DC values in the left and right postcentral gyrus of patients with non-NP-SLE were higher, while values in the orbital part of the left superior frontal gyrus (LFMO) were lower (figure 1 and table 2).

Correlations between DC values and clinical and neuropsychological data

In both subject groups, the DC values of the left and right postcentral gyrus were negatively correlated with MMSE scores (r=−0.386, p=0.004, figure 2A; r=−0.391, p=0.003, figure 2B, respectively), whereas the DC values of the LFMO were positively correlated with MMSE scores (r=0.471, p<0.001; figure 2C). In patients with non-NP-SLE, the DC values of the right postcentral gyrus were positively correlated with IgA levels (r=0.482, p=0.009; figure 2D) and the DC values of the LFMO were positively correlated with IgA levels (r=0.483, p=0.009; figure 2E) and SLEDAI scores (r=0.531, p=0.04; figure 2F).

Table 1 Demographic and clinical characteristics of patients with non-NP-SLE and HC

Items	Non-NP-SLE (n=28)	HC (n=27)	z/X^2 value	P value
Age (years)	46.2±10.0	45.1±4.7	−1.467	0.142*
Disease duration (years)	8.1±6.1	–		–
Education (years)	9.7±3.4	12.3±3.8	−2.445	0.014*
MMSE	26.89±2.77	29.59±0.57	−4.942	<0.001*
HADS-A	7.39±5.01	1.74±1.77	−4.753	<0.001*
HADS-D	5.75±4.33	1.07±1.07	−4.890	<0.001*
FSMC-C	29.71±9.03	–		
FSMC-M	30.71±9.51	–		
C3 (g/L)	0.89±0.23			
C4 (g/L)	0.16±0.71			
IgA	2.24±1.62			
IgM	0.88±0.33			
SLEDAI	3.61±3.21			

P<0.05 was considered to indicate significant difference.
*Significant difference between groups.
FSMC-C, Fatigue Scale for Motor and Cognitive Functions-subscale for cognitive fatigue; FSMC-M, Fatigue Scale for Motor and Cognitive Functions-subscale for motor fatigue; HADS-A, Hospital Anxiety and Depression Scale-anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-depression subscale; HC, healthy control; MMSE, Mini-Mental State Examination; non-NP-SLE, non-neuropsychiatric systemic lupus erythematosus ; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

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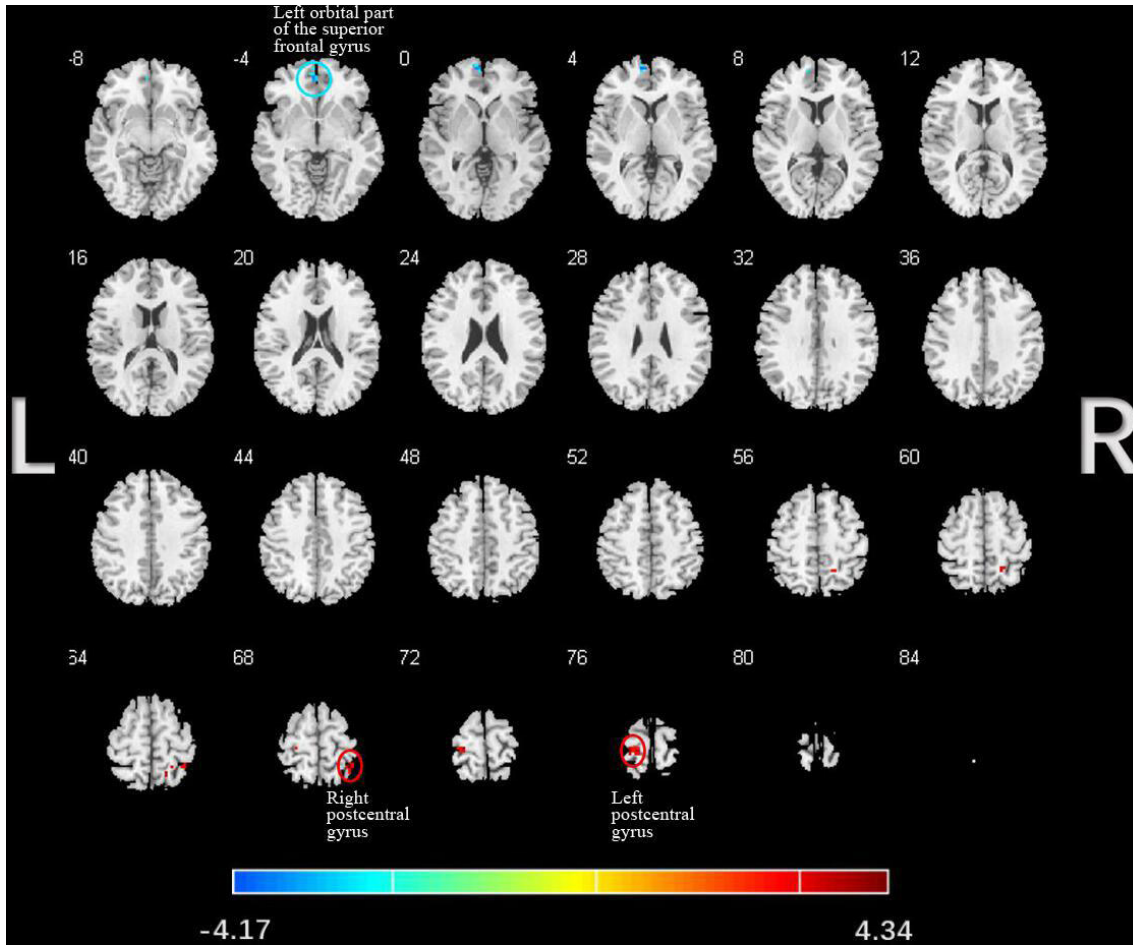

Figure 1 Differences in zDC values between the two subject groups. Red and blue colors indicate higher and lower zDC values, respectively, in patients with non-NP-SLE than in healthy controls. Results are displayed at p<0.05 corrected by AlphaSim (voxel-level p<0.01, cluster-level p<0.05, cluster size >27 voxels). DC, degree centrality; L, left; non-NP-SLE, non-neuropsychiatric systemic lupus erythematosus; R, right.

However, no correlation was found between DC values and the course of disease or HADS scores (all p>0.05).

ROC analysis

For the differentiation of patients with non-NP-SLE from HCs, ROC analysis of regional DC values showed AUCs of 0.865 for the right postcentral gyrus, 0.812 for the left postcentral gyrus, and 0.139 for the LFMO (figure 3 and table 3).

Table 2 Brain regions with different zDC values between two groups

Region	Cluster size (voxels)	MNI coordinates (mm)			t value
		x	y	z	
Non-NP-SLE > HC					
RPG	32	33	−48	69	4.34
LPG	29	−24	−30	75	3.96
Non-NP-SLE < HC					
LFMO	28	−6	51	−6	−4.17

Results are displayed at p<0.05 corrected by AlphaSim (voxel-level p<0.01, cluster-level p<0.05, cluster size >27 voxels).
DC, degree centrality; HC, healthy control; LFMO, orbital part of the left superior frontal gyrus; LPG, left postcentral gyrus; MNI, Montreal Neurological Institute; non-NP-SLE, non-neuropsychiatric systemic lupus erythematosus; RPG, right postcentral gyrus.

DISCUSSION

In the present study, we used a voxel-wise DC method to investigate differences in spontaneous brain activity between patients with non-NP-SLE and HCs, and explored the correlation between differences in DC values and clinical and neuropsychological data. In comparison with HCs, we observed higher DC values in the bilateral postcentral gyrus of patients with non-NP-SLE, but lower values in the LFMO. Correlation analysis indicated that in both subject groups the DC values of the bilateral postcentral gyrus were negatively correlated with MMSE scores, whereas the DC values in the LFMO were positively correlated with MMSE scores. In patients with non-NP-SLE, the DC values of the right postcentral gyrus were positively correlated with IgA levels and the DC values of the LFMO were positively correlated with SLEDAI score and IgA levels. Through ROC analysis, we found that differences in DC values in specific encephalic regions are useful in differentiating patients with non-NP-SLE from HCs.

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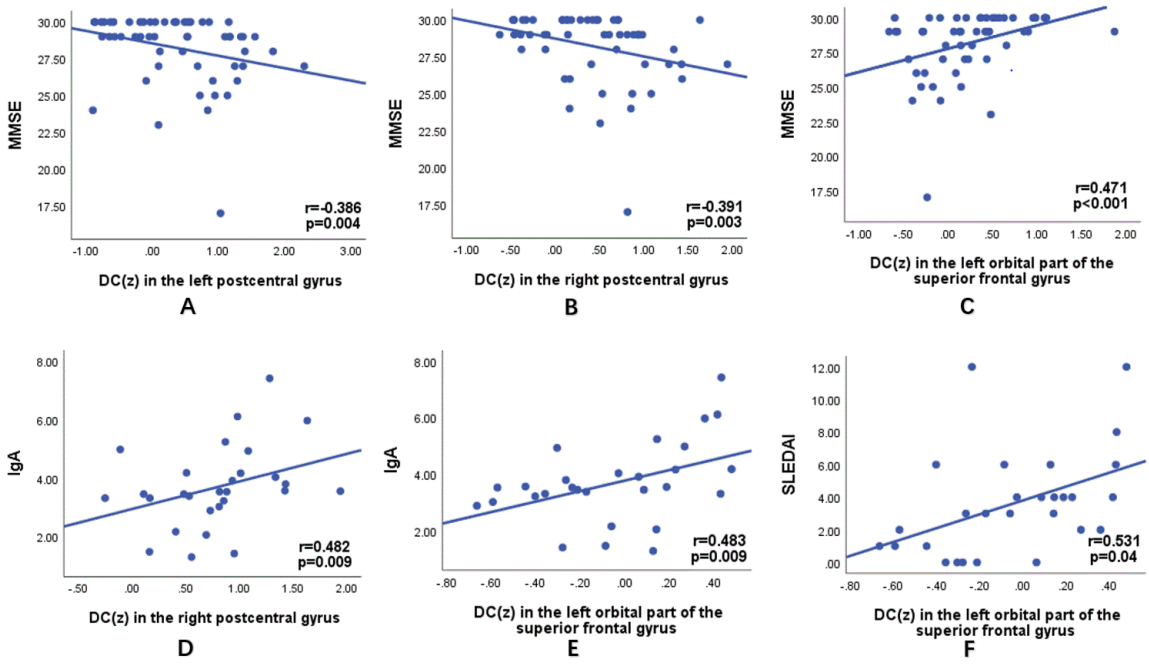

Figure 2 Correlations between zDC values and clinical and neuropsychological data. DC, degree centrality; MMSE, Mini-Mental State Examination; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

The postcentral gyrus, also called the primary somatosensory cortex (S1), is one of the brain areas important in the sensorimotor network (SMN) and plays an important role in the sense of touch and pain.[16] SMN was the first resting-state brain network to be found by Biswal *et al*.[17] Nystedt *et al*[18] pointed out that, compared with HCs, patients with SLE showed increased functional connectivity within the SMN and between the SMN and other networks. Zhang *et al*[10] found that brain activity in the bilateral postcentral gyrus was unusually high in patients with non-NP-SLE. Yu *et al*[19] found that the per cent amplitude of fluctuation values of the postcentral gyrus were significantly correlated with C3 (an immune system protein) in patients with non-NP-SLE.

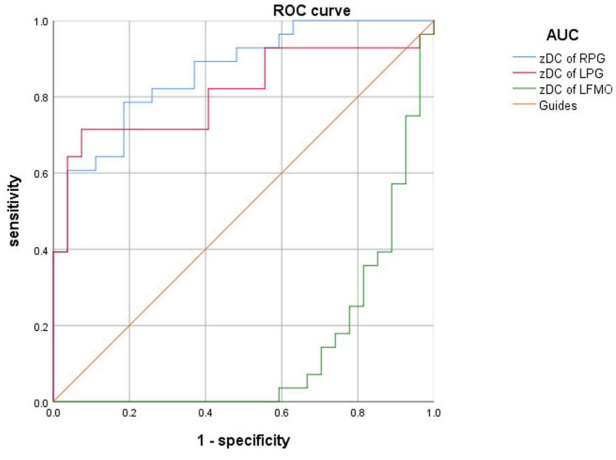

Figure 3 ROC curve analysis of the zDC values of altered brain regions. AUC, area under the curve; DC, degree centrality; LFMO, orbital part of the left superior frontal gyrus; LPG, left postcentral gyrus; ROC, receiver operating characteristics; RPG, right postcentral gyrus.

In this study, the DC values of the bilateral postcentral gyrus were higher in patients with non-NP-SLE than in HCs. We speculate that non-NP-SLE may be associated with functional reorganization of the bilateral postcentral gyrus.

Our findings showed low DC values in the LFMO in patients with non-NP-SLE, suggesting dysfunction of this region. The LFMO is located in the medial orbitofrontal cortex[20] and belongs to the limbic system, which is mainly involved in cognitive and executive functions of the brain; it is also the main brain region responsible for cognitive impulse control.[21–23] A previous study found that application of transcranial direct current stimulation over the orbitofrontal cortex could improve subjects' ability to suppress inappropriate responses.[24] Mackay *et al*[8] demonstrated that patients with SLE exhibited increased resting metabolism in the orbitofrontal cortex, which was correlated with impaired performance on a working memory test. We speculate that the inhibition of this brain region may be associated with cognitive impairment and requires further investigation.

Cognitive dysfunction is frequently reported in SLE, predominantly effects on memory, attention, and verbal fluency. The MMSE is the most commonly used tool to assess cognitive functions, including spatial and temporal orientation, immediate memory, attention, calculation, verbal fluency, and visual construction.[25] An MMSE score below 24 indicates cognitive dysfunction. However, the scores of the MMSE are somewhat subjective and can easily be affected by factors such as the person asking the questions and the educational level of the patients. In this study, we found that high DC values in the bilateral postcentral gyrus and low DC values in the LFMO were associated with low MMSE scores. We speculate that activation of the bilateral postcentral gyrus may be related to cognitive impairment. The LFMO may be the specific brain region involved in

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Table 3 ROC analysis of the zDC values of altered brain regions

Brain regions	AUC	P value	95% CI	Sensitivity	Specificity	Cut-off
RPG	0.865	0.000	0.772 to 0.958	0.815	0.786	0.472
LPG	0.812	0.000	0.692 to 0.932	0.926	0.714	0.631
LFMO	0.139	0.000	0.036 to 0.242	0.964	0.037	−0.597

AUC, area under the curve; DC, degree centrality; LFMO, the orbital part of the left superior frontal gyrus; LPG, left postcentral gyrus; ROC, receiver operating characteristics; RPG, right postcentral gyrus.

the inhibition of cognitive deficits, a result consistent with the findings of Mackay *et al*.[8] Cognitive dysfunction can be identified by early observation of abnormal DC values in the postcentral gyrus and the LFMO, signs that are more objective than MMSE scores and that are not easily influenced by the subject's educational level. We speculate that alterations in DC values in these regions can be used as imaging markers for the early detection of cognitive dysfunction.

The assessment of disease activity in patients with SLE plays an important role in guiding their treatment and prognosis. However, assessment of the SLEDAI is very complex, including several clinical and laboratory variables. In this study, we used SLEDAI-2K to assess disease activity in patients with non-NP-SLE. Our correlation analysis suggests that disease activity increases with activation of the LFMO, a finding consistent with our speculation and further suggesting that the LFMO may be a specific brain region involved in the pathogenesis of non-NP-SLE. The DC values of this brain region might be used as an imaging marker for evaluating disease activity in patients with non-NP-SLE. In future clinical practice, physicians may be able to evaluate changes in treatment efficacy and clinical manifestations by monitoring alterations in DC values in the LFMO.

SLE is characterized by abnormal activation of immune cells and release of cytokines, leading to multiple organ damage.[26] SLE involves the formation and deposition of autoantibodies and immune complexes. Circulating immune complexes can induce type I interferon responses and promote B cell activation and humoral autoimmunity.[27] We found that IgA levels were elevated in some patients with non-NP-SLE. The DC values of the right postcentral gyrus and the LFMO were positively correlated with IgA levels in patients with non-NP-SLE, indicating that as the DC values of these two brain regions increase, the IgA levels increase. We speculate that the right postcentral gyrus and the LFMO may be specific targets of immune response in patients with non-NP-SLE, and that IgA levels might be used as a potential biomarker to monitor the functional activity of these brain regions.

To assess the performance of DC values in differentiating patients with non-NP-SLE from HCs, we performed ROC curve analysis on the DC values of specific regions, showing differences between the two subject groups. The AUC of the ROC curve represents the diagnostic performance, with an AUC of 0.5–0.7 indicating low accuracy, 0.7–0.9 indicating moderate accuracy, and values >0.9 indicating high accuracy.[28] ROC analysis showed AUCs of 0.865 for DC values of the right postcentral gyrus, 0.812 for the left postcentral gyrus, and 0.139 for the LFMO. These results suggest that DC values of the bilateral postcentral gyrus could be used as an imaging marker for non-NP-SLE.

The present study has some limitations. First, the sample size was small and future study with a larger sample size is needed to verify the current findings. Second, there are currently no clear criteria for the diagnosis of cognitive dysfunction in patients with non-NP-SLE, and the lack of objective and specific neurocognitive assessments limits our interpretation of the results; therefore, prospective longitudinal assessment may be needed in further studies. Third, many studies have shown that the immunosuppressive agents used to treat SLE may inhibit the production of immunoglobulins, which may have influenced our findings. Therefore, the relationships between immunoglobulin levels and brain functional activities need to be further investigated.

Our findings demonstrate that the DC values of many brain regions differed between patients with non-NP-SLE and HCs and that differences in specific brain regions were correlated with neuropsychiatric test scores, disease activity, and IgA levels, suggesting that altered DC values in specific brain areas could possibly be used as imaging markers for non-NP-SLE.

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Contributors JX acts as guarantor. JX, JC, and HZ designed the study and revised the manuscript. XL, PZ, WZ, YL, ZS, and JC performed the experiments and collected the data. PZ, WZ, YL, and ZS analyzed the data. XL drafted the manuscript. All authors reviewed and edited the manuscript and approved the final version.

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and was approved by the Institutional Review Board (IRB) of Taizhou People's Hospital (no. KY20-011-01). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request.

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