Aberrant functional hubs and related networks attributed to cognitive impairment in patients with anti-N-methyl-D-aspartate receptor encephalitis

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Abstract. Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis results in severe neuropsychiatric symptoms and persistent cognitive impairment; however, the underlying mechanism is still not fully understood. The present study utilized the degree centrality (DC), functional connectivity (FC) and multivariate pattern analysis (MVPA) to further explore neurofunctional symptoms in patients with anti-NMDAR encephalitis. A total of 29 patients with anti-NMDAR encephalitis and 26 healthy controls (HCs) were enrolled for neuropsychological assessment and resting-state functional MRI (rs-fMRI) scans. DC, FC and MVPA were examined to investigate cerebral functional activity and distinguish neuroimaging characteristics between the patient and HC groups based on the rs-fMRI data. Compared with the HCs, the patients exhibited cognitive deficits, anxiety and depression. In the DC analysis, the patients exhibited significantly decreased DC strength in the left rectus gyrus, left caudate nucleus (LCN) and bilateral superior medial frontal gyrus, as well as increased DC strength in the cerebellar anterior lobe, compared with the HCs. In the subsequent FC analysis, the LCN showed decreased FC strength in the bilateral middle frontal gyrus and right precuneus. Furthermore, correlation analysis indicated that disrupted cerebral functional activity was significantly correlated with the alerting effect and Hamilton Depression Scale score. Using DC maps and receiver operating characteristic curve analysis, the MVPA classifier exhibited an area under curve of 0.79, and the accuracy classification rate was 76.36%, with a sensitivity of 79.31% and a specificity of 78.18%. The present study revealed that the disrupted functional activity of hub and related networks in the cerebellum, including the default mode network and executive control network, contributed to deficits in cognition and emotion in patients with anti-NMDAR encephalitis. In conclusion, the present study provided imaging evidence and primary diagnostic markers for pathological and compensatory mechanisms of anti-NMDAR encephalitis, with the aim of improving the understanding of this disease.

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Abbreviations: anti-NMDAR encephalitis, anti-N-methyl-D-aspartate receptor encephalitis; DC, degree centrality; FC, functional connectivity; HC, healthy control; ROI, region of interest; DMN, default mode network; ECN, executive control network; PFC, prefrontal cortex; MoCA, Montreal Cognitive Assessment; HAMA, Hamilton Anxiety Scale; HAMD24, Hamilton Depression Scale; rs-fMRI, resting-state functional MRI; MVPA, multivariate pattern analysis; BSMFG, bilateral superior medial frontal gyrus; LCN, left caudate nucleus; LRG, left rectus gyrus

Key words: anti-NMDAR encephalitis, DC, FC, MVPA

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, the most common type of autoimmune encephalitis, was first described by Vitaliani *et al* (1) in 2005, and related autoantigens were first reported in 2007 (2). Anti-NMDAR encephalitis is attributed to a disrupted autoimmune mechanism and the relevant autoantibodies mainly target the NR1 subunit of NMDARs on the neuronal surface or synaptic protein (2). Patients with anti-NMDAR encephalitis often present with psychiatric/behavioral abnormalities, cognitive impairment, seizures and movement disorders, and may have a favorable prognosis with early and comprehensive treatment, especially immunotherapy (3,4). A previous study has demonstrated that the cognitive recovery process in patients with anti-NMDAR encephalitis is time-dependent and improves gradually after initial treatment (5). Immunotherapy is the most important treatment for anti-NMDAR encephalitis, and various clinical symptoms are examined to evaluate the degree of cognitive impairment, including alertness, which is expected to improve gradually after treatment (6-8). However, the majority of patients still suffer from long-term deficits, particularly cognitive abnormalities such as memory deficit (9).

To better understand the potential pathogenetic mechanism of anti-NMDAR encephalitis, multimodal imaging investigations have been increasingly conducted to explore the influence of functional and structural abnormalities on neuropsychological disorders (10).

Reversible damage to neurons can be attributed to the elimination of anti-NMDAR antibodies, which can be observed on a small scale. However, cerebral functional and structural abnormalities involving neural functional activity, cortical and subcortical volumes, white matter and cerebral blood perfusion have also been reported on a larger scale in previous studies. For instance, Peer *et al* (11) found that in patients with anti-NMDAR encephalitis, functional connectivity (FC) was disrupted between and within subnetworks, including the default mode network (DMN), medial-temporal lobe network, sensorimotor network and visual network. Furthermore, connections between brain regions were also disrupted and mostly located in the frontal lobe, medial temporal lobe and inferior parietal lobe on the large-scale network level. Using surface-based morphometric analyses, decreased cortical and subcortical volumes have been found in the DMN, language network and left cornu ammonis 1 region of the hippocampus, and these changes were suggested to contribute to different aspects of cognitive impairment (12). Analysis of white matter has revealed a widespread reduction in fractional anisotropy across the entire white matter skeleton, which was prominently located in the bilateral cingulum, right middle temporal gyrus and left middle cerebellar peduncle (13,14). Widespread superficial white matter impairments have been observed in patients with anti-NMDAR encephalitis (15). An abnormal glucose metabolic pattern has also been identified in patients with anti-NMDAR encephalitis, which dynamically changes between hypermetabolism and hypometabolism, based on the recovery mode, disease course and clinical features (16-18). The studies mentioned above may contribute to elucidating the pathophysiology of anti-NMDAR encephalitis and providing promising diagnostic methods for treating this disease from different perspectives, including functional activity, brain structure, neuropsychological deficits and disease course. Although a certain understanding of the cerebral damage in patients with anti-NMDAR encephalitis from the perspective of multimodal imaging exists, relevant reports are scarce and are insufficient for evaluating other neurological comorbidity, such as seizure, depression and psychiatric symptoms. Furthermore, little attention has been given to the functional hubs and related networks contributing to cognitive impairment in patients with anti-NMDAR encephalitis based on the previous studies (12-14).

The brain is a complex system in which certain regions perform primary functions, and other adjacent or even distant brain regions need to closely cooperate to form neural networks and complete different tasks together. In a previous study by our group (19), voxel-mirrored homotopic connectivity was used to estimate the resting-state FC between a voxel within one hemisphere and its mirrored counterpart within the opposing hemisphere, which was found to serve an important role in the diagnosis of encephalitis. To date, a graph theory-based approach has been used to explore the changes in the functional and structural neural networks in patients with anti-NMDAR encephalitis. By combining multimodal MRI data and graph-based network approaches, various network parameters, including global network metrics, nodal metrics and connections between different brain regions, have been shown to be altered in patients with anti-NMDAR encephalitis (13-15). Furthermore, in graph theory-based analysis, degree centrality (DC) is the most reliable property for investigating abnormalities in the FC matrix at the large-scale level, when the regions of interest (ROIs) are not initially defined (20,21). DC can be used to evaluate the importance of each node in the brain network by determining its direct association with the remaining nodes in the whole brain at the global network level. Therefore, DC is a measure of the hub distribution that reflects information processing and communication abilities throughout functional brain networks (22,23). By defining hubs as ROIs in subsequent analyses using a traditional FC approach, disrupted networks between the hub and other brain regions can be further displayed at the global level to reveal pathogenetic mechanisms from different perspectives (24). However, to the best of our knowledge, this combination analysis has not been applied to patients with anti-NMDAR encephalitis. The present study aimed to combine DC and seed-based FC to explore abnormal cerebral functional activity in patients with anti-NMDAR encephalitis in a comprehensive manner.

In the present study, abnormal functional activity at the local and global cerebral levels in patients with anti-NMDAR encephalitis was explored, and its effects on neuropsychological impairments were examined. The DC method was first used to compare the distribution of abnormal functional hubs at the local level between 26 healthy controls (HCs) and 29 patients with anti-NMDAR encephalitis based on resting-state functional MRI (rs-fMRI). Subsequently, brain regions with significant DC differences between groups were defined as ROIs for subsequent FC analysis to investigate the potential disrupted hub network in the entire brain. Furthermore, correlation analysis was performed to reveal the influence of the aberrant functional activity and related networks of cerebral hubs on cognitive impairment in patients with anti-NMDAR encephalitis. Finally, multivariate pattern analysis (MVPA) was performed to explore neuroimaging characteristics based on the rs-fMRI data of the patients. The present study could be conducive to revealing the functional hub distributions and abnormalities in patients with anti-NMDAR encephalitis, and to further elucidate the pathological mechanisms of clinical deficits in these patients.

Subjects and methods

Subjects. The present study was approved by the Medical Research Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (approval no. 2015-KY-National Fund-064; Nanning, China). All participants provided detailed written informed consent for the entire study. A total of 29 patients (age range, 18-65 years) with anti-NMDAR encephalitis after 3 months after their first diagnosis were recruited at the Department of Neurology, The First Affiliated Hospital of Guangxi Medical University (Nanning, China), between January 2019 and December 2020. All patients met the diagnostic standard for anti-NMDAR encephalitis as follows: i) Typical clinical features, such as psychological

and behavioral abnormalities, cognitive deficits, seizures, disturbance of consciousness, and autonomic dysfunction, were observed rapidly <3 months from onset; and ii) anti-NMDAR IgG antibodies were detected to be present in the cerebrospinal fluid of the patients (25). Patients who suffered from other central nervous system disorders, such as intracranial infection, metabolic diseases or brain tumors, were excluded. A total of 26 HCs matched for age (age range, 18-65 years), sex and education level were enrolled. The HCs had no neuropsychological disease. All participants were right-handed and completed the entire experimental process. The Montreal Cognitive Assessment (MoCA) test was used to evaluate cognitive function (26), and the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD24) were used to assess anxiety and depression, respectively (27). Furthermore, the participants underwent attention network tests to assess alertness (28).

Rs-fMRI data acquisition. Rs-fMRI scans were performed at The First Affiliated Hospital of Guangxi Medical University. An Achieva 3T MRI scanner (Philips Medical Systems Nederland B.V.) was used for the acquisition of MRI data. The parameters of the gradient-echo planar image sequence were as follows: Repetition time, 2,000 msec; echo time; 30 msec, flip angle, 90˚; field of view, 220x220 mm; voxel size, 3.44x3.44x3.50 mm; matrix size, 64x64; slice number, 41; slice gap, 0.5 mm; and volume number, 225 slices. During the scanning process, all participants were kept in a quiet and relaxed state, without any particular thoughts, keeping their eyes closed and staying awake. Spongy pads provided stability for the head, and wearing headphones helped to minimize the impact of noise. The entire scanning process lasted ~8 min.

Rs-fMRI data preprocessing. Rs-fMRI data were preprocessed using Data Processing & Analysis of Brain Imaging version 5.0 (DPABI 5.0, http://rfmri.org/dpabi) and Statistical Parametric Mapping 12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12). The detailed procedure was as follows: Conversion to the Neuroimaging Informatics Technology Initiative format; removal of the first 10 volumes; slice timing correction; head movement correction (displacement <2 mm or angular rotation <2 in all directions); normalization to the Montreal Neurological Institute template (29); resampling to 3x3x3 mm^3 resolution; temporal bandpass filtering between 0.01 and 0.08 Hz; spatial smoothing with a 6-mm full-width at half-maximum Gaussian kernel and nuisance signal regression, including 24 head motion parameters; and mean white matter signals and cerebrospinal fluid signals.

Functional activity analysis. After preprocessing, the rs-fMRI data were subjected to DC and FC analyses using DPABI software. For the DC analysis, the voxel-based functional Pearson correlation coefficients of all pairs of brain voxels were first calculated to obtain the 'n x n' matrix depicting the FC pattern across the entire brain. Subsequently, functional correlation coefficients were subjected to Fisher's z-score transformation. An undirected adjacency matrix was obtained by setting the suprathreshold correlation value at 0.25 to eliminate possible spurious connectivity at the individual level. Furthermore, DC was subsequently calculated by counting the number of remaining functional correlations at the individual level. The resulting data were spatially smoothed with a Gaussian kernel of 6x6x6 mm^3 full width at half-maximum. Finally, DC z-maps from each group were compared using a two independent-samples t-test (Gaussian random field correction; voxel-level P<0.001; cluster-level P<0.05).

FC analysis was performed based on the ROIs. The brain regions with significant differences in DC between groups were selected as ROIs for subsequent FC analyses. The average time series from each ROI was extracted, and correlation analyses were subsequently performed with the remaining voxels in the entire brain. Subsequently, Fisher's-to-z transformation was conducted for a z-score FC map for each participant. The z-score FC maps in each group were subjected to a two independent-samples t-test (false discovery rate correction, P<0.01) for between-group comparisons. Age, sex and education level served as nuisance covariates in the group comparisons. T-values were used to represent the strength of functional activity of the cerebral regions with significant differences between groups.

MVPA. MVPA has gained increasing attention for analysis of specific characteristics of brain signals in MRI data (30,31). MVPA was applied to the DC signals of each participant in the two groups using PRONTO software 2.0 version on the MATLAB2018 platform (https://ww2.mathworks.cn) (32). A binary support vector machine was employed to construct the anti-NMDAR encephalitis and HC group classification model. A permutation test was performed 1,000 times to assess the statistical significance of the differences in brain region voxels. Ultimately, the classification plot, receiver operating characteristic curve and weight map for the different brain regions were used to present the diagnostic value of the DC maps in differentiating the patient and HC groups.

Statistical analysis. SPSS 16.0 (SPSS, Inc.) software was used for statistical analyses. The data are presented as the mean ± standard deviation or numbers. Two independent-samples t-tests were used for group comparisons of age, education level, alerting effect, MoCA, HAMA and HAMD24 scores. The χ^2 test was used for sex comparisons. The functional activity strengths of the significant brain regions in the FC and DC analyses were extracted to analyze their Pearson correlation with clinical features. P<0.05 was considered to indicate a statistically significant difference.

Results

Demographic information and clinical characteristics. A total of 29 patients with anti-NMDAR encephalitis (13 men and 16 women) and 26 sex-, age- and education-matched HCs (11 men and 15 women) were recruited. The patients participated in the study after 3 months after their first diagnosis. There was no difference in alertness between the patients with anti-NMDAR encephalitis and HCs. However, although the scores were within the normal range, the HAMA and HMAD24 scores of anti-NMDAR patients were significantly higher than those of the normal control group (4.10±3.27 vs. 0.11±0.43, P<0.001; 5.69±5.66

Table I. Clinical information of all participants.

Characteristic	Patients with anti-NMDAR encephalitis	HCs	P-value
Age, years	26.90±8.60	27.50±5.36	0.759
Sex, n (male/female)	13/16	11/15	0.851
Education, years	12.55±3.05	13.58±2.87	0.207
Disease duration, years	1.33±1.14	-	-
MoCA, score	23.93±4.14	28.54±1.70	<0.001
HAMD24, score	5.69±5.66	0.69±1.05	<0.001
HAMA, score	4.10±3.27	0.11±0.43	<0.001
Alerting effect RT, msec	52.47±14.35	54.10±14.97	0.683
Abnormalities in conventional MRI, n	11	0	<0.001
Neuropsychiatric symptoms, n	23	0	<0.001
Cognitive deficit, n	9	0	<0.001
Memory disorder, n	6	0	<0.001
Seizure, n	23	0	<0.001

HC, healthy control; NMDAR, N-methyl-D-aspartate receptor; MoCA, Montreal Cognitive Assessment; HAMA, Hamilton Anxiety Scale; HAMD24, Hamilton Depression Scale; RT, reaction time.

vs. 0.69±1.05, P<0.001). As expected, MOCA scores were lower in NMDAR-resistant patients than in normal controls (23.93±4.14 vs. 28.54±1.70, P<0.001). The patient group (11/29) showed abnormal T2 or fluid-attenuated inversion recovery signals on conventional brain MRI. These signals were mainly located unilaterally or bilaterally in the frontal lobe, temporal lobe and limbic system, and even in the deep brain nuclei and meninges. Typical clinical manifestations in the patient group included at least one of the following syndromes: Acute neuropsychiatric symptoms, cognitive deficits, memory impairments and seizures. The detailed clinical characteristics of all participants are presented in Table I.

DC analysis. The differences between the patient group and the HC group according to the results of the DC analysis are shown in Fig. 1 and Table II presents the value of the different brain regions in DC. As indicated in Fig. 1 and Table II, compared with the HCs, the patients with anti-NMDAR encephalitis exhibited increased DC strength in the anterior lobe of the cerebellum. Furthermore, the patient group also exhibited decreased DC strength in the left rectus gyrus (LRG), left caudate nucleus (LCN) and bilateral superior medial frontal gyrus (BSMFG).

FC analysis. The AAL template has a total of 116 regions, but only 90 belong to the brain, and the remaining 26 belong to the cerebellar structure, which is less studied. In the present study, 116 brain regions were compared between the two groups. Brain regions exhibiting statistically significant differences in DC density were selected as ROIs for subsequent seed-based FC analyses. Compared with the HCs, the patients with anti-NMDAR encephalitis showed decreased FC strength between the LCN and the left precuneus and bilateral middle frontal gyrus (Fig. 2 and Table III). Table III presents the value of the different brain regions in FC strength corresponding

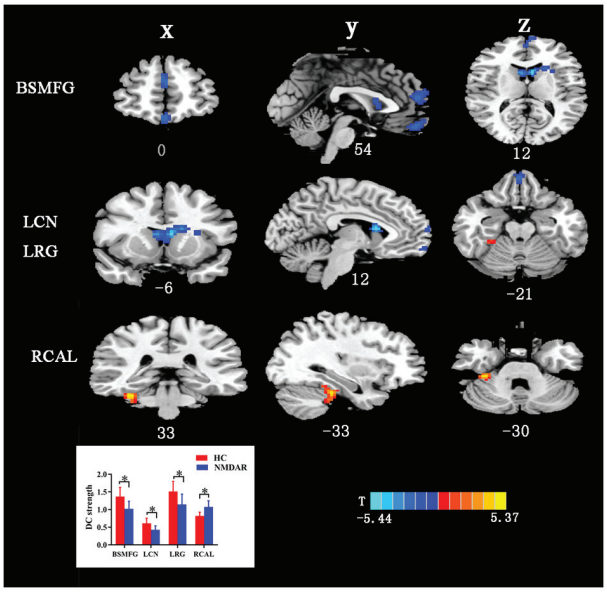

Figure 1. Alterations in DC strength in patients with anti-NMDAR encephalitis. The altered brain regions were located in the BSMFG, LCN, LRG and RCAL. Gaussian random field correction was set at voxel-level P<0.001 and cluster-level P<0.05. The color bar with T-values indicates the strength of functional activity (a warm color represents increased functional strength, while a cool color represents decreased functional strength). *P<0.05. X, coronal plane; Y, sagittal plane; Z, transverse plane; numbers, coordinates. BSMFG, bilateral superior medial frontal gyrus; LCN, left caudate nucleus; LRG, left rectus gyrus; RCAL, right cerebellum anterior lobe; DC, degree centrality; NMDAR, N-methyl-D-aspartate receptor; HC, healthy control.

to Fig. 2. The other brain ROIs of Anatomical Automatic Labeling exhibited no differences in functional maps at the whole-brain level between the patient and HC groups.

Correlations between clinical features and functional activity. Correlations between clinical features (disease duration, alerting effect, MoCA, HAMA and HAMD24

Table II. Brain regions with significant differences between patients with anti-N-methyl-D-aspartate receptor encephalitis and HCs according to degree centrality analysis.

Brain region	FS in HCs	FS in patients	Cluster size (voxel)	MNI coordination (x, y, z)	T-value
Cerebellar anterior lobe_R	0.8204±0.1063	1.0768±0.1729	75	33, -33, -30	5.7453
Rectal gyrus_L	1.5119±0.2853	1.1465±0.2899	55	0, 51, -21	-4.5669
Caudate nucleus_L	0.6117±0.1438	0.4246±0.1145	171	-6, 12, 12	-5.8239
Bilateral superior medial frontal gyrus	1.3678±0.2600	1.0220±0.2121	104	0, 54, 12	-4.5116

Gaussian random field correction was set at voxel-level P<0.001 and cluster-level P<0.05. T-values were used to represent the strength of functional activity of the cerebral regions with significant differences between groups. HC, healthy control; MNI, Montreal Neurological Institute; R, right; L, left; FS, functional strength.

Table III. Brain regions showing functional connectivity alterations in patients with anti-N-methyl-D-aspartate receptor encephalitis compared with HCs.

Brain region	FS in HCs	FS in patients	MNI coordination (x, y, z)	Cluster size (voxel)	T-value
Left precuneus	-0.0218±0.0973	-0.2229±0.1506	-9, -72, 15	55	-5.1393
Right middle frontal gyrus	-0.0356±0.0654	-0.2389±0.1318	30, 18, 45	123	-6.3482
Left middle frontal gyrus	-0.0290±0.0726	-0.2272±0.1287	-27, 9, 48	45	-5.774

The left caudate nucleus was used as the seed region. False discovery rate correction was set at P<0.01. T-values were used to represent the strength of functional activity of the cerebral regions with significant differences between groups. HC, healthy control; MNI, Montreal Neurological Institute; FS, functional strength.

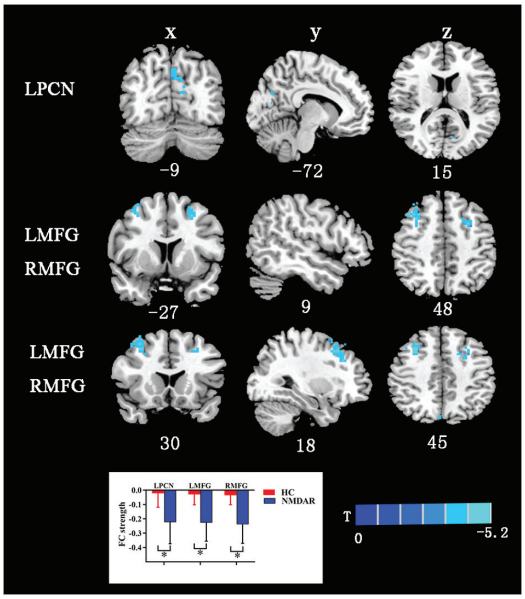

Figure 2. Differences in FC between patients with anti-NMDAR encephalitis and HCs. The regions with significant degree centrality values were selected as seeds for FC analysis. The FC between left caudate nucleus with LMFG, RMFG and RPCN was decreased. False discovery rate correction was performed at P<0.01. The color bar with T-values indicates the functional strength (a warm color indicates increased functional strength, while a cool color indicates decreased functional strength). *P<0.05. X, coronal plane; Y, sagittal plane; Z, transverse plane; numbers, coordinates. LPCN, left precuneus; LMFG, left middle frontal gyrus; RMFG, right middle frontal gyrus; FC, functional connectivity; NMDAR, N-methyl-D-aspartate receptor; HC, healthy control.

scores) and functional activity in the brain regions exhibiting significant differences in the DC and FC analyses were further analyzed (Fig. 3). The DC strength in the LRG was positively correlated with the HAMD24 score (r=0.425; P=0.022; Fig. 3C), while negative associations were observed between the alerting effect and the DC strength in the LCN (r=-0.445; P=0.016; Fig. 3B) and BSMFG (r=-0.401; P=0.031; Fig. 3A) in the patient group. According to the FC analysis, the FC strengths between the LCN and the right and left middle frontal gyri were both negatively correlated with the alerting effect (r=-0.461; P=0.012; and r=-0.466; P=0.011; Fig. 3D and E, respectively).

MVPA. In the present study, MVPA was used to analyze neural signals based on DC maps to identify specific spatial functional activities in patients with anti-NMDAR encephalitis compared with HCs. The specific brain regions were mainly located in the cerebellum, left middle orbital frontal gyrus, left superior orbital frontal gyrus, right precuneus, right postcentral gyrus, right superior medial frontal gyrus, right inferior parietal gyrus, right supplementary motor area, left medial orbital frontal gyrus, right superior parietal gyrus, left angular gyrus and LCN (Table IV). These regions together yielded an area under the curve of 0.79 (Fig. 4B), with an overall classifier accuracy, sensitivity and specificity of 76.36, 75.86 and 76.92%, respectively (Fig. 4A). Based on this analysis, the MVPA classifier can be used to distinguish patients with anti-NMDAR encephalitis from HCs.

Table IV. Brain regions with the largest ROI weight between patients with anti-N-methyl-D-aspartate receptor encephalitis and healthy controls using multivariate pattern analysis classification.

Brain region	ROI size, voxels	ROI weight, %
Cerebellum_9_L	599	1.8768
Vermis_9	75	1.7412
Cerebellum_8_R	517	1.6727
Vermis_1_2	41	1.5827
Cerebellum_7b_R	129	1.5812
Parietal_sup_R	558	1.4246
Cerebellum_3_L	550	1.4048
Cerebellum_7b_L	507	1.3974
Frontal_med_orb_L	614	1.3081
Frontal_sup_medial_R	785	1.3008
Cerebellum_crus2_L	726	1.2649
Parietal_inf_R	662	1.2065
Cerebellum_crus2_R	556	1.2021
Postcentral_R	993	1.2012
Angular_L	547	1.1960
Supp_motor_area_R	627	1.1869
Frontal_sup_orb_L	1,089	1.1839
Cerebellum_8_L	124	1.1745
Caudate_L	200	1.1702
Frontal_mid_orb_L	1,431	1.1599
Precuneus_R	1,041	1.1184

ROI, region of interest; R, right; L, left; sup, super; supp, supplementary; orb, orbital; inf, inferior; mid, middle; med, medial.

Discussion

The present study investigated alterations in the hub distribution and functional activities at the local and global cerebral levels based on DC and FC analyses in patients with anti-NMDAR encephalitis. The patient group exhibited increased DC in the cerebellum anterior lobe and decreased DC in the LRG, LCN and BSMFG, compared with the HC group. In subsequent FC analyses based on the ROIs of the aforementioned brain regions, the LCN showed decreased FC with the left precuneus and bilateral middle frontal gyrus in the patient group compared with HCs. Furthermore, these abnormal functional activities were associated with cognitive and psychological impairments. By performing MVPA, disrupted DC maps could distinguish patients with anti-NMDAR encephalitis from HCs with high classification accuracy and sensitivity. In summary, the present study effectively revealed the features of disrupted functional hubs and related networks in patients with anti-NMDAR encephalitis, which provides a more comprehensive understanding of the mechanism underlying pathological damage in this disease.

Brain regions are closely connected and coordinated with each other while engaging in task processes, and different regions may display predominant functions in diverse neurological states (33). DC analyses can indicate the ability of each voxel to process information by evaluating its number of direct connections with other voxels (34). Disrupted functional activities of hub regions are considered to participate in processes underlying abnormal neuropsychological function. In the present study, it was demonstrated that brain regions with abnormal strength were mainly located in the cerebellar anterior lobe, LRG, LCN, BSMFG, left precuneus and bilateral middle frontal gyrus. These findings indicated that disrupted functional activities were not limited to the limbic system, but were also widely distributed from the frontal lobe to the subcortical region and even the distant cerebellum in patients with anti-NMDAR encephalitis. These results provide evidence that anti-NMDAR encephalitis is a brain network disease.

The prefrontal lobe is the association cortex of the frontal lobe and constitutes nearly one-third of the neocortex (35). The superior medial frontal gyrus, middle frontal gyrus and rectus gyrus are important parts of the prefrontal lobe. A total of five separate prefrontal functions exist, namely energization, task setting, monitoring, meta-cognition and behavioral/emotional regulation (36). It has been widely recognized that the prefrontal lobe is the predominant brain region that transmits signals to and receives signals from other cortical regions, subcortical structures and even the remote cerebellum in high-cognitive processes (36-39). The prefrontal cortex (PFC) is the key node in the executive control network (ECN), and disrupted functional and structural parameters of the PFC contribute to neuropsychological dysfunction, including executive disorders and anxiety (38). It has been demonstrated that older subjects with amnestic mild cognitive impairment exhibited reduced regional cerebral blood flow in the PFC in a retrieval task, causing memory deficit (40). Using the Delis-Kaplan Executive Function Scale and a classic neuropsychological test, a previous study indicated that a larger volume of the lateral PFC was related to greater executive function (41). The correlation analysis in the present study also indicated that disrupted PFC activity was negatively correlated with alerting function. Thus, disruptions of the PFC in the ECN may contribute to complex and diverse clinical disorders of neuropsychological function in patients with anti-NMDAR encephalitis.

The deep nuclei act as information transfer stations in information processing (42). The caudate nucleus is one of the brain regions in the extrapyramidal system involved in motor regulation, and abnormalities in the caudate nucleus cause deficits in motor performance (43). However, converging evidence has indicated that the caudate nucleus receives outputs from the PFC and contributes to different cognitive processes (42). This has been demonstrated in various cognitive tasks such as reading and language showing increased activity both in the caudate nucleus and prefrontal and temporal-parietal lobes (41). Furthermore, the caudate nucleus is also a subcortical component of the DMN and is implicated in numerous clinical disorders such as temporal lobe epilepsy and attention-deficit hyperactivity disorder, including memory, emotion, cognitive function and the processing of emotionally salient stimuli (44,45). In older patients with depression, psychomotor retardation is an important cognitive symptom, and this phenomenon can be predicted through the observation of a reduced volume in the caudate nucleus (40). The present

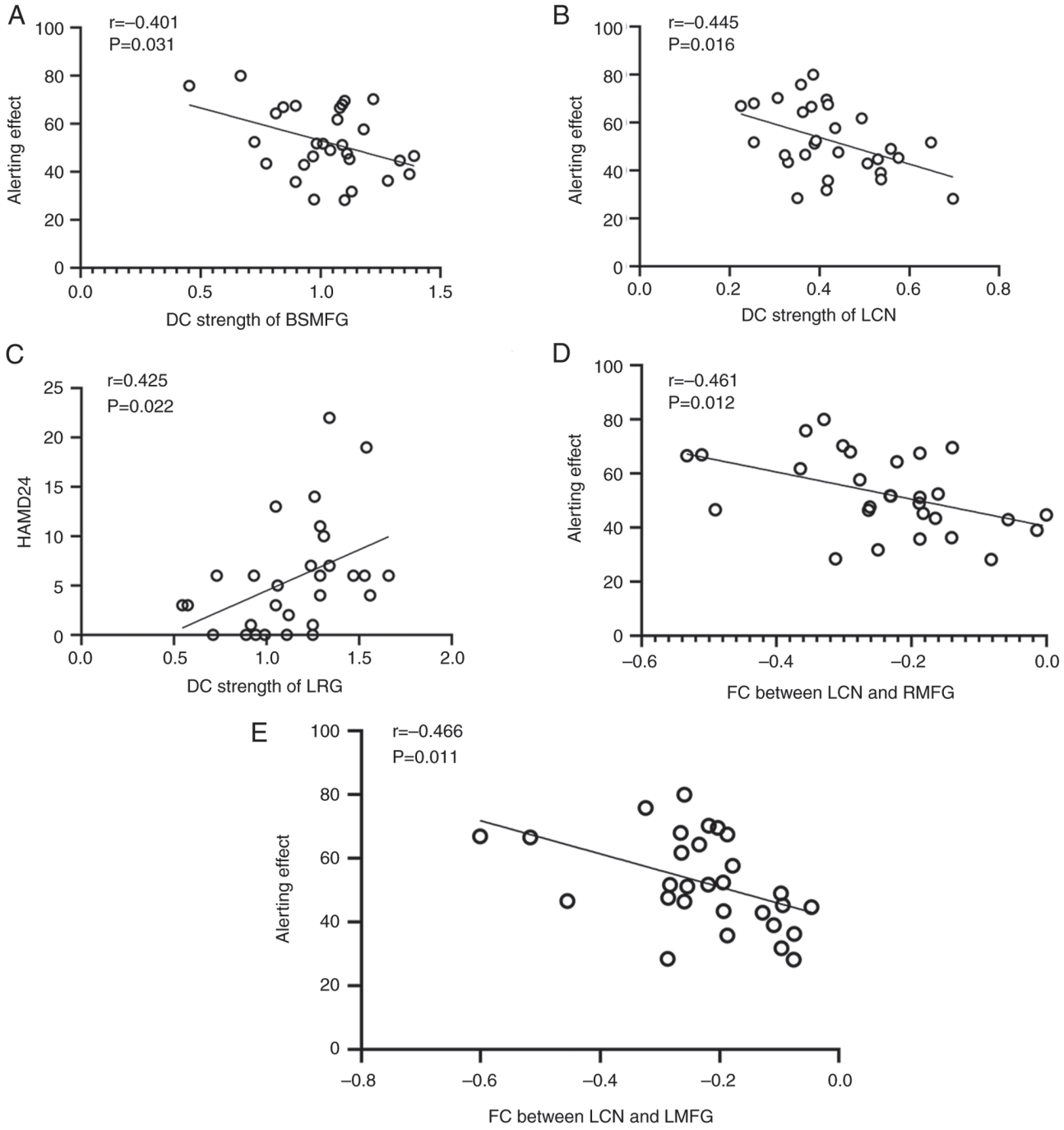

Figure 3. Analysis of correlations between clinical parameters and functional activity features. (A) The DC strength of the BSMFG was negatively correlated with the alerting effect (r=-0.401; P=0.031). (B) The DC strength of the LCN was negatively correlated with the alerting effect (r=-0.445; P=0.016). (C) The DC strength of the LRG was positively correlated with the HAMD24 score (r=0.425; P=0.022). (D) The FC between the LCN and RMFG was negatively correlated with the alerting effect (r=-0.461; P=0.012). (E) The FC between the LCN and LMFG was negatively correlated with the alerting effect (r=-0.466; P=0.011). BSMFG, bilateral superior medial frontal gyrus; LCN, left caudate nucleus; LRG, left rectus gyrus; LMFG, left middle frontal gyrus; RMFG, right middle frontal gyrus; DC, degree centrality; FC, functional connectivity; HAMD24, Hamilton Depression Scale.

study demonstrated that the LCN exhibited abnormal FC with the left precuneus and bilateral middle frontal gyrus in patients with anti-NMDAR encephalitis. The precuneus is also the core node in the DMN and has been demonstrated to participate in a wide spectrum of higher-order cognition, consciousness and attention regulation (46). There are four specific major types of anatomic connections of the precuneus, namely connections with the superior parietal lobule, occipital cortex, frontal lobe and temporal lobe, which provide an additional illustration of the integration of higher-order information throughout the entire brain network (47). Hebscher *et al* (48) reported that the precuneus serves a causal role in the retrieval of autobiographical memories and that precuneus stimulation leads to disrupted dynamics in the retrieval process. Combined with the findings of previous studies (47,48), our findings suggest that abnormal FC between the caudate nucleus and the ECN and DMN may contribute to higher-order and motor deficits in patients with anti-NMDAR encephalitis.

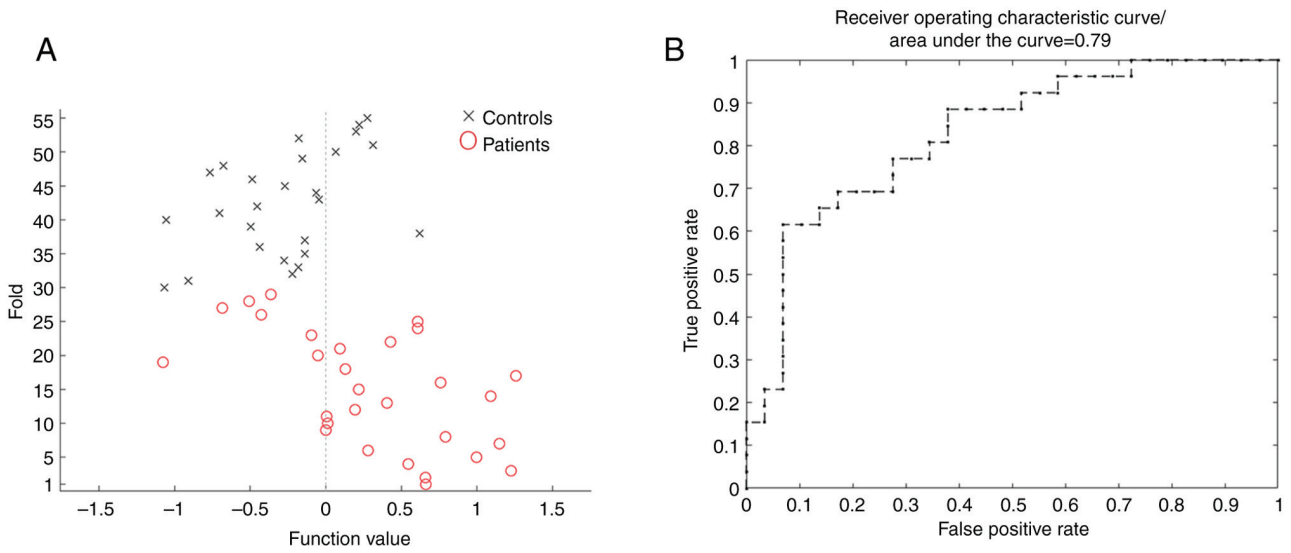

Figure 4. Predictive value of the DC. (A) Voxel-based predictive pattern. The DC was able to distinguish between anti-NMDAR encephalitis and HC subjects. (B) Region-based pattern localization map computed from the voxel-based predictive pattern. Receiver operating characteristic curve of the anti-NMDAR encephalitis-HC group classification model based on DC maps with an accuracy of 76.36% (sensitivity, 79.31%; specificity, 78.18%). DC, degree centrality; NMDAR, N-methyl-D-aspartate receptor; HC, healthy control.

In the DC analysis, disrupted activities in the cerebellum were also observed. The cerebellum has been traditionally recognized as the dominant region of motor regulation. However, with the increasing knowledge of the cerebellar function, its role in non-motor tasks, such as emotion, social behavior, executive function and working memory language function, has been widely recognized (49,50). In functional and structural explorations, widespread connections from/to the cerebellum in the cerebrum were identified, involving the frontal lobe, parietal lobe, temporal lobe, occipital lobe and subcortical brain regions, which are the basis of motor and non-motor functions (49,51,52). Lesions in the cerebellum are considered to contribute to cerebellar cognitive affective syndrome, which is associated with more pronounced cognitive deficits (53). In previous studies, abnormal functional activity and fiber damage in the cerebellum have been observed in patients with anti-NMDAR encephalitis (14,54). Recently, compensatory effects in the cerebellum in neurodegenerative disease such as Parkinson's disease have been proposed (55), and increased functional activity, increased volume and metabolic enhancement are considered to alleviate clinical symptoms and delay the course of the disease. Thus, the increased DC strength in the cerebellum observed in the patient group in the present study indicates a more intensive information processing ability that could enhance motor and cognitive function in patients with anti-NMDAR encephalitis.

In the present study, correlation analyses were performed between clinical parameters and the brain regions with significant differences in DC and FC analyses. It was observed that the DC strength of the BSMFG and LCN was negatively correlated with the alerting effect, the DC strength of the LRG was positively correlated with the HAMD24 score, and the FCs between LCN and the right and left middle frontal gyri were negatively correlated with the alerting effect, while the other clinical parameters were not affected by the abnormal brain regions. The correlation analysis results demonstrated that abnormal DCs or FCs in affected brain regions contribute to cognitive impairment or depression, as indicated in our previous study (19). Our previous study demonstrated that the alerting effect of patients with anti-NMDAR encephalitis was decreased compared with that of HCs (19); however, no difference was found in the alerting effect between patients and HCs in the present study, which may be due to a gradual recovery of cognitive function over time. The results of the correlation analysis suggested that the alerting function was affected by the area of brain damage in patients with anti-NMDAR encephalitis, and brain impairment could be observed even when the alerting function was close to normal in the late recovery period, which highlighted the importance of rs-fMRI in the study of anti-NMDAR encephalitis.

MVPA can be used as a potential diagnostic approach for categorizing individuals by investigating spatial and temporal information from neuroimaging data in numerous neurological and psychiatric diseases, such as mild cognitive impairment, major depressive disorder, obsessive-compulsive disorder and temporal lobe epilepsy (42-45). In clinically atypical patients with anti-NMDAR encephalitis, the clinical symptoms are mild, and there are no obvious abnormalities on MRI, electroencephalogram or negative cerebrospinal fluid anti-NMDAR antibody (56). Multimodal imaging may be an auxiliary diagnostic method, which is expected to have certain diagnostic value for the clinically confirmed patients (57). Although rs-fMRI needs more time to finish scanning and coordinate to keep headless motion, it can be used as a potentially important diagnostic method to neurological and psychotic disorders, such as schizophrenia or attention deficit hyperactivity disorder (58). Therefore, multimodal imaging may provide novel supporting evidence for the diagnosis of anti-NMDAR encephalitis, particularly in undiagnosed patients or patients in the convalescence period. In the present study, by performing MVPA using DC maps, the regions that were more important in discriminating between patients

with anti-NMDAR encephalitis and HCs were predominantly located in the cerebellum, prefrontal lobe, parietal lobe and LCN. These brain regions were consistent with those identified in the DC and FC analyses of the present study. As aforementioned (39,53,59), these regions are involved in cognitive function and psychosis, and are associated with clinical symptoms, such as psychiatric/behavioral abnormalities, cognitive impairment, seizures and movement disorders, in patients with anti-NMDAR encephalitis. In the present study, correlation analyses also showed that abnormal DC and FC values in affected brain regions were correlated with cognitive deficits, and further demonstrated that these abnormalities in brain regions were involved in the clinical disorder. In brief, DC analysis is conducive to revealing the imaging parameters involved in the development of clinical symptoms, and when combined with the MVPA approach, DC analysis may be a powerful tool for diagnosing anti-NMDAR encephalitis, especially in patients with no abnormalities on regular MRI or with non-specific imaging findings.

Several limitations should be considered in the present study. First, the small sample in our research maybe lack representativeness and homogeneity, reduces statistical power and can only partially reflect real-world evidence results (for example, the alerting effect did not differ between patients and HCs in the present study). Therefore, more participants in both groups should be recruited to establish the stability and reliability of the research results. Furthermore, obtaining data from patients with anti-NMDAR encephalitis during the acute stage may be important for exploring potential imaging alterations that illustrate clinical features. In addition, as patients may present various symptoms, subgroup analysis based on different clinical symptoms may be helpful for elucidating the pathogenesis of the corresponding symptoms. Patients may have a favorable prognosis after early and comprehensive treatment; however, most patients still suffer from long-term deficits in different aspects (5). Therefore, a longitudinal study may be useful for identifying vulnerable brain regions responsible for persistent neuropsychological dysfunction.

In summary, the current study revealed the presence of disrupted DC and FC in the entire brain, which were predominantly located in the cerebellar network, DMN and ECN in patients with anti-NMDAR encephalitis. Furthermore, it was demonstrated that by combining DC maps with MVPA and disrupted functional activity may yield high accuracy, sensitivity and specificity for the primary diagnosis of anti-NMDAR encephalitis. These abnormal functional activities may be associated with severe and complex clinical symptoms, and could provide pathological and compensatory imaging evidence for a deeper understanding of anti-NMDAR encephalitis.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JZ and BF conceived the study, designed the methodology, analyzed data and wrote the manuscript. XZ, LP, LQ and CL analyzed data. XZ wrote the manuscript. BF and LP interpreted data and edited the manuscript. All authors have read and approved the final manuscript. JZ and BF confirm the authenticity of all the raw data.

Ethics approval and consent to participate

All subjects were informed in detail about the study and provided written informed consent. The study was approved by the Medical Research Ethics Committee of The First Affiliated Hospital of Guangxi Medical University (approval no. 2015-KY-National Fund-064; Nanning, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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