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ORIGINAL ARTICLE

Limited cerebellar gradient extension in temporal lobe epilepsy with dystonic posturing

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Abstract

Objective: Dystonic posturing (DP) is a common semiology in temporal lobe epilepsy (TLE). We aimed to explore cerebellar gradient alterations in functional connectivity in TLE patients with and without DP.

Methods: Resting-state functional MRI data were obtained in 60 TLE patients and 32 matched healthy controls. Patients were further divided into two groups: TLE with DP (TLE + DP, 31 patients) and TLE without DP (TLP-DP, 29 patients). We explored functional gradient alterations in the cerebellum based on cerebellar–cerebral functional connectivity and combined with independent component analysis to evaluate cerebellar–cerebral functional integration and reveal the contribution of the motor components to the gradient.

Results: There were no obvious differences in clinical features and postoperative seizure outcomes between TLE + DP and TLE-DP patients. Patients and controls all showed a clear unimodal-to-transmodal gradient transition in the cerebellum, while TLE patients demonstrated an extended principal gradient in functional connectivity compared to healthy controls, which was more limited in TLE + DP patients. Gradient alterations were more widespread in TLE-DP patients, involving bilateral cerebellum, while gradient alterations in TLE + DP patients were limited in the cerebellum ipsilateral to the seizure focus. In addition, more cerebellar motor components contributed to the gradient alterations in TLE + DP patients, mainly in ipsilateral cerebellum.

Significance: Extended cerebellar principal gradients in functional connectivity revealed excessive functional segregation between unimodal and transmodal systems in TLE. The functional connectivity gradients were more limited in TLE + DP patients. Functional connectivity in TLE patients with dystonic posturing involved more contribution of cerebellar motor function to ipsilateral cerebellar gradient.

Dong Zhou and Dongmei An contributed to this work equally.

Plain Language Summary: Dystonic posturing contralateral to epileptic focus is a common symptom in temporal lobe epilepsy, and the cerebellum may be involved in its generation. In this study, we found cerebellar gradients alterations in functional connectivity in temporal lobe epilepsy patients with and without contralateral dystonic posturing. In particular, we found that TLE patients with dystonic posturing may have more limited cerebellar gradient in functional connectivity, involving more contribution of cerebellar motor function to ipsilateral cerebellar gradient. Our study suggests a close relationship between ipsilateral cerebellum and contralateral dystonic posturing.

KEYWORDS

cerebellum, dystonic posturing, functional gradient, motor components, temporal lobe epilepsy

1 | INTRODUCTION

Dystonic posturing, which usually occurs in the upper limb, characterized by sustained muscle contractions with unnatural posturing and a rotational component such as flexion of the wrist, is a common lateralizing semiology in temporal lobe epilepsy (TLE).[1–4] Contralateral dystonic posturing is usually expected in well-localized TLE, especially TLE with hippocampus sclerosis,[5] which may help to differentiate mesial from neocortical temporal origin.[6] Studies also revealed that contralateral ictal dystonic posturing in TLE was related to less possibility of contralateral propagation and secondary generalization, as well as longer seizure duration, suggesting the propagation to contralateral hemisphere might be inhibited.[7]

Spread of ictal epileptiform discharges from mesial temporal lobe structures to ipsilateral basal ganglia has been considered as the possible underlying pathophysiological mechanism of ictal dystonic posturing.[1,8–10] However, studies in primary dystonia have demonstrated that dystonia may arise from the dysfunction of a complex motor network including basal ganglia and the cerebellum, rather than one isolated motor system.[11–14]

Cerebellar atrophy and dysfunction have been reported in various types of epilepsy.[15,16] Ictal hyperperfusion of cerebellum was also observed in TLE.[17] Even the cerebellum itself was thought to have the capability of generating epileptic activity and seizure.[18,19] In addition, the cerebellum has been regarded as a potential intervention target for seizures control.[20,21] In our previous study, we also found increased amplitude of low-frequency fluctuation in ipsilateral cerebellar vermis after successful TLE surgery, indicating postoperative functional remodeling in the cerebellum.[22] In view of the fact that ipsilateral cerebellum is involved in well-localized TLE, we hypothesize that the cerebellum ipsilateral to the TLE focus may take part in the generation of contralateral ictal dystonic posturing.

Key points

- Temporal lobe epilepsy showed a clear unimodal-to-transmodal gradient transition in the cerebellum.
- Cerebellar functional gradient changed differently in temporal lobe epilepsy with and without dystonic posturing.
- The functional connectivity gradients were more limited in temporal lobe epilepsy with dystonic posturing.
- Functional connectivity in temporal lobe epilepsy with dystonic posturing involved more contribution of cerebellar motor function to ipsilateral cerebellar gradient.

Gradient analysis provides a new method to capture the connectome topography in a low dimensional but a macroscale space by decomposing the functional connectivity (FC) into distinct gradients. The principal functional gradient of the cortex was found to span from unimodal (primary sensory/motor regions) to transmodal regions (known as the default mode network [DMN] in humans),[23] which was in accord with the neural basis of the spectrum from sensory to cognitive processing. There is growing evidence that the cerebellum has been involved not only in motor control and coordination but also in non-motor function, including cognition, emotion, and behavior.[24,25] Similar primary-to-transmodal gradient was also observed in the cerebellum.[26] The gradients were normal and expected between primary to secondary networks in the cerebrum and cerebellum. However, specific

gradient alterations with higher/lower-than-normal segregation between these network categories were found to be associated with psychiatric and neurological diseases, such as autism, schizophrenia, major depressive disorder, and ischemic stroke.[27–30] Recently, Meng et al. found an extended principal gradient in patients with genetic generalized epilepsy with tonic–clonic seizure, suggesting an excessive functional segregation between unimodal and transmodal systems.[31] Mo et al. revealed gradient alterations on the temporal neocortex in focal cortical dysplasia (FCD) type IIIa and indicated neuroimaging gradient alterations were more widespread in the non-seizure-free cohort, as compared to the seizure-free cohort.[32] Exploring cerebellar gradient alterations in TLE may help us understanding the pathogenesis of ictal dystonic posturing.

In this present study, we used gradient analysis to explore cerebellar–cerebral FC in TLE patients with and without ictal dystonia posturing. These results may reveal the gradient alterations in the cerebellum of TLE patients and whether ipsilateral cerebellum took part in the generation of contralateral DP.

2 | METHODS

2.1 | Participants

Patients with unilateral TLE and ictal video EEG were initially screened at West China Hospital. Semiology, ictal and interictal EEG, brain MRI, and sometimes positron emission tomography (PET) were combined to localize the seizure focus. If patients underwent resective surgery after multidisciplinary preoperative evaluation, postoperative seizure outcomes were followed up according to the International League Against Epilepsy (ILAE) classification.[33]

The inclusion criteria were as follows: (1) patients were diagnosed with TLE according to the ILAE criteria[34]; (2) patients with at least one usual seizure recorded by video EEG and with clear ictal semiology that could distinguish dystonic posturing; (3) patients with seizure onset from unilateral mesiotemporal regions demonstrated by video EEG; and (4) patients with normal brain MRI or with unilateral hippocampal sclerosis compatible with EEG findings.

The exclusion criteria were as follows: (1) patients with other neurological or psychiatric disorders; (2) patients with active substances abuse; (3) patients with other structural lesions except unilateral hippocampal sclerosis that may contribute to seizures; and (4) patients without usual seizures or clear ictal symptoms during video EEG monitoring.

Based on ictal symptoms recorded by video EEG, patients were divided into two groups: TLE patients with dystonic posturing (TLE + DP) and TLE patients without dystonic posturing (TLE-DP). Two of the authors (W.L. and D.A.) performed independent review of ictal semiology. Final decision was made according to the agreement of two authors, with a third opinion (from D.Z.) taken into account in case of discrepancy.

In addition, we included age- and gender-matched healthy controls without any neurological or psychiatric disorders for comparison. Resting-state functional MRI (rs-fMRI) data were obtained in all participants with the same scan protocol.

This study was approved by the ethics committee on biomedical research, West China Hospital of Sichuan University. Written informed consent was obtained from all subjects prior to the study.

2.2 | Image acquisition

The MRI data were acquired from a 3.0 T MRI scanner (Tim Trio; Siemens, Erlangen, Germany) at the MRI center of West China Hospital with an eight-channel phased array head coil. Rs-fMRI was gained using an echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; field of view (FOV) = 240 × 240 mm^2; matrix size = 64 × 64; voxel size = 3.75 × 3.75 × 5 mm^3; slice thickness = 5 mm (no slice gap); flip angle = 90°; 30 axial slices per volume; and 200 image volumes in a run. All participants were instructed to relax with their eyes closed and keep their heads still during the whole scanning. We used foam pads to reduce head movement and earplugs to reduce scanner noise.

2.3 | Image processing

Data were pre-processed using Data Processing & Analysis for Brain Imaging (DPABI, version 6.1, http://rfmri.org/dpabi), including (1) dropping the first 10s (5 TRs); (2) slice-time correlation; (3) head motion correction; (4) spatial normalizing to Montreal Neurological Institute (MNI) template and resampling the voxel size to 3 × 3 × 3 mm^3; (5) regressing out nuisance covariates including 24 motion parameters, white matter, and cerebrospinal fluid signals; and (6) band-pass filtering (bandwidth 0.01–0.08 Hz). No spatial smoothing and no removal of the whole-brain mean signal were applied. In addition, the participants were excluded if they had obvious structural lesions except for hippocampus sclerosis.

2.4 | Cerebellar–cerebral functional connectivity

The cerebellum and cerebrum were defined by the templates in SPM8 and resampled to 3 mm isotropic voxels in MNI space, including 6323 voxels in cerebellum and 44 123 voxels in cerebrum. Cerebellar–cerebral functional connectivity was evaluated by calculating Pearson's correlation coefficients between time series of each voxel in the cerebellum and time series of all the voxels in cerebral cortex, resulting in a connectivity matrix of 6323 × 44 123 for each subject. Fisher-z transformation was applied the connectivity matrix for data normalization.

2.5 | Cerebellar–cerebral functional gradient analyses

To obtain the overall functional architecture of the cerebellum, gradient analysis was applied to cerebellar–cerebral FC matrix. First, only top 10% connections between the cerebellum and cerebrum were retained. Then, the similarity matrix (6323 × 6323) was generated by calculating the cosine distance between each pair of voxels of cerebellum. Afterward, a diffusion map embedding approach (see Supplementary materials for details) was used to identify multiple continuous gradients for each subject, which captures the FC similarity of each voxel along continuous space.[23,26,27] In addition, a group-level gradient template was generated by applying diffusion map embedding approach on averaged connectivity matrixes of all participants. All individual gradients were aligned to the group-level template using Procrustes rotation and smoothed using a full-width at half-maximum (FWHM) Gaussian kernel of 6 mm. To maximize the reliability and reproducibility of our analysis, we only focused on the first components (principal gradient) accounting for the most connectivity variance, which also represented the principal axis of the macroscale functional hierarchy in the cerebellum. The smoothed principal gradient value was compared among TLE + DP, TLE-DP, and controls using one-way ANOVA ($p < 0.005$).

2.6 | Contribution of cerebellar motor to gradient

We also tested whether cerebellar motor function contributed to abnormal cerebellar functional gradients in TLE, similar to our previous study.[35] First, cerebral motor components were identified by performing spatial independent component analysis (ICA) in cerebellar voxel-based FC maps (see Supplementary materials for details). Then, a multiple linear regression model was constructed to assess the association of cerebral motor components to connectivity maps of each cerebellar voxel, in which motor-related components were used as independent variables ($k \times 44\,123$) and cerebellar voxel-based FC maps were used as dependent variables ($6323 \times 44\,123$), generating corresponding cerebellar motor components ($k \times 6323$) for each subject. Cerebellar motor components were spatially smooth with a 6-mm FWHW Gaussian kernel. To explore the influence of cerebellar motor components on the cerebellar hierarchical structure (which was characterized by gradients), we employed a multiple linear regression model to assess the contribution of each cerebellar motor component to the gradients (Figure S1). Among them, all cerebellar motor components were used as independent variables and the gradients as dependent variables, generating a β value for each voxel of each component. Consequently, each group obtained k cerebellar β maps. The formula was given as follows:

$$y_{(i)} = \sum_{j=1}^{k} \beta_{(j,i)} \bullet V_{motor(j,i)} + \varepsilon$$

(For every voxel in the cerebellum, $i = 1,2,3, \ldots, 6323$; for every motor component of cerebellum, $j = 1, \ldots, k$).

$y_{(i)}$ represents the gradients value of the ith voxel for all subjects in the group; $V_{motor(j,i)}$ represents the value of the ith voxel of the jth cerebellar motor component of all subjects in the group. $\beta_{(j,i)}$ represents the contribution of the ith voxel of the jth component of all subjects in the group to the ith voxel of the gradient, and ε is the residual of the regression model. Finally, k cerebellar β maps were attained for each group. Between-group differences were detected using a permutation-based statistical test ($p < 0.01$), which constructed a null model by randomly shuffling subjects 5000 times.

Notably, we performed above analyses in the left-sided TLE (LTLE) and right-sided TLE (RTLE) groups separately to rule out possible structural and functional differences between the left and right hemispheres and to explore the potential lateralization value of cerebellar gradient.

3 | RESULTS

3.1 | Participants

Finally, ictal dystonic posturing was recorded in 31 TLE + DP patients (14 males, 22.68 ± 5.42 years old). The epileptogenic focus was located in left temporal lobe in 20 patients and in right temporal lobe in 11 patients. We also included 29 TLE-DP patients (15 males,

25.79 ± 7.08 years old) and 32 healthy controls (13 males, 24.78 ± 5.29 years old). All participants were native Chinese speakers and right-handed. Detailed clinical and demographic information of all participants is summarized in Table 1.

No statistical differences in age, gender, and framewise displacement were found among TLE + DP patients, TLE-DP patients, and healthy controls. There were also no significant differences in age at seizure onset, disease duration, seizure type, seizure frequency, laterization of seizure focus, history of febrile seizure, number of antiseizure drugs, hippocampus sclerosis on MRI, and postoperative seizure-free rate between TLE + DP and TLE-DP patients.

3.2 | Macroscale gradient in the cerebellum

We used a spatially unbiased infratentorial template (SUIT) (https://www.diedrichsenlab.org/imaging/suit.htm) to identify the cerebellar regions and overlapped gradients with cerebellar resting-state network map (Figure S2) identified by previous studies[26] to show the relationship of functional gradients with resting-state networks. Both TLE patients and healthy controls showed a clear transition from the somatomotor network (SMN) to DMN in the principal gradient of the cerebellum (Figure 1).

Compared with healthy controls, both TLE + DP and TLE-DP patients demonstrated a relatively extended principal gradient in the cerebellum. The extension of cerebellar principal gradient was more obvious in TLE-DP patients than in TLE + DP patients. Specifically, in the cerebellar principal gradient, the top of the triangle-shaped scatter plots consisting of DMN was increased in TLE + DP patients but decreased in TLE-DP patients, while the bottom of the triangle-shaped scatter plots consisting of SMN was consistently decreased in TLE + DP and TLE-DP patients (Figure 1).

3.3 | Aberrant cerebellar functional gradient in TLE

The cerebellar principal gradient was compared between TLE patients and healthy controls.

As shown in Figure 2, more widespread cerebellar gradient alterations were observed in TLE-DP patients in both LTLE and RTLE groups, involving bilateral cerebellum, while cerebellar gradient alterations in TLE + DP patients were limited in ipsilateral cerebellar regions (Table S1 for details).

In detail, compared with healthy controls, LTLE+DP patients showed no obvious cerebellar gradient changes, while LTLE-DP patients presented increased cerebellar gradient in left lobule VIIb and VIIIa and decreased cerebellar gradient in right crus I and II. Furthermore, LTLE+DP patients demonstrated increased cerebellar gradient in left lobule VI and decreased cerebellar gradient in left lobule VIIb and VIIIa than LTLE-DP patients. In addition, compared with healthy controls, RTLE+DP patients

TABLE 1 Clinical and demographic characteristics of the subjects.

	TLE + DP ($n = 31$)	TLE-DP ($n = 29$)	HC ($n = 32$)	p value
Gender (male/female)	14/17	15/14	13/19	0.382
Age (year)	22.68 ± 5.42 (14–39)	25.79 ± 7.08 (17–41)	24.78 ± 5.29 (16–36)	0.122
Mean FD (mm)	0.17 ± 0.06	0.17 ± 0.08	0.16 ± 0.06	0.925
Age at seizure onset (year)	13.61 ± 8.02 (1–37)	14.19 ± 8.79 (1–35)	-	0.557
Disease duration (year)	8.74 ± 7.10 (2–28)	11.59 ± 7.08 (1–31)	-	0.132
Seizure focus (L/R)	20/11	13/16	-	0.126
Seizure type (FS/FS, FBTCS)	12/19	10/19	-	0.734
Seizure frequency				
Daily/weekly/monthly/yearly	2/10/15/4	7/11/9/2	-	0.177
History of febrile seizure	13 (42%)	10 (34%)	-	0.553
Number of ASM (1/2/3)	12/12/7	8/11/10	-	0.520
Hippocampal atrophy on MRI	24 (77%)	21 (72%)	-	0.655
Postsurgical seizure-free rate (seizure-free/surgical patients)	80% (16/20)	76% (16/21)	-	0.768

Abbreviations: ASM, antiseizure medicine; FBTCS, focal to bilateral tonic–clonic seizure; FD, framewise displacement; FS, focal seizure; HC, healthy controls; L, left; R, right; TLE + DP, temporal lobe epilepsy with dystonic posturing; TLE-DP, temporal lobe epilepsy without dystonic posturing.

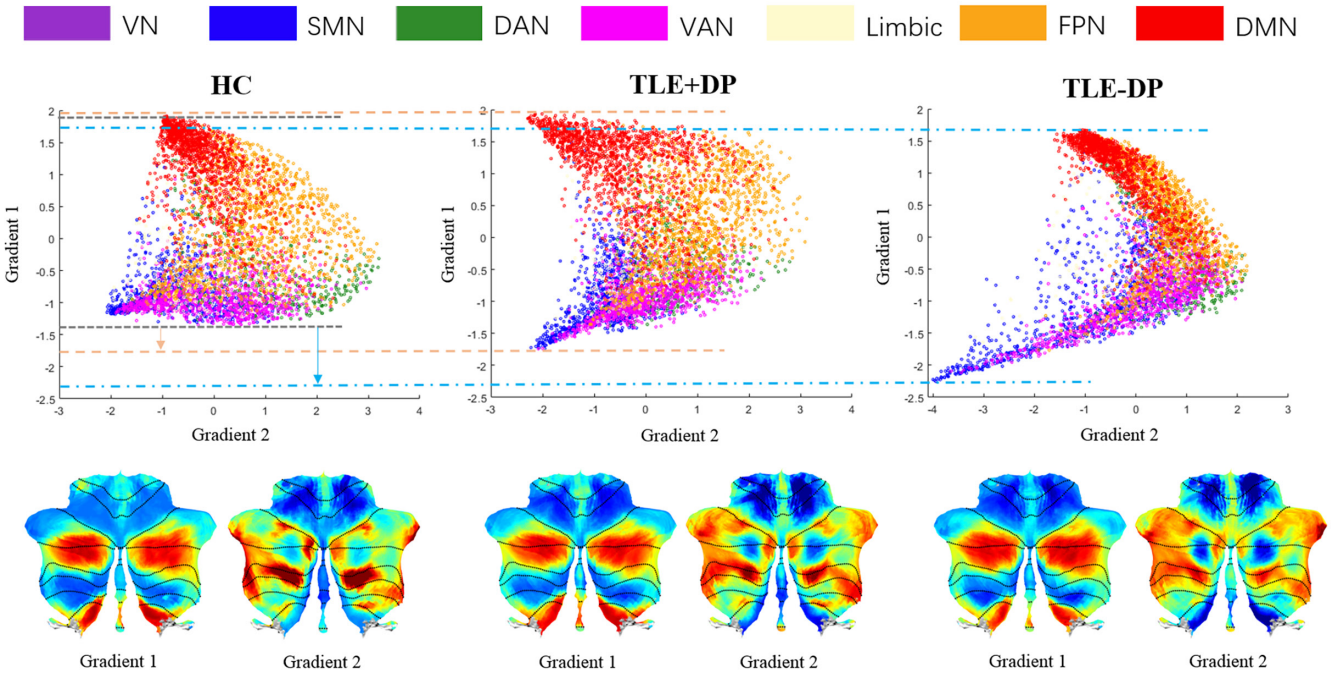

FIGURE 1 Cerebellar connectivity gradients in healthy controls (HC) and TLE patients with (TLE + DP) or without (TLE-DP) dystonic posturing and relationship with discrete resting-state maps. Gradient 1 explains the largest portion of variability in resting-state connectivity patterns within the cerebellum and is interpreted as the main axis of macroscale functional organization of the cerebellar cortex. Gradient 2 is the component accounting for the second-most variance and is interpreted as a secondary axis of functional organization. As showed in the scatterplots of three groups, each dot corresponds to a cerebellar voxel and its position corresponds to the Gradient 1/2 value. The color of each dot indicates whether each voxel belongs to a specific resting-state network (represented by different colors). The *y*-axis denotes the principal gradient (Gradient 1) of the cerebellum, which spans from primary (motor), to attentional/executive areas, to transmodal regions. Thus, primary somatomotor network (blue dots) is localized in the bottom of Gradient 1, and the default mode network (red dots) is located in the top. Ventral/dorsal attentional networks (violet/green dots) and frontoparietal network (orange dots) are situated between the two extreme ends. The *x*-axis denotes the secondary gradient (Gradient 2) which isolates attentional networks (violet and green dots). There are several dotted lines on the tops and the bottoms of the triangle-shaped scatter plots which represent the biggest gradient scores in default mode network and somatomotor network. Compared with HC group, both TLE + DP and TLE-DP groups demonstrate a relatively extended Gradient 1. However, the bottoms consistently decrease in TLE + DP and TLE-DP groups, while the top increases in TLE + DP group but decreases in TLE-DP group. DAN, Dorsal attention network; DMN, Default mode network; FPN, Frontoparietal network; HC, Healthy controls; Limbic, Limbic network; SMN, Somatomotor network; TLE + DP, Temporal lobe epilepsy with dystonic posturing; TLE-DP, Temporal lobe epilepsy without dystonic posturing; VAN, Ventral attention network; VN, Visual network.

showed increased cerebellar gradient in right lobule VI and crus I, while RTLE-DP patients presented increased cerebellar gradient in bilateral lobule VI and crus I. There was no cerebellar gradient difference between RTLE+DP and RTLE-DP patients.

3.4 | Unbalanced contribution of cerebellar motor components to cerebella–cerebrum gradient in TLE

We applied a model order of 50 components, and four motor components were selected from the ICA, including the left primary sensorimotor area (including left precentral and postcentral gyrus), right primary sensorimotor area, supplementary motor area (SMA), and paracentral lobule. See Figure 3 for details.

Correspondingly, we found the four cerebellar motor components of the controls and TLE had different contributions to different cerebellar regions of the cerebellar–cerebral gradient (Figure 4). Compared with healthy controls, altered contribution of four cerebellar motor components to the cerebellar gradient was observed in LTLE+DP patients. Specifically, the left primary sensorimotor area contributes more to the cerebellar gradient in the left VI. The contribution of the paracentral lobule to the cerebellar gradient increased in the left Crus I and Crus II and decreased in the right VIIIa area. Moreover, the contribution of the right primary sensorimotor area and SMA to the cerebellar gradient decreased in the left cerebellum. In patients with LTLE-DP, only the paracentral lobule and SMA showed decreased contribution to the cerebellar gradient in the right cerebellum (Table S2 for details).

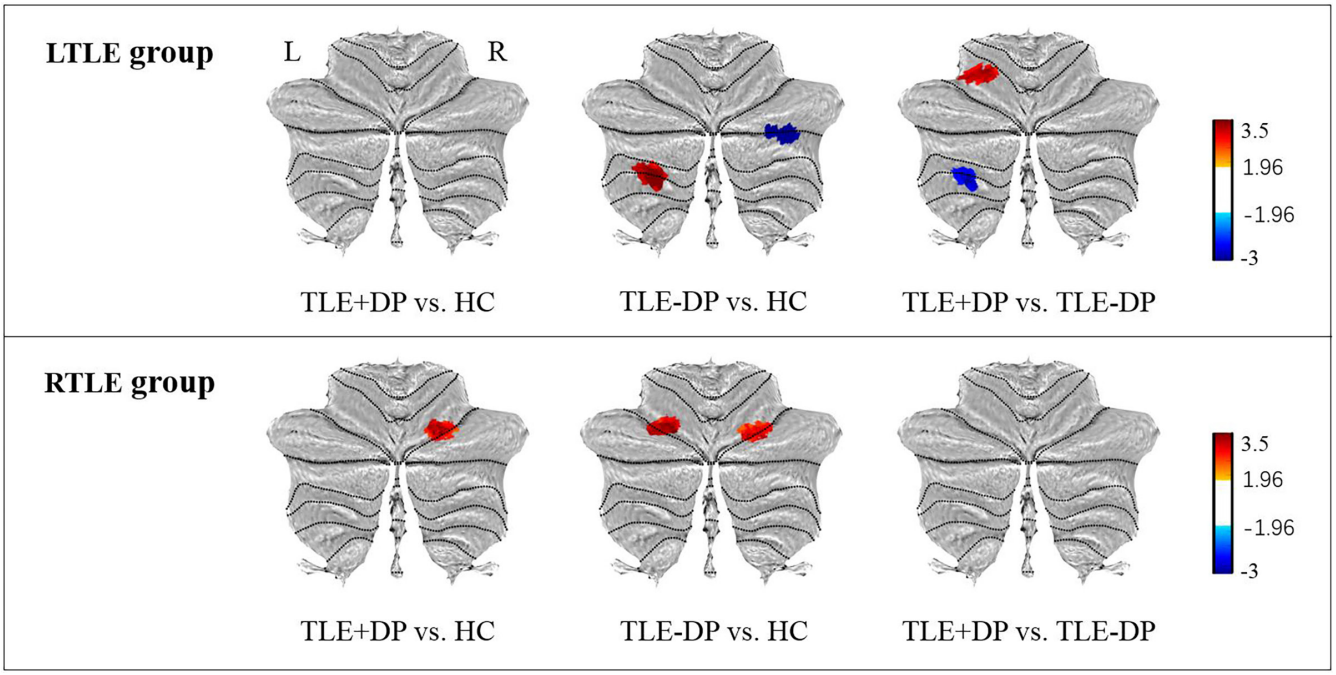

FIGURE 2 Aberrant functional gradient in TLE. The different colors represent intergroup differences. Red indicates the increase, and the blue represents the decrease. In left TLE group, TLE-DP shows increased gradient in left lobule VIIb/VIIIa and decreased gradient in right crus I/II when compared with HC. TLE + DP demonstrates increased gradient in left lobule VI and decreased gradient in left lobule VIIb/VIIIa than TLE-DP, while in right TLE group, only increased gradients are found in right lobule VI/crus I in TLE + DP and bilateral lobule VI/crus I in TLE-DP when compared with HC. HC, Healthy controls; LTLE, Left-sided temporal lobe epilepsy; RTLE, Right-sided temporal lobe epilepsy; TLE + DP, Temporal lobe epilepsy with dystonic posturing; TLE-DP, Temporal lobe epilepsy without dystonic posturing.

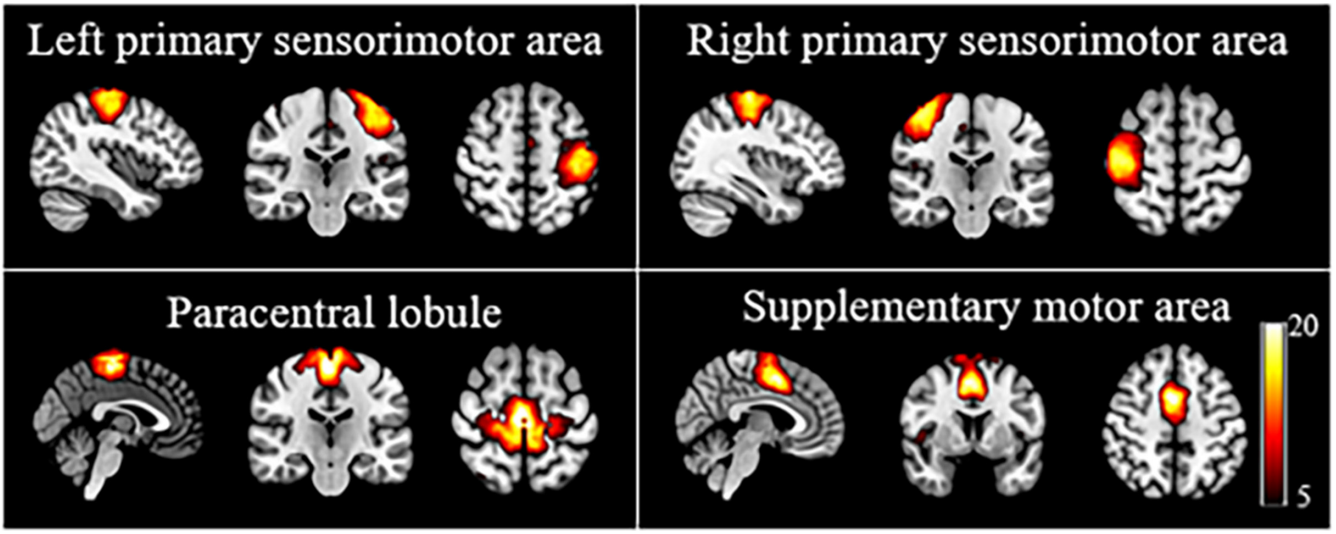

FIGURE 3 Four cerebral motor components were identified by independent component analysis.

Interestingly, in patients with RTLE, only two motor components have significantly different contributions to the cerebellar gradient in the right side of the cerebellum. Respectively, compared with the healthy control, the left primary sensorimotor area contributes more to the cerebellar gradient in the right Crus I in RTLE+DP. Meanwhile, compared with RTLE-DP patients, the contribution of the paracentral lobule to the right cerebellar Crus I, Crus

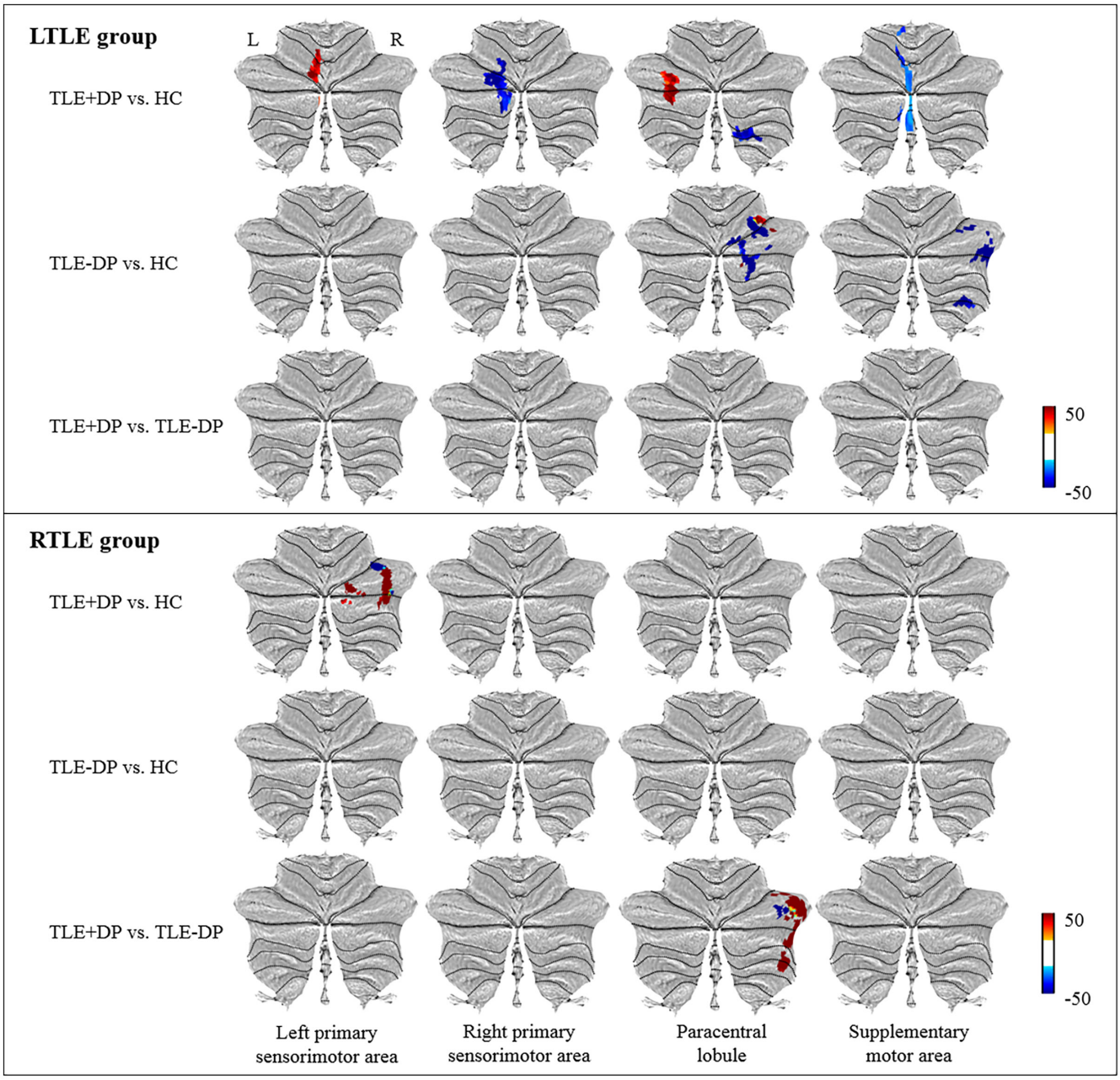

FIGURE 4 Disturbance of the contribution of cerebellar motor components to cerebella–cerebrum gradient in TLE. The different colors represent intergroup differences. Red indicates the increase, and the blue represents the decrease. The contributions of cerebellar motor components to the cerebellar gradient are more common in TLE + DP when compared with HC. TLE + DP shows increased contribution of paracentral lobule to the gradients in right cerebellar Crus I/II/VIIb/VIIIa than TLE-DP. HC, Healthy controls; LTLE, Left-sided temporal lobe epilepsy; RTLE, Right-sided temporal lobe epilepsy; TLE + DP, Temporal lobe epilepsy with dystonic posturing; TLE-DP, Temporal lobe epilepsy without dystonic posturing.

II, VIIb, and VIIIa areas increased in TLE + DP patients. There was no significant difference between RTLE-DP and the healthy control.

4 | DISCUSSION

The cerebellum is thought to be closely associated with dystonia. In clinical practice, a lot of evidences had linked different forms of dystonia to structural cerebellar lesions, such as cervical dystonia, focal limb dystonia, oromandibular dystonia, blepharospasm, torticollis, and even hemidystonia.[14,25] In animal models, the sign of dystonia was also considered to be due to cerebellar dysfunction and could be abolished following surgical removal of the cerebellum.[25] However, whether the cerebellum mediated episodic dystonic posturing in epilepsy or transient ictal dystonic posturing induced continuous cerebellar dysfunction remained unclear.

This present study explored cerebellar functional gradient in TLE patients related to dystonic posturing. There were no obvious differences between our TLE + DP and TLE-DP patients in clinical features and postoperative seizure outcomes. TLE patients and healthy controls all showed an apparent transition from SMN to DMN in the principal gradient of the cerebellum, while TLE patients demonstrated an extended cerebellar principal gradient than healthy controls, more limited in TLE + DP patients. In both left and right TLE groups, cerebellar gradient alterations were more widespread in TLE-DP patients, involving bilateral cerebellum, while cerebellar gradient alterations in TLE + DP patients were limited in ipsilateral cerebellum. In addition, the contribution of cerebellar motor components to ipsilateral cerebellar gradient alterations was more obvious in TLE + DP patients and more extensive in left TLE group.

In the principal gradient of the cerebellum, all our patients and healthy controls demonstrated an apparent transition from SMN to DMN, which was in keeping with previous finding of cerebellar functional gradients[26] and further confirmed the reproducibility and reliability of cerebellar gradient analysis. Functional gradient provided a global fingerprint for brain connectome[36] and a unified framework to probe potential pathological state.[27,28,30,31] Compared with healthy controls, both TLE + DP and TLE-DP patients exhibited an obviously extended principal gradient in the cerebellum, which suggested enhanced functional segregation between unimodal and transmodal systems in TLE. To our knowledge, this was the first study to systematically report cerebellar gradient alteration in TLE. Recently, extended principal gradient was also observed in cerebral cortex in generalized epilepsy,[31] indicating similar gradient alterations in different types of epilepsy. Moreover, cerebellar gradient extension was more obvious in TLE-DP than TLE + DP patients. It was reported that the occurrence of unilateral ictal limb dystonia might reduce the possibility of contralateral propagation and secondary generalization in TLE.[7] Similarly, dystonic posturing, to some extent, may limit the extent of cerebellar gradient damage in TLE.

In more detail, the top of the triangle-shaped scatter plots consisting of DMN was increased in TLE + DP patients but decreased in TLE-DP patients, while the bottom of the triangle-shaped scatter plots consisting of SMN was consistently decreased in TLE + DP and TLE-DP patients. Based on rs-fMRI and ICA, aberrant intrinsic activity and FC within DMN have been reported in many TLE studies.[37,38] In our previous study, we also found several abnormal FC between DMN and other resting state networks in TLE.[39] In view of altered DMN function have been reported to be associated with cognitive impairment in epilepsy,[40] our finding of cerebellar gradient changes in DMN further confirmed the impairment of high-level cognition in TLE, from the perspective of cerebellar gradient for the first time. In fact, there was accumulating evidence that the cerebellum has been involved not only in motor control but also in high-level cognitive and affective processing.[26,41,42] Moreover, different DMN gradient changes indicated that TLE + DP and TLE-DP patients have different functional impairments in the DMN, which was also not reported before. In addition, there was evidence that TLE patients presented decreased FC within SMN.[43] In this study, we found reduced cerebellar gradient of SMN in both TLE + DP and TLE-DP patients, suggesting consistent cerebellar gradient impairments of SMN in TLE patients. Furthermore, the extent of SMN gradient impairment was more obvious in TLE-DP patients as well.

Regarding aberrant cerebellar functional gradient of TLE compared with healthy controls, LTLE-DP patients presented increased cerebellar gradient in left lobule VIIb and VIIIa and decreased cerebellar gradient in right Crus I and II, while RTLE-DP patients presented increased cerebellar gradient in bilateral lobule VI and crus I. Previous resting-state and task fMRI analysis have revealed two motor areas (lobule I-VI, lobule VIII) and three nonmotor areas (lobule VI, Crus I/II/lobule VIIb, lobule IX/X) of cerebellar representation.[26,44] Cerebellar gradient alterations in TLE-DP patients involved bilateral motor and nonmotor regions, indicating that cerebellar function impairments in TLE-DP were not limited in primary motor function but also in high-level cognitive function. However, in TLE + DP patients, only RTLE+DP group presented increased cerebellar gradient changes in right lobule VI and crus I (nonmotor regions). Moreover, TLE-DP patients, whatever in left or right-sided subgroup, demonstrated more widespread cerebellar gradient alterations involving bilateral cerebellum, while TLE + DP patients only presented principal cerebellar gradient alterations in ipsilateral cerebellar regions when compared with healthy controls or TLE-DP patients. These results suggested that dystonic posturing may not only limit the extent of cerebellar gradient damage in TLE but also confine the gradient abnormality in ipsilateral cerebellum. It is interesting that TLE patients with DP, such a clear motor symptom, showed obvious cerebellar gradient alterations mainly in the nonmotor areas. Referring to cerebellar resting-state networks, these areas involved attention network, frontoparietal network, and default mode network. These findings indicated that, although with obvious motor symptom, TLE patients were associated with many high-level cognitive functional deficits. These functional deficits may result from recurrent seizures, antiseizure drugs, or underlying pathological mechanism of TLE. Further studies and detailed cognitive tests were needed to confirm these guesses.

In addition, the cerebellum is linked to the cerebrum via polysynaptic circuits, forming a complex motor topography.[44,45] In this study, we also tested whether cerebellar motor function contributed to abnormal cerebellar functional gradients in TLE. We found four cerebellar motor components had different contributions to different cerebellar regions of the cerebellar–cerebral gradient. Interestingly, more cerebellar motor components contributed to the gradient alterations in TLE + DP patients, mainly in ipsilateral cerebellum. These results suggested except aforementioned aberrant cerebellar principal gradient alterations, motor topography impairments in TLE + DP patients were also limited in ipsilateral cerebellum. Besides, the contribution of cerebellar motor function to cerebellar gradient was more extensive in LTLE group, which was similar to previous findings that functional abnormalities were more extensive in left-sided TLE.[46,47] Although our study could not verify the causality, we did provide preliminary evidence that ictal dystonic posturing in TLE was closely related to ipsilateral cerebellar gradient anomaly, which was also related to cerebellar motor network.

5 | LIMITATIONS

Several limitations were needed to be addressed. Firstly, our sample size was relatively small. Further study enrolled more subjects were needed to increase our statistical power. Secondly, we could not totally rule out possible seizures with dystonic posturing out of EEG monitoring in TLE-DP group. We tried to capture as much usual seizures as possible and excluded TLE-DP patients with suspicious ictal dystonic posturing according to their symptom descriptions. Thirdly, potential effects of antiseizure medications (ASMs) could not be ruled out. And we failed to conduct cognitive tests when acquiring the MRI data, which limited the correlation analysis with our gradient results. We may improve it in our further studies. Finally, further studies were needed to reveal the relationship or interaction between the cerebellum and basal ganglia in the pathogenesis of ictal dystonic posturing in TLE.

6 | CONCLUSION

Extended cerebellar principal gradients in functional connectivity revealed excessive functional segregation between unimodal and transmodal systems in TLE. The functional connectivity gradients were more limited in TLE patients with dystonic posturing. Functional connectivity in TLE patients with dystonic posturing involved more contribution of cerebellar motor function to ipsilateral cerebellar gradient.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Anonymized data will be shared by reasonable request from any qualified investigators.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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