ORIGINAL RESEARCH

Patterns of intrinsic brain activity in essential tremor with resting tremor and tremor-dominant Parkinson's disease

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Abstract

The clinical pictures of essential tremor (ET) with resting tremor (rET) and tremor-dominant Parkinson's disease (tPD) are often quite mimic at the early stage, current approaches to the diagnosis and treatment therefore remain challenging. The regional homogeneity (ReHo) method under resting-state functional magnetic resonance imaging (rs-fMRI) would help exhibit the patterns in neural activity, which further contribute to differentiate these disorders and explore the relationship between symptoms and regional functional abnormalities. Sixty-eight Chinese participants were recruited, including 19 rET patients, 24 tPD patients and 25 age- and gender-matched healthy controls (HCs). All participants underwent clinical assessment and rs-fMRI with a ReHo method to investigate the alterations of neural activity, and the correlation between them. Differences were compared by two-sample t-test (corrected with AlphaSim, $p < 0.05$). Compared with HCs, patients' groups both displayed decreased ReHo in the default mode network (DMN), bilateral putamen and bilateral cerebellum. While tPD patients specifically exihibited decreased ReHo in the bilateral supplementary motor area (SMA) and precentral gyrus (M1). The correlation analysis revealed that ReHo in the bilateral putamen, right SMA and left cerebellum_crus I were negatively correlated with the UPDRS-III score, respectively, in tPD group. Our results indicated the rET patients may share part of the pathophysiological mechanism of tPD patients. In addition, we found disorder-specific involvement of the SMA and M1 in tPD. Such a distinction may lend itself to use as a potential biomarker for differentiating between these two diseases.

Keywords Essential tremor · Rest tremor · Parkinson's disease · Regional homogeneity · rs-fMRI

Introduction

Essential tremor (ET) is a tremor disorder which is characterized by a typical 4–12 Hz postural or kinetic/action tremor mainly involving the hands and forearms (Louis 2005). However, rest tremor, the major characteristic of Parkinson's disease (PD), is also observed in about 18.8% of ET patients (rET) (Benito-Leon and Louis 2006; Cohen et al. 2003), which poses challenges for differentiating rET from tremor-

dominant PD (tPD) in the early stage (Yoon et al. 2016). Previous studies posted that 30–50% of supposed ET cases have been misdiagnosed as PD or other forms of tremor (Jain et al. 2006), as certain diagnostic tests or potential biomarkers in tremor classification are still scarce. Considering the different therapeutic strategies and prognoses between patients with rET and tPD, there is an urgent demand to find a way to helping identify these disorders with overlap symptoms at an early stage.

Over the past decade, certain electrophysiological (Nistico et al. 2011), neurometabolic (Barbagallo et al. 2017) and structural imaging studies (Cherubini et al. 2014) have explored the differences between the patients of rET and tPD, and have found different potential biomarkers to distinguish the two tremor diseases. For example, the electrophysiological study disclosed that the patients with rET presented a synchronous pattern whereas tPD patients had an alternating pattern, suggesting that the electromyographic pattern of rest tremor may help to

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differentiate rET from tPD (Nistico et al. 2011). In addition, an proton MR spectroscopy (^{1}H-MRS) study provided evidence that thalamic neurometabolic abnormalities only occur in tPD but was absent in rET, suggesting that ^{1}H-MRS can help to distinguish the two diseases (Barbagallo et al. 2017). When combing the predictors from voxel-based morphometry and diffusion tensor imaging in a support vector machine, Cherubini et al. exhibited a model with 100% accuracy to distinguish rET from tPD (Cherubini et al. 2014). However, so far, few studies on the intrinsic brain activity of patients with rET and tPD were reported. In 2015, a functional magnetic resonance imaging (fMRI) study showed the dysfunction of internal globus pallidus in rET without any morphometric changes (Nicoletti et al. 2015), showing the early brain functional alterations of rET. Much early functional disruption may exist in these diseases prior to structural alteration evidence of the brain. Considering the limitation and heterogeneities in imaging studies under brain topography, the differences in neural activity are called for discovering to understand the pathophysiology of rET and tPD.

Resting-state functional MRI (rs-fMRI) is a non-invasive imaging method that can be used to investigate functional changes in the brain without the need for deliberate stimulation or intentional movement (Su et al. 2015). Regional homogeneity (ReHo) measurement of rs-fMRI has been used to analyze the blood oxygen level-dependent (BOLD) signal of the brain, and to measure local synchronization of spontaneous fMRI signals by calculating the similarity of dynamic voxel fluctuations within a given cluster (Zang et al. 2004). It's a data-driven approach without prior knowledge and with good test-retest reliability (Zuo et al. 2013). This well-established quantification method has been successfully used in patients with PD (Wu et al. 2009) and Alzheimer disease (AD) (Wang et al. 2015). However, limited knowledge was found in the spontaneous brain activity between patients with rET and tPD.

In the present study, we aim to research the regional neural activity in patients with rET and tPD relative to age- and gender- matched healthy controls (HCs) applying ReHo method to find the different brain activity alteration between the rET and tPD patients.

Materials and methods

Participants

Twenty-four patients with tPD (4 males, 20 females), 19 patients with rET (4 males, 15 females) were consecutively recruited from the outpatient clinic at the West China Hospital of Sichuan University from September 2015 to March 2017. All tPD and rET patients were diagnosed by a movement disorder specialist based on the established criteria (Deuschl et al. 1998; Hughes et al. 1992). Twenty-five age and gender-matched HCs (4 males, 21 females) were recruited from the local area by poster advertisements. All subjects were provided with written informed consent and signed it prior to any procedures. This study was approved by the Ethics Committee of Sichuan University. All the subjects were right-handedly measured by the Edinburgh Inventory (Oldfield 1971) and were screened by the Mini-Mental State Exam (MMSE) in Chinese version (Katzman et al. 1988), those who failed to reach the following points were excluded: ≤ 17 for illiterate subjects, ≤ 20 for grade-school literate, and ≤ 23 for junior high school and higher education literate (Katzman et al. 1988; Zhang et al. 1990).

Historical data, including age, age at onset (AAO), gender, handedness, disease duration, and clinical symptoms were collected using a standard questionnaire prior to MRI examination on the same day. The Unified Parkinson's Disease Rating Scale (UPDRS) Part III (Goetz et al. 2008) and the Hoehn and Yahr (H&Y) stage (Hoehn and Yahr 2001) were used to evaluating the motor disability and disease severity of patients with tPD, respectively. The UPDRS Part III was also used to assess the motor disability of rET patients to further confirmed the diagnosis. For each patient of rET and tPD, eight items were used to compute the mean tremor scores (UPDRS-II, 1 item: tremor; UPDRS-III, 5 items: rest tremor of the face/lips/chin and each limb; and 2 items: action or postural tremor of the hands) (Stebbins et al. 2013). The Fahn-Tolosa-Marin rating scale score (TRS) (Louis 2005) was conducted to assess the tremor severity of patients with rET. The scale consists of three parts: TRS part A, B and C. The TRS part A and B were combined as TRS-A&B to obtain a single score and was used to evaluate the tremor severity, location and the drawing and writing function of the hand. The TRS-C was assessed by self-evaluation to evaluate the quality of life for rET patients. All rET patients were drug naïve, while all tPD patients were medication-free for at least 12 h before participation,

Exclusion criteria for all patients were a moderate-severe head tremor, a history of head injury, stroke, or other neurologic diseases. Moreover, PD patients with secondary Parkinsonism, Parkinson-plus syndrome or non-tremor dominant PD were excluded. Patients of rET combining with parkinsonism who had orthostatic hypotension, gaze palsy, as well as those with a secondary cause of tremor, including Wilson's disease, thyroid disease were excluded. In addition, all rET patients had been excluded the symptom of bradykinesia and rigidity through carrying out a clinical examination by two neurologists. HCs were excluded if they had any neurologic illness (e.g. PD) and family history of ET, after clinical evaluation and medical records, or structural brain defects on T1- or T2- weighted images.

MRI acquisition

MRI was performed on a 3.0-T MR imaging system (Tim Trio; Siemens Medical System, Erlangen, Germany) by using 8-channel phased array head coil. Resting-state functional images sensitive to changes in BOLD signal levels were obtained via an echo-planar imaging sequence (EPI) (repetition time = 2000 milliseconds, echo time = 30 milliseconds, flip angle = 90 degrees). The slice thickness was 5 mm (no slice gap) with a matrix size of 64 × 64 and a field of view of 240 × 240 mm^2, resulting in a voxel size of $3.75 \times 3.75 \times 5$ mm^3. Each brain volume comprised of 30 axial slices, and each functional run contained 240 image volumes, resulting in a total scan time of 480 s for each participant. The fMRI scanning was performed in darkness, and the participants were instructed to relax, close their eyes, to lie awake and not to think of anything during the fMRI acquisition. Foam padding was used to minimize the head motion and earplugs were used to reduce scanning noise.

Processing of fMRI data and quality assurance

The toolbox of DPABI on version 2.3(Yan et al. 2016) was used to conduct the data pre-processing. We discarded the first 10 functional images in order to ameliorate the possible effects of scanning instability and participants' adaptation to scanning noise. The remaining EPI images were preprocessed by the following steps: slice timing, motion correction, spatial normalization to the standard Montreal Neurological Institute (MNI) EPI template in SPM12, and resample to $3 \times 3 \times 3$ mm^3, followed by spatial smoothing with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel. Through linear regression, the influences of linear trends were subsequently removed from the data. Finally, a temporal filter (0.01 Hz < f < 0.08 Hz) was applied to remove low-frequency drifts and high-frequency noise. According to the record of head motions within each fMRI run, all participants had less than 1.5 mm maximum displacement in the x, y, or z directions and 1.5° of angular rotation about each axis for head movement assessment.

ReHo analysis

Individual ReHo image was performed on a voxel-by-voxel basis by calculating Kendall's coefficient of concordance (KCC) of time series of a given cluster of neighbouring voxels within a whole-brain mask, which was provided by DPABI and excluded non-brain areas. Here, we used the cubic clusters of 27 voxels and assigned the ReHo value of every cubic cluster to the central voxel. A larger ReHo value for a given voxel suggested a higher local synchronization of rs-fMRI signals among neighbouring voxels. To minimize the whole brain effect, voxel ReHo values were standardized by dividing each subject's value by the mean value of their whole-brain ReHo. Differences in ReHo changes were compared with data for between-group by two-sample t-test with AlphaSim multiple comparison corrections, head motion, age, gender, mean education years and disease duration as covariates (AlphaSim correction, $p < 0.05$).

Clinical statistical analysis and correlation analyses

We performed the Pearson X^2 test, one-way ANOVA, or two-sample t-test as appropriate to analyze the differences between groups in terms of demographic and clinical variables. Based on the two-sample t-test findings, to investigate the underlying relationship between different ReHo values and the clinical features (e.g. TRS score, UPDRS III score and AAO) of in rET group and tPD group, partial correlation analysis was carried out in the patient groups to control for the effects of age, gender, mean education years and disease duration.

Results

Demographic and clinical characteristics

Demographic and clinical features of the three group samples are summarized in Table 1. No significant differences were found in age, gender and MMSE score among the three groups. Although there was no significant difference in AAO and UPDRS tremor score between rET and tPD, the rET subjects have an obvious longer disease duration than that of tPD patients (two-sample t-test, $p = 0.006$, two-tailed) but tPD patients showed more serious motor symptoms than that of rET patients (two-sample t-test, $p < 0.000$, two-tailed). A significant difference was found in the mean education years among the three groups (one-way ANOVA, $p = 0.006$).

ReHo analysis

Comparison of ReHo values between rET patients and controls

Compared with HCs, rET patients showed increased ReHo values in the left middle frontal and orbitofrontal gyri, the bilateral inferior orbitofrontal gyri, the right superior temporal gyrus, the bilateral middle and inferior temporal gyri, the right olfactory and the left cerebellum_crus I and cerebellum_crus II; decreased ReHo values in the bilateral insula, bilateral putamen, left anterior and posterior cingulate gyrus (ACC/PCC), and the right cerebellum (lobule IX) ($p < 0.05$, AlphaSim corrected; Table 2 and Fig. 1).

Table 1 Demographic and clinical features of rET, tPD, and HCs

Measure	rET	tPD	HCs	P value
Age	48.32 ± 13.16	53.13 ± 8.49	49.12 ± 11.81	0.995[a]
Gender(male: female)	4:15	4:20	4:21	0.898[a]
Education(years)	8.53 ± 4.73	6.42 ± 3.76	9.92 ± 2.82	0.006[a]/c
MMSE	25.68 ± 4.30	26.84 ± 2.99	27.16 ± 2.25	0.237[a]
Age of onset (years)	36.32 ± 15.10	49.04 ± 10.28	NA	0.057[b]
Disease duration (years)	13.15 ± 10.39	3.35 ± 3.36	NA	0.006[b]
Family history	9(9/19)	0(0/24)	NA	
TRS-A&B	18.26 ± 8.10	NA	NA	
TRS-C	8.32 ± 3.46	NA	NA	
UPDRS-motor	5.84 ± 2.32	24.00 ± 16.47	NA	<0.000[b]
UPDRS-tremor score	7.37 ± 2.77	6.83 ± 4.44	NA	0.646[b]
Gait or posture abnormality	NA	19(19/24)	NA	
H&Y	NA	2.20 ± 0.87	NA	
LEDD (mg)		316.94 ± 402.25		

rET, essential tremor with resting tremor; tPD, tremor-dominant Parkinson's disease; HCs, healthy controls; NA, not applicable; TRS, Fahn-Tolosa-Marin Tremor Rating Scale; TRS-A&B, Fahn-Tolosa-Marin Tremor Rating Scale part A and B; TRS-C, Fahn-Tolosa-Marin Tremor Rating Scale part C; UPDRS, Unified Parkinson's disease rating scale; H&Y, Hoehn and Yahr stage; LEDD, L-dopa equivalent daily dose

[a] one - way ANOVA

[b] two-samples t-test

c, r ET vs. t PD $p = 0.213$; r ET vs. HCs $p = 0.637$; t PD vs. HCs $p = 0.005$

Comparison of ReHo values between tPD patients and controls

When compared with HCs, tPD patients showed significantly increased ReHo values in the right supramarginal gyrus, the right angular gyrus and the bilateral cerebellum (lobule VIIb, lobule VII, crus I and crus II) (($p < 0.05$, AlphaSim corrected; Table 3 and Fig.2). A significantly decreased ReHo was observed in tPD patients ($p < 0.05$, AlphaSim corrected; Table 3 and Fig.2), including the bilateral superior frontal gyri, right middle frontal gyrus, left superior temporal gyrus, bilateral insula, left hippocampus, bilateral precentral gyri (M1, primary motor cortex) and bilateral postcentral gyri (S1, primary sensory cortex), bilateral middle cingulate gyri, bilateral precuneus (PCu), bilateral supplementary motor area (SMA), bilateral putamen and right cerebellum (lobe IV_V and VI).

Comparison of ReHo value between rET group and tPD group

In contrast to tPD patients, the rET subjects exhibited higher ReHo values in the left superior and middle frontal gyri, bilateral middle and inferior temporal gyri, right superior parietal gyrus, right M1 and S1, bilateral middle cingulate gyri and bilateral precuneus. While a significantly lower ReHo value was observed in the right angular gyrus, right supramarginal gyrus, left insula, right hippocampus, left cerebellum (lobe VII, IX, and X) and Vermis X ($p < 0.05$, AlphaSim corrected; Table 4 and Fig. 3).

Correlation analyses

After controlling for the effects of age, gender, mean education years and disease duration, we found that the ReHo values in the cerebellum_crus I_L were significantly positively correlated with the AAO in the rET patients (r = 0.586, $p = 0.022$, Fig.4). Additionally, a significantly positive correlation with the MMSE score (r = 0.587, $p = 0.022$, Fig.4) was found in the left ACC in the rET patients. Furthermore, the UPDRS-III score was negatively correlated with the left putamen (r = −0.559, $p = 0.013$, Fig.5), the right putamen (r = −0.608, $p = 0.006$, Fig.5), cerebellum_crus II_R (r = −0.480, $p = 0.038$, Fig.5), cerebellum_IV_V_R (r = −0.485, $p = 0.035$, Fig. 5) and the right SMA (r = −0.569, $p = 0.011$, Fig. 5) in the tPD patients.

Discussion

In this study, we first applied the ReHo method to describe the local connectivity in the rs-fMRI among rET patients, tPD patients and HCs. Our findings indicated that both patients groups displayed ReHo alterations in brain regions overlapping with the so-called default mode network (DMN, e.g. ACC, PCC/PCu, angular gyrus), putamen and cerebellum, while tPD group specially decreased ReHo in the bilateral precentral and postcentral gyri and bilateral SMA. By direct comparison

Table 2 Regions showing ReHo differences between rET and HCs by two-sample *t* test

Brain region(AAL)	BA	coordinate MNI			Clusters size(mm³)	T value
		X	Y	Z		
rET<HC						
Insula_L	48	−44	−1	−2	60	0
Insula_R	48	36	6	12	73	−3.560
Putamen_L	48	−29	6	8	99	−3.840
Putamen_R	48	30	10	12	112	−2.610
Cingulum_Mid_R		13	−23	44	77	−2.710
Cingulum_Ant_L	32	−12	30	27	88	−3.450
Cingulum_Post_L	23	0	−35	31	68	−2.330
Cerebelum_9R		12	−42	−54	75	−3.050
rET>HC						
Frontal_Mid_L	47	−41	47	4	87	3.028
Frontal_Mid_Orb_L	11	−35	60	−12	89	2.694
Frontal_Inf_Orb_L	11	−23	20	−23	92	2.644
Frontal_Inf_Orb_R	11	21	20	−23	88	3.323
Temporal_Sup_R	22	67	−16	−5	90	2.557
Temporal_Mid_L	21	−64	−27	−12	95	2.452
Temporal_Mid_R	21	61	−23	−12	119	3.301
Temporal_Inf_L	20	−27	−3	−42	82	4.318
Temporal_Inf_R	20	60	−51	−9	84	3.478
Olfactory_R	11	17	13	−19	73	2.591
Fusiform_R	20	42	−33	−18	84	3.869
Cerebellum_Crus1_L		−31	−85	−27	82	3.092
Cerebellum_Crus2_L		−34	−82	−32	85	2.931

rET: essential tremor with resting tremor, HCs: healthy controls, BA: Brodmann; AAL, Anatomical Automated Labeling Atlas; MNI, Montreal Neurologic Institute; R right, L left, Mid middle, Inf inferior, Supp_Motor_Area supplementary motor area; Inf, inferior; Mid, middle; Sup, superior; Orb; orbital; Ant, anterior; Post, posterior

of rET and tPD groups, the results showed that ReHo differences between the two groups located mostly in the cerebellum, precentral and postcentral gyrus, PCu, frontal and temporal lobe.
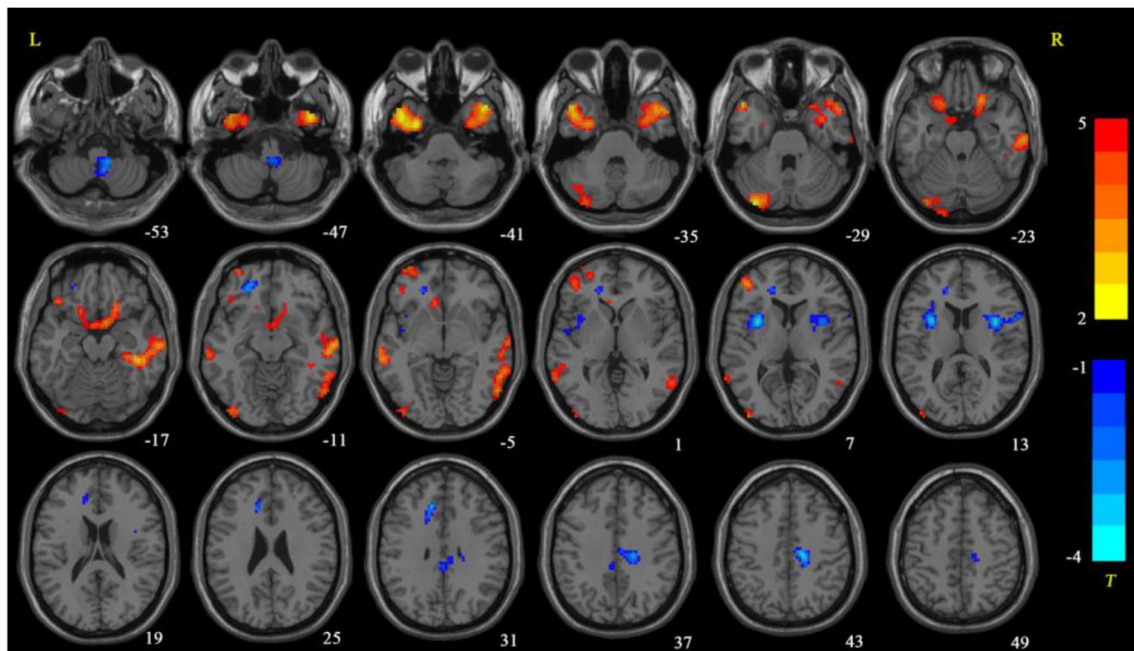

Fig. 1 Regions showing ReHo differences between rET patients and HCs. Compared with HCs, the increased ReHo values in rET is illustrated by the warm color (*p* < 0.05, corrected by AlphaSim, cluster size >101mm³). ReHo, regional homogeneity; rET, essential tremor with resting tremor; HCs, healthy controls

Table 3 Regions showing ReHo differences between tPD and HCs by two-sample *t* test

Brain region(AAL)	BA	coordinate MNI			Clusters size(mm^3)	T value
		X	Y	Z		
tPD>HC						
SupraMarginal_R	40	60	−44	39	89	2.288
Angular_R	39	48	−61	50	96	2.300
Rectus_R	11	8	24	−21	83	2.495
Cerebellum_7b_L		−40	−45	−43	102	2.527
Cerebellum_7b_R		36	−59	−43	107	2.428
Cerebellum_8_L		−36	−44	−43	93	2.307
Cerebellum_Crus1_L		−35	−79	−30	99	3.161
Cerebellum_Crus1_R		34	−77	−30	100	3.677
Cerebellum_Crus2_L		−36	−76	−43	83	2.523
Cerebellum_Crus2_R		45	−71	−43	90	3.367
tPD<HC						
Frontal_Sup_L	6	−26	−8	56	91	−4.000
Frontal_Sup_R	8	28	3	56	90	−3.070
Frontal_Mid_R	45	37	44	19	111	−2.530
Temporal_Sup_L	48	−37	−32	13	85	−2.400
Fusiform_R	19	22	−56	−11	85	−2.910
Insula_L	48	−35	−22	19	72	−2.700
Insula_R	48	35	27	7	83	−2.570
Hippocampus_L	20	−29	−18	−11	76	−2.520
Precentral_L	44	−48	4	27	75	−2.620
Precentral_R	4	46	−11	43	105	−2.780
Postcentral_L	6	−47	−11	45	99	−3.150
Postcentral_R	3	28	−34	52	107	−2.940
Cingulum_Mid_L	24	−3	3	37	77	−2.860
Cingulum_Mid_R	24	4	2	43	83	−3.380
Precuneus_L		−7	−46	43	76	−3.180
Precuneus_R		3	−43	45	81	−3.150
Supp_Motor_Area_L		−7	−15	52	104	−3.600
Supp_Motor_Area_R		0	0	52	58	−3.670
Putamen_L	48	−30	−5	7	103	−3.080
Putamen_R	48	29	0	7	100	−2.770
Cerebellum_4_5_R	37	19	−49	−19	87	−2.800
Cerebellum_6_R	37	27	−53	−21	90	−2.860

tPD, tremor-dominant Parkinson's disease; HCs, healthy controls; BA, Brodmann; AAL, Anatomical Automated Labeling Atlas; MNI, Montreal Neurologic Institute; R right; L left; Mid middle; Inf inferior; Supp_Motor_Area, supplementary motor area

Abnormal ReHo in the DMN

In contrast to HCs, tPD patients showed significantly decreased ReHo values in the bilateral precuneus and rET patients had decreased ReHo values in the left ACC/PCC. Moreover, the ReHo values in the ACC in rET group were positively correlated with the MMSE score. The DMN plays a crucial role in cognitive processing both in normal ageing and neurodegenerative disorders (Agosta et al. 2012; Sambataro et al. 2010; Tessitore et al. 2012). One meta-analysis revealed that precuneus is the major cognitional activation brain area in patients with AD in contrast to elderly controls (Sadigh-Eteghad et al. 2014). Our findings were consistent with previous studies which found that PD patients presented with altered ReHo values in the DMN (Wu et al. 2009; Yang et al. 2013) and the functional connectivity changes occurred in the DMN of ET patients
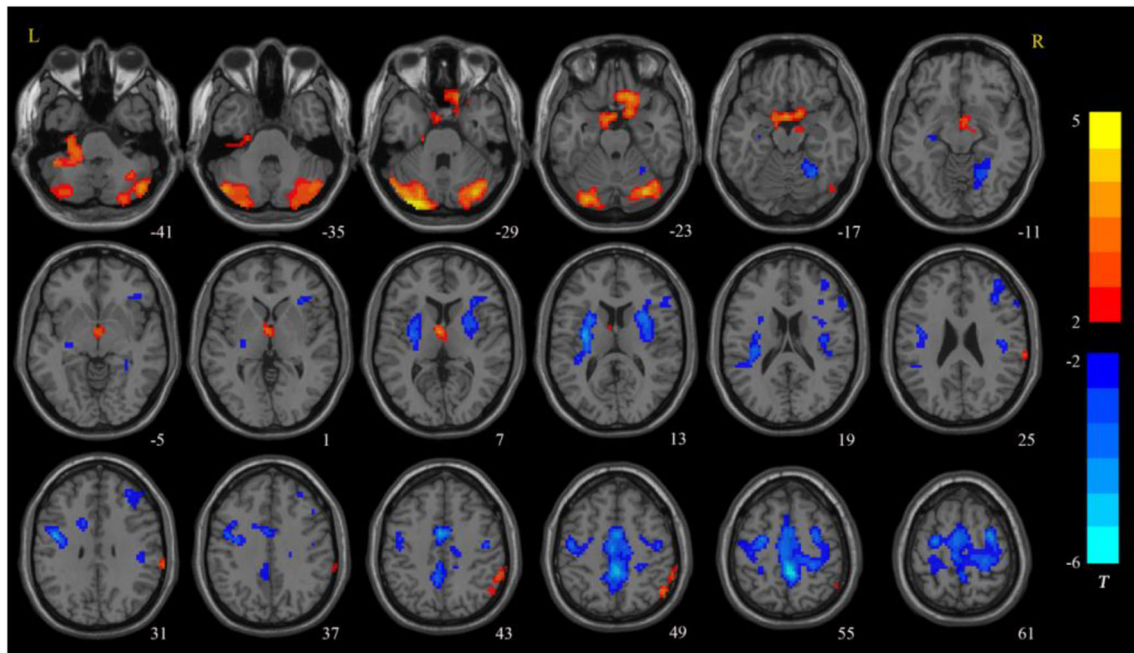
Fig. 2 Regions showing ReHo differences between tPD patients and HCs. Compared with HCs, the decreased ReHo values in rET is illustrated by the cold color, while the increased ReHo values is illustrated by the warm color ($p < 0.05$, corrected by AlphaSim, cluster size >101mm^3). ReHo, regional homogeneity; tPD, tremor-dominant Parkinson's disease; HCs, healthy controls

Table 4 Regions showing ReHo differences between rET and tPD by two-sample *t* test

Brain region(AAL)	BA	coordinate MNI			Clusters size(mm^3)	T value
		X	Y	Z		
rET>tPD						
Frontal_Sup_L	6	−22	−2	63	105	2.833
Frontal_Mid_L		−25	1	61	42	2.525
Temporal_Mid_L	21	−61	−46	−5	98	4.728
Temporal_Mid_R	21	59	−39	−5	100	2.833
Temporal_Inf_L	37	−61	−48	−15	85	2.861
Temporal_Inf_R	20	51	−44	−15	113	2.615
Fusiform_R	20	44	−37	−22	91	2.971
Parietal_Sup_R	5	17	−51	69	103	2.957
Precentral_R	4	40	−23	55	100	2.402
Postcentral_R	3	21	−39	69	105	3.457
Paracentral_Lobule_ R	4	10	−32	69	87	2.947
Cingulum_Mid_L		0	−38	49	52	2.377
Cingulum_Mid_R		3	−11	49	84	2.855
Precuneus_L		−13	−46	43	101	2.249
Precuneus_R		6	−36	56	95	2.447
rET<tPD						
Angular_R	39	51	−62	47	88	−2.540
SupraMarginal_R	40	60	−44	40	89	−2.850
Insula_L	48	−44	8	−5	82	−2.240
Hippocampus_R	28	24	−2	−20	81	−2.450
Cerebellum_8_L		−27	−39	−43	91	−2.460
Cerebellum_9_L		−5	−45	−38	52	−2.870
Cerebellum_10_L		−24	−36	−43	85	−2.520
Vermis_10		2	−42	−32	31	−3.080

rET, essential tremor with resting tremor; tPD, tremor-dominant Parkinson's disease; BA, Brodmann; AAL, Anatomical Automated Labeling Atlas; MNI, Montreal Neurologic Institute; R right, L left, Mid middle; Inf inferior; Sup, superior
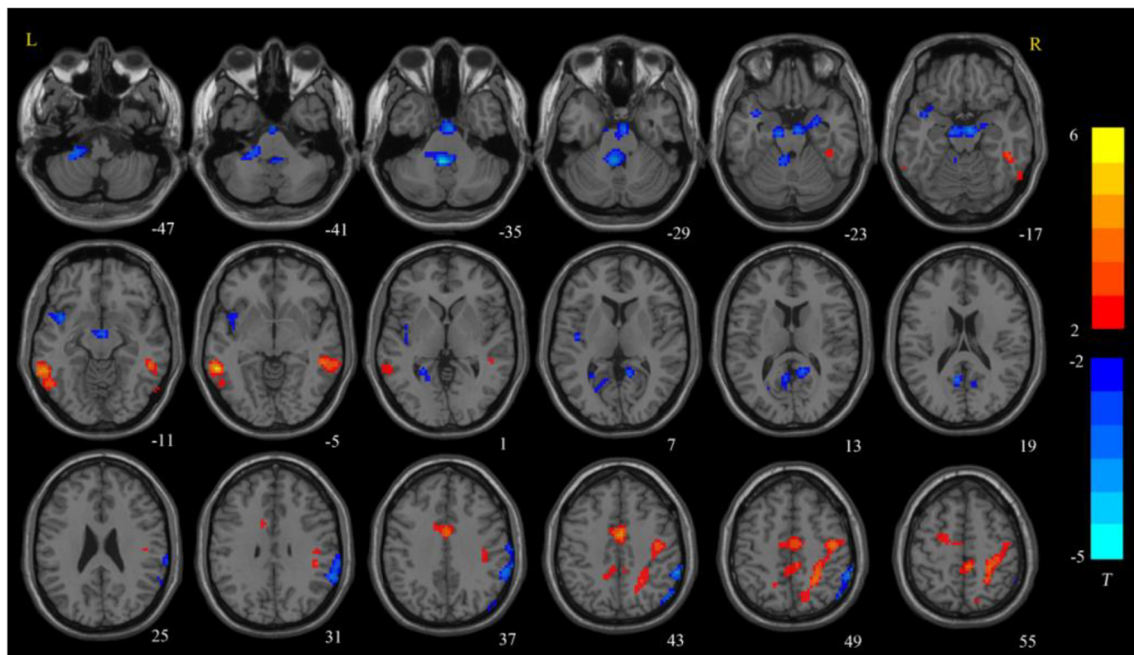
Fig. 3 Regions showing ReHo differences between rET patients and tPD patients. Warm color indicates the regions with larger ReHo value in rET than tPD, while cold color indicates those with decreased ReHo in rET ($p < 0.05$, corrected by AlphaSim, cluster size >101mm^3). ReHo, regional homogeneity; tPD, tremor-dominant Parkinson's disease; rET, essential tremor with resting tremor

(Fang et al. 2015). Researchers found decreased functional integrity of the DMN in PD patients without cognitive dysfunction at rest (Tessitore et al. 2012), which reflected that there was an early functional disruption of DMN in PD prior to clinical evidence of cognitive impairment. Moreover, some clinical studies found that ET and PD exhibited similar deficits in specific aspects of neuropsychological functioning, even with the latter being the most affected (Puertas-Martín et al. 2016; Sanchez-Ferro et al. 2017). Therefore, our results further confirmed that both rET and tPD patients were prone to impair cognition although without clinical evidence at the early stage.

Abnormal ReHo in the putamen

Compared with HCs, both rET and tPD patients showed decreased ReHo in the bilateral putamen. The putamen is thought to be mainly involved in motor function (Bhatia and Marsden 1994) and it is generally believed that PD patients reduced dopamine uptake in the striatum with the putamen being most severely affected (Brooks et al. 1990). In our study, we found the ReHo values in the bilateral putamen negatively correlated with the UPDRS III score in tPD patients, suggesting that the regional alteration is probably linked with motor severity in tPD patients. Our finding of less functional synchronization of the putamen in tPD is consistent with the previous studies on PD
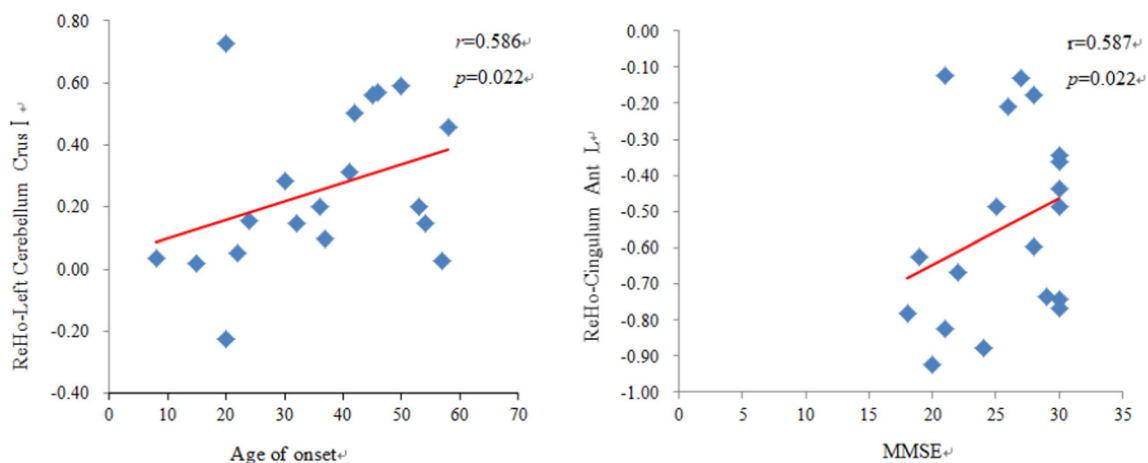

Fig. 4 Significantly correlation between ReHo values of regions where patient-control groups showed significant differences and the clinical indices in patients with rET. ReHo, regional homogeneity; rET, essential tremor with resting tremor; MMSE, the Mini-Mental State Exam
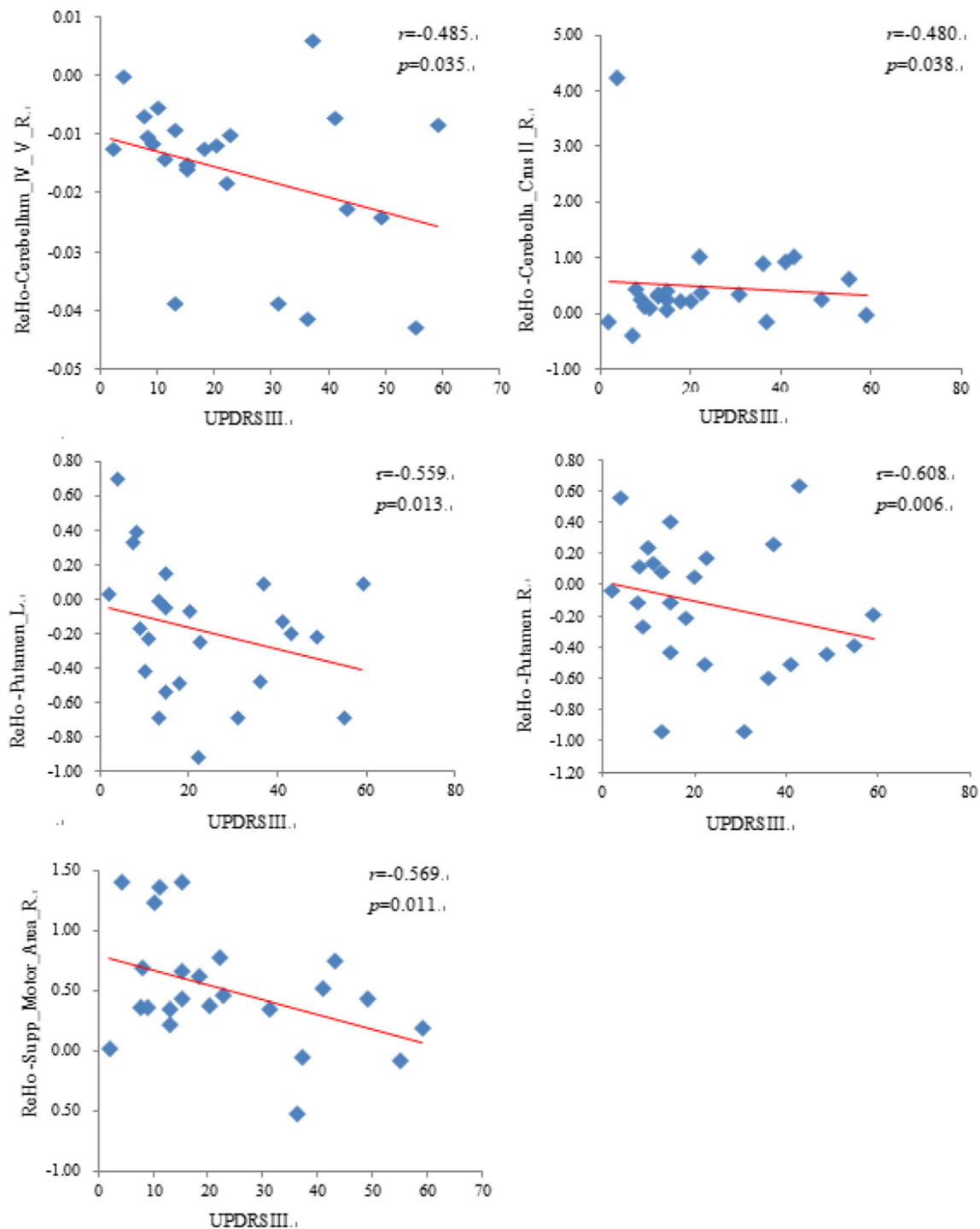
Fig. 5 Significantly correlation between ReHo values of regions where patient-control groups showed significant differences and the clinical indices in patients with tPD. ReHo, regional homogeneity; tPD tremor-dominant Parkinson's disease; UPDRSIII, Unified Parkinson's Disease Rating Scale Part III

(Wu et al. 2009; Zhang et al. 2015). Of note, early fMRI studies hadn't confirmed any abnormal brain activities in the putamen in ET patients (Benito-Leon et al. 2015; Fang et al. 2013). Some PET studies, however, have found a significant presynaptic dopaminergic deficit in ET group compared with HCs, and the dopamine transporter loss in ET patients was marked but yet less

severely than PD (Gerasimou et al. 2012). Consistent with these results, our study found the decreased ReHo in the bilateral putamen in the rET group, suggesting that rET and tPD patients may have a relationship with striatal dopamine depletion. Therefore, we speculate that rET patients may share part of the pathophysiological mechanisms in tPD patients. It maybe

explain why patients with ET had a 4–5-fold higher risk of developing incident PD than participants without baseline ET (Benito-Leon et al. 2009).

Abnormal ReHo in the cerebellum

Relative to HCs, we displayed decreased ReHo values in cerebellum both in rET group (cerebellum_IX) and tPD group (cerebellum_IV_V and VI). The cerebellum takes part in the cerebello-thalamo-cortical (CTC) network, which is activated during a tremor and is known as the tremor network (Sharifi et al. 2014). A growing body of imaging studies indicated that the parkinsonian tremor was strongly associated with the CTC circuit (Helmich et al. 2012; Mure et al. 2011; Zhang et al. 2015). According to the prior researches, fMRI studies showed that tPD patients exhibited abnormal neuromagnetic activities (Pollok et al. 2004) and morphological alterations (Benninger et al. 2009) in the cerebellum. However, either compensation or pathological changes in the CTC circuit contributing to parkinsonian resting tremor are still obscure. Recently, the cerebellum was also found to be a key hub involved in heterogeneous symptoms of ET (Fang et al. 2015) and decreased connectivity was observed in the CTC network in the brain of ET patients (Caligiuri et al. 2017). In addition, Fang et al. observed an altered ReHo in the cerebellum of ET patients when compared to HCs (Fang et al. 2013), which was consistent with our results. Although Novellino et al. (Novellino et al. 2016) showed that rET patients had intermediate values of the microstructural changes in the cerebellum compared to HC and ETwr, some early functional disruption in the cerebellum may occur prior to structural alteration evidence of the brain. Thus, our findings further confirmed that the dysfunction of cerebellum and CTC network played an important role in the potential pathophysiology both in rET and tPD.

Abnormal ReHo in motor-related cortical areas

Relative to HCs, tPD group especially exhibited decreased ReHo in the bilateral SMA and M1, and there was a significant negative correlation between UPDRS-III score and ReHo value of the right SMA. Moreover, the UPDRS-III score of tPD group is significant higher than that of rET group, but no significant difference was found in the UPDRS-tremor score between the two groups. Dysfunction of SMA had been taken into account to explain the pathogenesis of bradykinesia (Hamada et al. 2009; Lefaucheur 2005), which is the cardinal symptom of PD. The absence of bradykinesia in our rET group to some extent would explain why only tPD group displayed abnormal ReHo in SMA neither rET group. In line with previous imaging findings, our rs-fMRI based on ReHo method further confirmed that the SMA hypoactivation has been frequently linked to the pathogenesis of bradykinesia in tPD patients. Moreover, neurons in the SMA and M1 were

related to the regulation of stepping and posture under normal circumstances (Drew et al. 2004). Hence, when these regions had some abnormal alterations, the decoupling between posture preparation by the SMA and step initiation by the M1 might occur in the brainstem reticular formation, where posture and gait are coordinated (Schepens et al. 2008). Furthermore, the crucial role of the M1 in posture control was demonstrated by a recent study revealing that transcranial pulsed current stimulation in this region improved balance and gait parameters in PD patients (Alon et al. 2012). Combined with the clinical characterizes of our tPD patients, 19 of 24 subjects have gait or posture abnormality, further confirming our results. Therefore, we speculate that declines in communication between SMA and M1 likely serve a role in the postural and gait disruptions seen in tPD patients but not in rET patients. Certain observations in our study suggested that ReHo alternations in the SMA and M1 might be potential biomarkers to diagnose and differentiate patients with rET and tPD.

Limitation

Several limitations should be considered. First, the evaluation of non-motor symptoms was limited. Second, the unified tremor scale was lacked to compare the tremor characteristics of rET and tPD patients in order to summarize the specific difference. Third, not all the tPD patients were untreated, the study cannot completely rule out the potential residual effects of chronic dopaminergic drugs, thereby further studies with more drug-naïve patients and a follow-up investigation will be needed. Fourth, physiologic noise, including respiratory and cardiac fluctuations, might have influenced our results. Fifth, the relatively small sample size might limit the interpretation of our results.

Conclusion

As shown in our study, we found that both rET and tPD subjects exhibited common changes of decreased ReHo in the DMN, putamen and cerebellum, demonstrating the similar pathophysiological mechanisms of two tremor-related disorders. Remarkably, tPD patients displayed more decreased neural activities in motor-related cortical areas (SMA and M1), suggesting that the particular clinical symptoms of tPD, such as bradykinesia, postural and gait disruptions, might be derived from the dysfunction of SMA and M1. As a result, the decreased ReHo may play a more specific role in following any brain damage caused by rET and tPD, and may, therefore, be used as biomarkers for the diagnosis of these movements disorders, as well as their clinical assessment.

Data availability All data generated or analysed during this study are included in this published article.

Compliance with ethical standards

Conflict of interests There is no conflict of interests in our research.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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