

Functional Connectivity of Vim Nucleus in Tremor- and Akinetic-/Rigid-Dominant Parkinson's Disease

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Keywords

Akinetic-rigidity; Connectivity; Parkinson's disease; Tremor; Vim nucleus.

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SUMMARY

Aims: The aim of this study was to investigate the involvement of the ventral intermediate nucleus of thalamus (Vim) in the tremor- and akinetic-/rigid-related networks in Parkinson's disease (PD). **Methods:** Tremor-dominant (TD) and akinetic-/rigid-dominant (ARD) PD patients were recruited and scanned by resting-state functional MRI. Functional connectivity from the Vim nucleus was analyzed. **Results:** In the TD patients, the Vim nucleus exhibited increased connectivity with the cerebellum/dentate nucleus, primary motor cortex (M1), supplementary motor area (SMA), premotor cortex, thalamus, globus pallidus, putamen, and parietal cortex compared with the controls, while the connections between the Vim nucleus and M1 and cerebellum/dentate nucleus had positive correlations with the tremor scores. In the ARD patients, the Vim nucleus only showed enhanced connectivity with the globus pallidus and limbic lobe compared with the controls, and no connectivity showed correlation against the akinetic-rigidity scores. TD patients had increased connectivity with the Vim nucleus in the cerebellum, M1, SMA, thalamus, globus pallidus, putamen, and parietal cortex compared with ARD patients. **Conclusions:** This study demonstrates that the Vim nucleus has an important role in the tremor-related network, but not in the akinetic-/rigid-related network. Our finding is helpful to explain the selective effect of Vim deep brain stimulation in PD.

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Introduction

Parkinson's disease (PD) is characterized by bradykinesia, tremor, rigidity, and gait disturbance. Based on the predominant motor symptoms, PD can be classified into tremor-dominant (TD; primary tremor with minimal rigidity, bradykinesia, and other symptoms) and akinetic-/rigid-dominant (ARD; primary rigidity and bradykinesia with minimal tremor) subtypes. Pathophysiological mechanisms underlying these two subtypes are different [1]. The generation of parkinsonian tremor has been associated with dysfunction of cerebello-thalamo-cortical pathway [2–4]. It suggests that the parkinsonian tremor is triggered from the basal ganglia and driven from the cerebello-thalamo-cortical pathway [5]. In contrast, the akinetic/rigid manifestations of PD are closely linked to functionally impaired cortico-basal ganglia-thalamo-cortical motor circuits [6].

The thalamus is involved in the pathophysiology of both TD and ARD subtypes. However, the role of the thalamus in these two subtypes remains not well understood. For example, it has been recognized that the ventral intermediate nucleus of thalamus (Vim) is involved in the tremor [4,5]. In contrast, whether the Vim has a role in the ARD subtype has not been investigated. The Vim is a cerebellar relay nucleus, but not a basal ganglia relay nucleus [7]. It is logical to speculate that the Vim nucleus has a key role in the tremor-related network, but not in the akinetic-/rigid-related network. However, this assumption has not been examined yet.

Resting-state functional MRI (rsfMRI) is a noninvasive method to investigate brain activity and neural network connectivity. This method is increasingly used in PD and has been proven helpful for our understanding of the pathophysiology of PD [5,8–10]. In the current study, we applied rsfMRI to investigate the involvement

of Vim nucleus in the tremor- and akinetic-/rigid-related networks. This work will provide new insights on our knowledge of the role of Vim nucleus in PD.

Materials and Methods

Subjects

This study included 84 PD patients (42 TD and 42 ARD patients) and 42 healthy control subjects. The diagnosis of PD was made by an experienced neurologist based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [11]. The UPDRS (Unified Parkinson's Disease Rating Scale) [12], the Hoehn and Yahr disability scale [13], and mini-mental state examination (MMSE) were assessed in PD patients while off their medications. The MMSE was ≥ 27 in all patients. The experiments were performed according to the Declaration of Helsinki and were approved by the Institutional Review Board. All subjects participated in this study had written informed consent.

The classification of TD and ARD was based on a numerical ratio which was derived from a patient's mean tremor score and mean akinetic-rigidity score [14–16]. The seven-item tremor scale was assessed in UPDRS: resting tremor of the head and four limbs (five items), as well as postural tremor of the right and left hands (two items). The akinetic-rigidity scale was composed of 12 items of UPDRS which included passive range of motion rigidity of the neck and each extremity (five items), hand movements (one item), finger taps (one item), arising from a chair (one item), posture (one item), gait (one item), postural instability (one item), and truncal bradykinesia and hypokinesia (one item). Each item was rated from 0 to 4, as the symptoms aggravate gradually. The mean of each scale was computed, and then, the ratio (mean TD/mean ARD score) was determined. Concur with previous studies, TD was defined with a ratio >1.0 , whereas ARD was defined with a ratio <0.8 . In this study, the average ratio for TD patients was 1.56 ± 0.58 (range 1.03–3.43) and for ARD patients was 0.27 ± 0.26 (range 0–0.76). The demographics and clinical data of the subjects are shown in Table 1. No significant differences were observed among the three groups in age, gender, and MMSE score. In addition, no significant differences in disease duration, UPDRS motor score, the Hoehn and Yahr stage, and levodopa daily dosage were found between the TD and ARD groups.

Data Acquisition

Scans were performed on a 3T MR scanner at Xuanwu hospital (Triosystem; Siemens Magnetom scanner, Erlangen, Germany). PD patients were scanned only after their medication had been withdrawn for at least 12 h. A standard head coil was used with foam padding to reduce head motion. Participants would be excluded if the clinically silent lesions were detected in high-resolution axial T1- and T2-weighted images.

High-resolution anatomical images were obtained by using 3D-MPRAGE sequences (TR = 2000 ms, TE = 2.19 ms, 176 sagittal slices, 1 mm slice thickness, field of view [FOV] = 224 mm \times 256 mm). fMRI data were acquired with gradient-echo echo-planar sequences (TR = 2000 ms, TE = 40 ms, 32 axial slices, 3.5 mm thickness, gap = 0, Flip angle = 90°,

Table 1 Demographics and clinical data of the subjects

	TD (n = 42)	ARD (n = 42)	Control (n = 42)
Age (years)	60.26 \pm 7.78	62.35 \pm 8.12	62.12 \pm 8.01
Sex	25 M, 17 F	24 M, 18 F	24 M, 18 F
Disease duration (years)	4.78 \pm 3.82	5.41 \pm 3.36	–
UPDRS III (off medication)	19.52 \pm 7.24	20.32 \pm 6.89	–
H&Y (off medication)	1.89 \pm 0.64	1.95 \pm 0.71	–
MMSE	28.68 \pm 1.59	28.36 \pm 1.73	29.02 \pm 1.32
Levodopa dosage (mg/day)	344.76 \pm 143.89	388.72 \pm 161.09	–
Tremor score	5.93 \pm 3.41	–	–
Akinetic-rigidity score	–	11.92 \pm 6.14	–

TD, tremor-dominant; ARD, akinetic-/rigid-dominant; M, male; F, female; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr Staging; MMSE, mini-mental state examination. Data are presented as mean \pm SD.

FOV = 256 mm \times 256 mm, matrix size = 64 \times 64). During the fMRI scanning, subjects were instructed to keep awake with eyes closed, and not think of anything. The fMRI scanning session lasted for 8 min.

Data Analysis

Data Preprocessing

Each fMRI time-series data contained 240 time points. The first 10 time points were discarded owing to the instability of the initial MRI signal and the adaptation of the subjects to the environment. The rest of the images were preprocessed using Statistical Parametric Mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) and Data Processing Assistant for Resting-State fMRI (DPARSF V2.0 Advanced Edition, <http://rfmri.org/DPARSF>) [17]. Time-series data were first corrected for slice time and aligned to the first image for motion correction. Each subject's head motion parameters were examined. Of all the subjects, no one had more than 1.5 mm maximum translation in *x*, *y*, or *z*, or 1.5° of maximum angular motion in the three axes. After correction, functional images of each subject were coregistered to anatomical images and spatially normalized into the standard Montreal Neurological Institute (MNI) brain space. The nuisance covariates of head motion parameters, cerebrospinal fluid signal, and white matter signal were regressed out. All images were then resampled into 3 \times 3 \times 3 mm³ voxels and smoothed with a 4 mm full width at half maximum Gaussian kernel. After linear drift was removed, a temporal filter (0.01–0.1 Hz) was applied to remove very low-frequency drifts and physiological high-frequency noise.

Definition of Regions of Interest (ROIs)

The bilateral Vim nuclei were chosen as the regions of interest (ROIs) for functional connectivity analysis. The centers of the

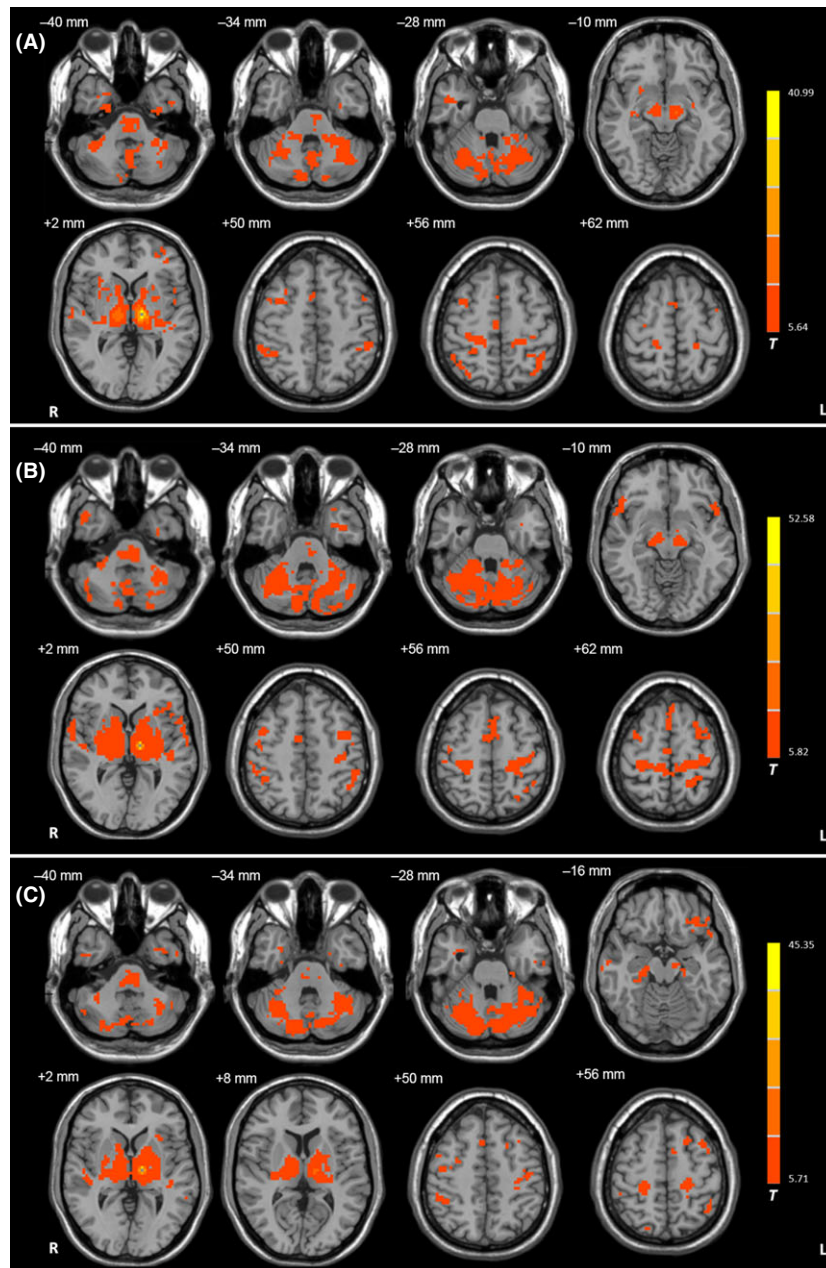


Figure 1 Functional connectivity in the left Vim nucleus. Brain regions showing significant connectivity with the left Vim nucleus in the resting state in (A) healthy control subjects, (B) tremor-dominant (TD), and (C) akinetic-rigid-dominant (ARD) patients (one-sample t -test, $P < 1 \times 10^{-5}$, FDR corrected). T value bar is shown on the right. Abbreviations: L, left; R, right.

ROIs were located at $x = -11.9$, $y = -15.2$, $z = 3.96$ (left) and $x = 12.4$, $y = -14.1$, $z = 3.61$ (right) according to a recent study [18], which defined the coordinates of the Vim nucleus from a high-resolution histological atlas [19] transformed using nonlinear deformation into Colin27 MRI space. This atlas follows neurosurgical labeling conventions as defined by Schaltenbrand and Wahren [20] and Hirai and Jones [7] and has been validated inter-operatively [21]. The radius of the ROIs was chosen as 1 mm.

Network Connectivity Analysis

Functional connectivity was analyzed using the REST Toolkit (<http://restfmri.net/forum/REST>) [22]. Firstly, by averaging the time courses within each ROI, we could obtain the seed reference time course. Subsequently, correlation analysis was performed in a voxel-wise manner between the seed reference and the whole brain. The individual correlation coefficients were further

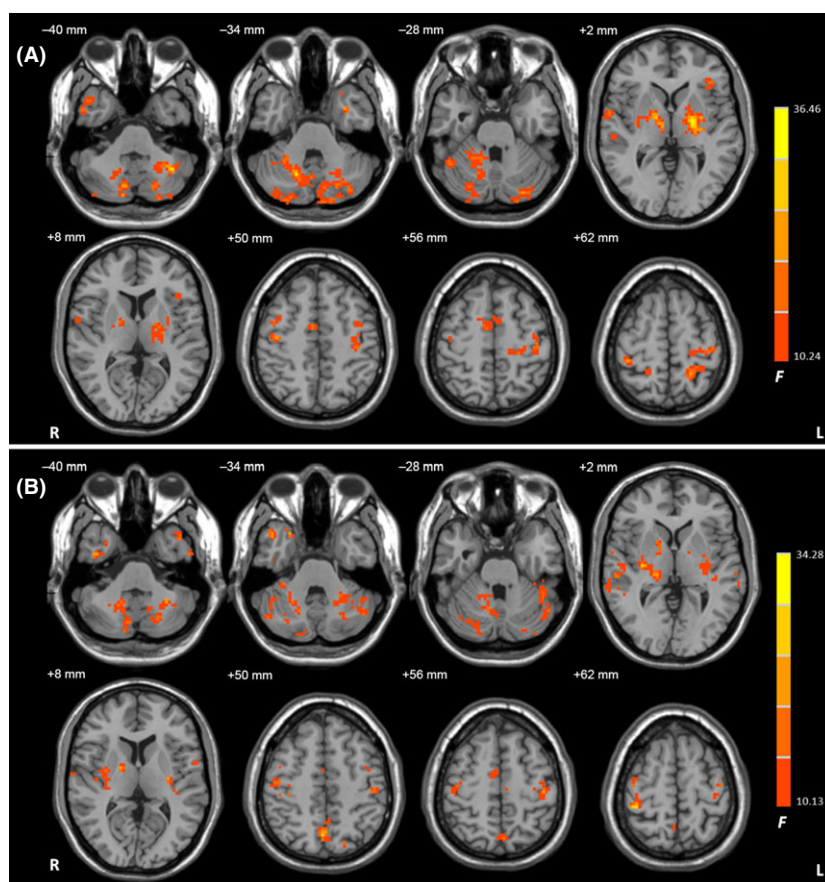


Figure 2 The results of ANCOVA. Brain regions showing significant differences in connectivity among the TD, ARD, and control groups in the left (A) and right (B) Vim nucleus (ANCOVA, $P < 0.05$, FDR corrected). *F* value bar is shown on the right. Abbreviations: L, left; R, right.

transformed to *z*-values using the Fisher *r*-to-*z* transformation. One-sample *t*-test was applied to investigate functional connectivity within each group. A one-way analysis of covariance (ANCOVA) was performed to examine differences of connectivity in each ROI among the three groups, with age and gender taken as covariant factors. A subsequent *post hoc* analysis was applied to explore the differences between the groups. In addition, a correlation analysis of functional connectivity results against the tremor scores in the TD group, or against the akinetic-rigidity scores in the ARD group was performed to explore whether the interactions of brain networks correlate with the severity of clinical symptoms.

As functional connectivity analysis is sensitive to gross head motion [23], we further evaluated effect of head motion on our results. Imaging data were motion-corrected with FSL (<http://www.fmrib.ox.ac.uk/fsl>), and then the differences among the three groups were analyzed with the same method described above.

Results

In all groups, the Vim nucleus had functional connectivity with the primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), parietal cortex, temporal lobe, thala-

mus, globus pallidus, putamen, cerebellum, midbrain, and pons (one-sample *t*-test, $P < 1 \times 10^{-5}$, false discovery rate (FDR) corrected; Figure 1). There were significant differences in connectivity among the TD, ARD, and control groups in the M1, PMC, SMA, parietal cortex, temporal lobe, putamen, globus pallidus, thalamus, and cerebellum (ANCOVA, $P < 0.05$, FDR corrected; Figure 2). Compared with the controls, TD patients exhibited increased connectivity with the Vim nucleus in several areas, including the cerebellum, M1, SMA, PMC, thalamus, globus pallidus, putamen, and parietal cortex (*post hoc* analysis, $P < 0.05$, FDR corrected; Figure 3A and Table 2). In contrast, ARD patients only showed enhanced connectivity with the Vim nucleus in the globus pallidus and limbic lobe compared with the controls (*post hoc* analysis, $P < 0.05$, FDR corrected; Figure 3B and Table 2). TD patients had increased connectivity with the Vim nucleus in the cerebellum, M1, SMA, thalamus, globus pallidus, putamen, and parietal cortex compared with ARD patients (*post hoc* analysis, $P < 0.05$, FDR corrected; Figure 3C).

The connections between the Vim nucleus and M1 and cerebellum had positive correlations with the tremor scores in the TD group (correlation analysis, $P < 0.05$, FDR corrected; Figure 4 and Table 3). In contrast, no connectivity showed significant correlation against the akinetic-rigidity scores in the ARD group.

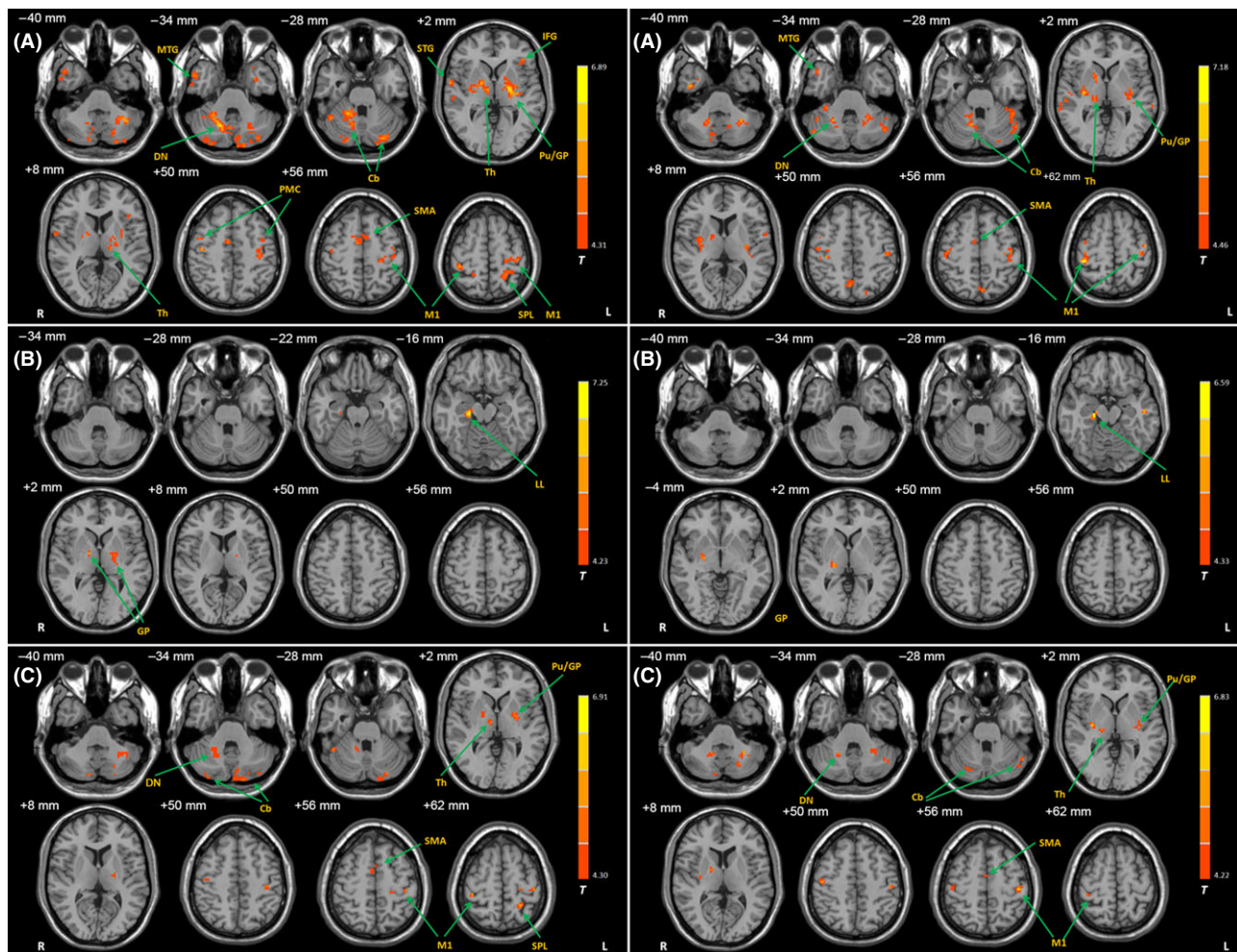


Figure 3 Differences of functional connectivity with the Vim nucleus between the groups. Brain regions showing significant increased connectivity with the left (left column) and right (right column) Vim nucleus in the TD patients compared with healthy controls (A), in the ARD patients compared with healthy controls (B), and in the TD patients compared with ARD patients (C). *post hoc* analysis, $P < 0.05$, FDR corrected. *T* value bars are shown on the right. Abbreviations: L, left; R, right; Cb, cerebellum; DN, dentate nucleus; GP, globus pallidus; IFG, inferior frontal gyrus; LL, limbic lobe; M1, primary motor cortex; MTG, middle temporal gyrus; PMC, premotor cortex; Pu, putamen; SMA, supplementary motor area; SPL, superior parietal lobule; Th, thalamus.

After motion-corrected with FSL, compared with controls, TD patients had increased connectivity with the cerebellum, M1, SMA, PMC, thalamus, globus pallidus, putamen, and parietal cortex; ARD patients showed enhanced connectivity with the globus pallidus and limbic lobe. In addition, TD patients had increased connectivity with the cerebellum, M1, SMA, thalamus, globus pallidus, putamen, and parietal cortex compared with ARD patients (*post hoc* analysis, $P < 0.05$, FDR corrected; Figure 5).

Discussion

In the current study, we investigated functional connectivity in the Vim nucleus in TD and ARD subtypes of PD. We have shown that the involvement of Vim nucleus in the tremor- and akinetic-/rigid-related networks is different. In the TD

patients, the Vim nucleus had enhanced connectivity with the cerebellum, M1, SMA, PMC, thalamus, globus pallidus, putamen, and parietal cortex compared with healthy controls, while the connections between the Vim nucleus and M1 and cerebellum positively correlated with the tremor scores. In contrast, the Vim nucleus only had increased connectivity with the globus pallidus and limbic lobe in the ARD patients. Our findings demonstrate that the Vim nucleus is important in the tremor-related network, but not in the akinetic-/rigid-related network in PD.

The Vim Nucleus in the Tremor-Related Network

The Vim nucleus functionally connected with extensive regions, including the M1, SMA, PMC, parietal cortex, globus pallidus, putamen, cerebellum, midbrain, and pons in all groups

Table 2 The difference of functional connectivity between PD patients and controls

Group	Brain region	Brodmann area	MNI coordinates			t Value	Cluster size (mm ³)
			x	y	z		
TD > Control	R Precentral Gyrus	4	41	-14	52	5.03	486
	L M1	4	-35	-26	62	5.59	2808
	R M1	4	37	-31	60	5.82	945
	L Superior Parietal Lobule	5	-22	-47	64	5.31	2376
	R Superior Parietal Lobule	5	21	-46	62	4.64	324
	L PMC	6	-39	-2	51	4.50	432
	R PMC	6	43	0	48	4.67	351
	R SMA	6	7	-4	56	5.27	1944
	R Middle Temporal Gyrus	21	53	7	-32	5.04	1134
	R Superior Temporal Gyrus	21	56	-23	-2	4.59	432
	R Superior Temporal Gyrus	22	62	-2	4	5.57	918
	L Limbic Lobe	28	-25	3	-30	4.47	486
	L Inferior Frontal Gyrus	47	-40	29	4	4.87	702
	L Thalamus, Pulvinar	-	-15	-23	8	5.23	513
	R Thalamus, Ventral Lateral Nucleus	-	9	-11	3	5.85	756
	L Globus Pallidus	-	-20	-11	3	6.89	2727
	R Globus Pallidus	-	18	-2	2	6.06	918
	L Putamen	-	-30	-2	9	4.79	378
	R Putamen	-	31	-5	4	5.11	567
	L Cerebellum, Posterior Lobe, Declive	-	-30	-84	-24	6.49	5859
	L Cerebellum, Posterior Lobe, Tonsil	-	-27	-54	-42	5.74	3132
	R Cerebellum, Anterior Lobe, Culmen	-	21	-47	-28	6.03	2511
	R Cerebellum, Anterior Lobe, Dentate	-	18	-62	-34	6.41	6345
R Cerebellum, Posterior Lobe, Uvula	-	30	-88	-32	5.23	1485	
ARD > Control	R Limbic Lobe	35	21	-21	15	7.25	729
	L Globus Pallidus	-	-20	-9	3	4.95	1107
	R Globus Pallidus	-	17	-6	4	5.71	324

L, left; R, right; ARD, akinetic-/rigid-dominant; TD, tremor-dominant; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area. The results are the comparison of functional connectivity in the left Vim nucleus between subtypes of PD patients and controls (*post hoc* analysis, $P < 0.05$, FDR corrected).

(Figure 1), which is largely consistent with a recent report [18]. The Vim nucleus had enhanced connectivity with the cerebellum/dentate nucleus in the TD patients compared with healthy controls (Figure 3A and Table 2). Moreover, this connectivity was correlated with the severity of parkinsonian tremor (Figure 4). The Vim nucleus chiefly receives excitatory glutamatergic input from the cerebellum/dentate nucleus [24]. And the dentate nucleus, acting as a major output source of cerebellar, projects to the motor, premotor, prefrontal, and parietal areas of cortex [25]. As described previously, dysfunction of cerebello-thalamo-cortical pathway has been recognized to play a critical role in parkinsonian tremor genesis [2–5]. The parkinsonian tremor is associated with an increased metabolism in the cerebellum/dentate nucleus [4], which could be reduced by deep brain stimulation (DBS) of Vim [4,26]. Our findings indicate that the enhanced Vim–cerebellum/dentate nucleus connectivity is associated with parkinsonian tremor; this connectivity is more strengthened as tremor becomes more severe.

Increased connectivity is found between the Vim nucleus and cortical motor regions, for example, the M1, SMA, and

PMC in TD patients (Figure 3A and Table 2). The Vim nucleus sends excitatory glutamatergic efferents to cortical motor regions. These cortical motor regions have been identified involving in tremor-related network [2–4,27]. The M1 has been suggested as the cortical area that drives the spinal motor neuron pool in parkinsonian tremor; meanwhile, the activity in PMC and SMA primarily projects to the M1 [3]. Vim DBS could reduce the metabolism in the M1 [4,26], which further suggests the treatment pathology of Vim DBS in PD tremor.

In addition, the Vim nucleus had increased connectivity with the globus pallidus and putamen in the TD patients compared with controls (Figure 3A and Table 2). As the Vim nucleus does not receive direct projections from the basal ganglia [28], the functional connectivity between the Vim nucleus and basal ganglia should via other regions, for example, cortical motor cortex. Our finding is consistent with a previous report that the basal ganglia (globus pallidus and putamen) had increased connectivity with the Vim–motor cortex–cerebellum circuit through the motor cortex in the TD patients [5].

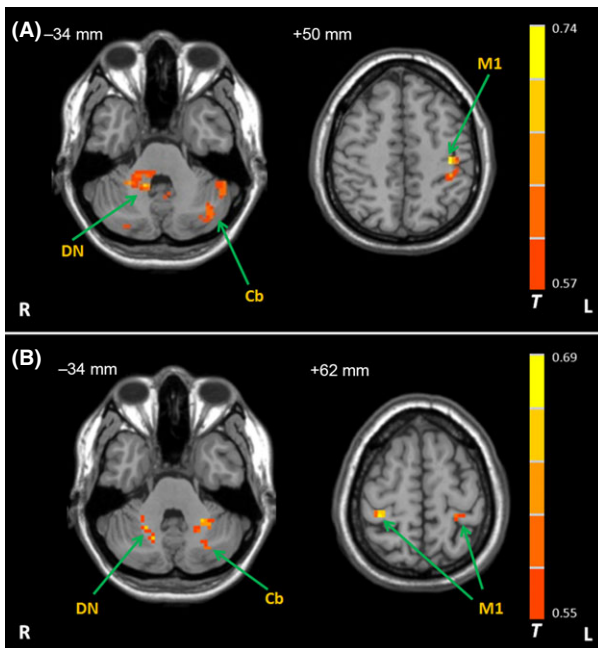


Figure 4 The results of correlation analysis. Brain regions showing significant correlation between connectivity results in the left (A) and right (B) Vim nucleus and tremor scores in TD patients (correlation analysis, $P < 0.05$, FDR corrected). T value bar is shown on the right. Abbreviations: L, left; R, right; Cb, cerebellum; DN, dentate nucleus; M1, primary motor cortex.

The Vim Nucleus in the Akinetic-/Rigid-Related Network

The Vim nucleus had enhanced connectivity only with the globus pallidus and limbic lobe in the ARD patients (Figure 3B and Table 2). Neuroimaging studies have shown that typical neural changes associated with akinesia include decreased activity in the putamen [29] and SMA [30], as well as increased activity in some other motor regions, like the PMC, parietal cortex, and cerebellum [31]. The SMA is acknowledged its key role in learning, planning and initiation a motor task [32]. The dysfunction of the SMA has been recognized as a crucial reason for akinesia [33]. The nature of the hyperactivation in these motor regions remains unclear. One likely explanation is that this phenomenon presents a functional compensation for the defective basal ganglia [31,34]. In the ARD patients, the Vim nucleus did not show any increased or decreased connectivity with these akinesia-related brain regions. Moreover, connectivity with the Vim nucleus showed no significant correlation against the akinetic-rigidity scores. These findings indicate that the Vim nucleus is not critical in the akinetic-/rigid-related network.

Vim DBS can immediately and almost completely suppress parkinsonian tremor [35], but has no effect on akinesia and rigidity. Vim DBS is considered only for TD and in the absence of pronounced rigidity or akinesia. Our finding showed that the Vim is heavily involved in the tremor-related network, but not in the

Table 3 Correlation between connectivity and tremor scores in the TD group

Brain region	Brodmann area	MNI coordinates			t Value	Cluster size (mm ³)
		x	y	z		
L Postcentral Gyrus	3	-37	-35	53	0.65	621
L M1	4	-38	-19	51	0.74	675
R Cerebellum, Anterior Lobe, Dentate	-	15	-45	-33	0.70	1863
L Cerebellum, Posterior Lobe, Tonsil	-	-52	-50	-38	0.61	1998
R Cerebellum, Anterior Lobe, Uvula	-	30	-83	-35	0.58	324

L, left; R, right; M1, primary motor cortex. Brain regions showed significant correlation between connectivity results in the left Vim nucleus and tremor scores in the TD group (correlation analysis, $P < 0.05$, FDR corrected).

akinetic-/rigid-related network provides a reasonable explanation why Vim DBS has a selective effect on different subtypes of PD.

The results before and after motion correction were largely consistent (Figures 3 and 5). In the current study, we have carefully examined head motion in our subjects; no one had more than 1.5 mm maximum translation in x , y , or z , or 1.5° of maximum angular motion in the three axes. In addition, head motion was corrected with DPARSF. Thus, head motion had no significant influence on our results.

A limitation of this study is that tremor in PD patients may have influence on our results. Future studies with simultaneous electromyography monitoring during fMRI scanning may help to regress out the influence of tremor. Another limitation is that we included both TD and ARD subtypes; most patients participated in this study did not receive Vim DBS. Thus, the effect of Vim DBS on the pattern of functional connectivity in the Vim nucleus was not examined. This will need to be investigated in future studies.

In conclusion, this study demonstrates that the Vim nucleus has a critical role in the tremor-related network, but not in the akinetic-/rigid-related network. Our finding is helpful to explain why Vim DBS can significantly improve tremor, but has no effect on akinesia and rigidity in PD.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

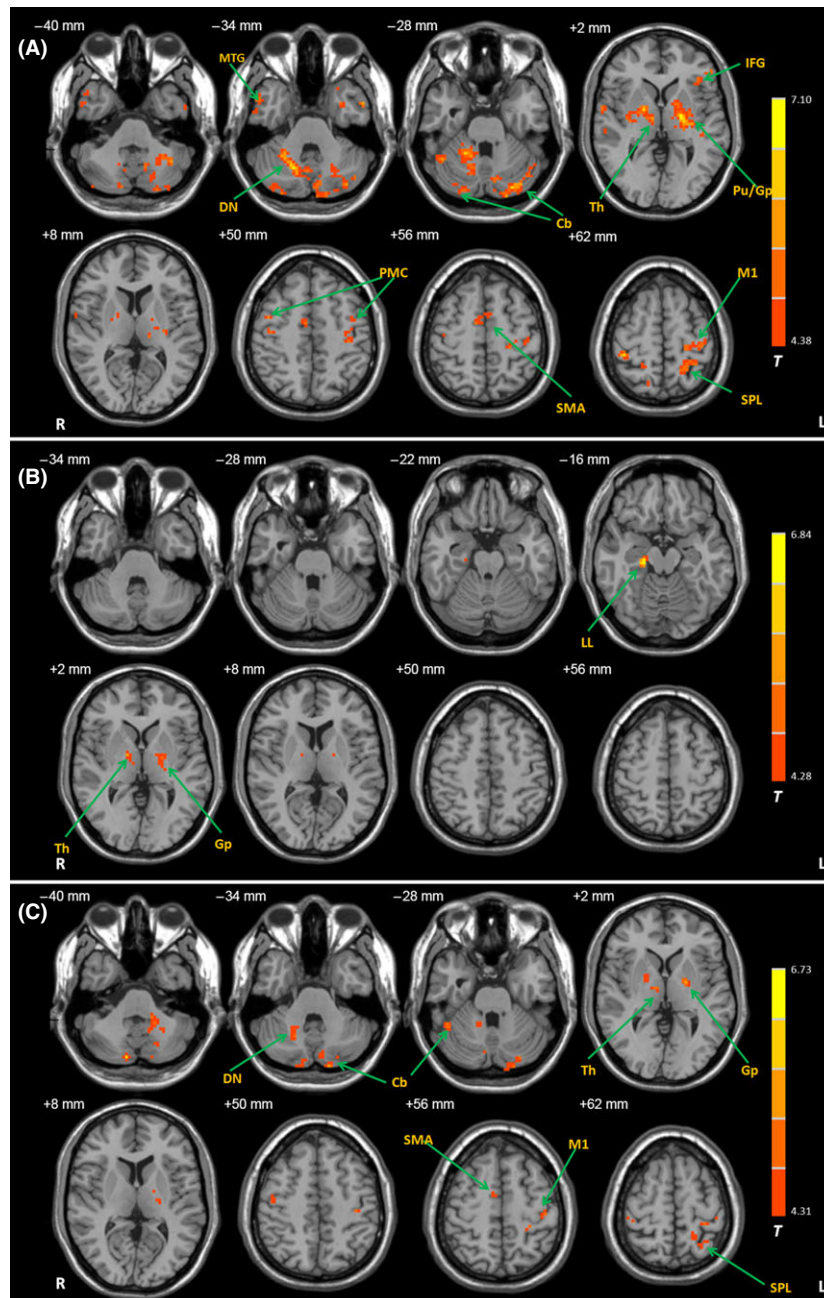


Figure 5 Differences of functional connectivity with the Vim nucleus between the groups after motion correction. Brain regions showing significant increased connectivity with the left Vim nucleus in the TD patients compared with healthy controls (**A**), in the ARD patients compared with healthy controls (**B**), and in the TD patients compared with ARD patients (**C**). Imaging data were motion-corrected with FSL. *post hoc* analysis, $P < 0.05$, FDR corrected. T value bars are shown on the right. Abbreviations: L, left; R, right; Cb, cerebellum; DN, dentate nucleus; GP, globus pallidus; IFG, inferior frontal gyrus; LL, limbic lobe; M1, primary motor cortex; MTG, middle temporal gyrus; PMc, premotor cortex; Pu, putamen; SMA, supplementary motor area; SPL, superior parietal lobule; Th, thalamus.

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