Brain Functional Specialization and Cooperation in Parkinson's Disease

Jinmei Sun

First Affiliated Hospital of Anhui Medical University <https://orcid.org/0000-0002-9295-2759>

Xiaoran Gao

Anhui Medical University

Qiang Hua

Anhui Medical University

Rongrong Du

Anhui Medical University

Pingping Liu

First Affiliated Hospital of Anhui Medical University

Tingting Liu

First Affiliated Hospital of Anhui Medical University

Jinying Yang

USTC: University of Science and Technology of China

Bensheng Qiu

USTC: University of Science and Technology of China

Gong-Jun Ji

First Affiliated Hospital of Anhui Medical University

Panpan Hu

First Affiliated Hospital of Anhui Medical University

Kai Wang (✉ wangkai1964@126.com)

First Affiliated Hospital of Anhui Medical University

Research Article

Keywords: Parkinson's disease, resting-state functional magnetic resonance imaging, cerebral specialization, inter-hemispheric cooperation

Posted Date: July 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-424088/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Brain Imaging and Behavior on August 24th, 2021. See the published version at <https://doi.org/10.1007/s11682-021-00526-4>.

Abstract

Background: Cerebral specialization and inter-hemispheric cooperation are two of the most prominent functional architectures of the human brain. Their dysfunctions may be related to pathophysiological changes in patients with Parkinson's disease (PD), who are characterized by unbalanced onset and progression of motor symptoms.

Objective: This study aimed to characterize the two intrinsic architectures of hemispheric functions in PD using resting-state functional magnetic resonance imaging.

Methods: Seventy idiopathic PD patients and 70 age-, sex-, and education-matched healthy subjects were recruited. All participants underwent magnetic resonance image scanning and clinical evaluations. The cerebral specialization (Autonomy index, AI) and inter-hemispheric cooperation (Connectivity between Functionally Homotopic voxels, CFH) were calculated and compared between groups.

Results: Compared with healthy controls, PD patients showed stronger AI in the left angular gyrus. Specifically, this difference in specialization resulted from increased functional connectivity (FC) of the ipsilateral areas (e.g., the left prefrontal area), and decreased FC in the contralateral area (e.g., the right supramarginal gyrus). Imaging-cognitive correlation analysis indicated that these connectivity were positively related to the score of Montreal Cognitive Assessment in PD patients. CFH between the bilateral sensorimotor regions was significantly decreased in PD patients compared with controls. No significant correlation between CFH and cognitive scores was found in PD patients.

Conclusions: This study illustrated a strong leftward specialization but weak inter-hemispheric coordination in PD patients. It provided new insights to further clarify the pathological mechanism of PD.

1. Background

Cerebral specialization and inter-hemispheric cooperation are two of the most prominent functional architectures of the human brain, which can prevent the occurrence of conflicting signals and thus allows more efficient information processing (Chi et al., 1977; Gazzaniga, 2000; Moorman and Nicol, 2015; Stark et al., 2008; Toga and Thompson, 2003). Specialization and cooperation are mutually reinforcing and inseparable. Typically, language is lateralized to the left hemisphere such that inter-hemispheric competitions between muscles that control speech are avoided (Toga and Thompson, 2003). However, in the process of listening to a story, predictive inferences initially activated in the right hemisphere (RH) and following coherence inferences are completed in the left hemisphere (LH). This indicates that bilateral hemispheres process semantic information differently, but must share some information (Beeman et al., 2000). A similar mechanism in the motor system is also important for supporting bilateral motor function, and its disruption may involve the pathological mechanism of movement disorders (Beaulé et al., 2012).

Parkinson's disease (PD) is one of the most common movement disorders, mainly manifested as resting tremors, rigidity, bradykinesia, and postural instability. These symptoms may be initially caused by the depletion of nigrostriatal dopamine (Hornykiewicz, 2006). Although the mechanism involving the dopamine deficit on behavior symptoms is still unknown, the unbalanced onset and progression of motor symptoms suggest an important role of brain functional specialization or cooperation in the development of PD (Cronin-Golomb, 2010; Kempster et al., 1989). In past decades, increasing studies have concentrated on these functions of PD.

Abnormal cerebral specialization in PD has been shown in studies from molecular biology and neuroimaging. For example, the asymmetry of DNA methylation in prefrontal cortex neurons is greater in PD patients than healthy controls, and has been linked to the disease course (Li et al., 2020). Diffusion tensor imaging studies also indicate abnormal structural asymmetry of the bilateral substantia nigra in PD patients (Prakash et al., 2012). However, resting-state functional magnetic resonance imaging (rs-fMRI) did not find abnormal hemispheric specialization in PD patients (Wu et al., 2020). Notably, this negative report was based on the region-of-interest level, which may not be sensitive to small volume abnormalities. Autonomy index (AI) is a novel measure of functional specialization that can be performed at the voxel level. More importantly, this connectome-based index does not always rely on structurally symmetric regions, thereby avoiding the potential bias of anatomical asymmetry. AI has been suggested as a reliable measurement for characterizing the functional specialization in both healthy and patient cohorts (Mueller et al., 2015; Wang et al., 2014a).

Inter-hemispheric cooperation reflects the ability to integrate information from bilateral hemispheres. Complex tasks, including sensory processing and motor control are dependent on information integration of homotopic regions (Davis and Cabeza, 2015). It has been suggested that the uncoordinated control of gait in PD is related to impaired inter-hemispheric cooperation (Li et al., 2018). In fMRI studies, this measure is usually quantified by the functional connectivity (FC) between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere (Zuo et al., 2010). However, bilateral hemispheres are actually anatomically asymmetric (LeMay, 1976). Investigators have normalized the individual's brain into a symmetry atlas, which may produce unexpected bias. A better choice is defining the homotopic regions based on functional rather than structural features (Jo et al., 2012). The advantages of functional correspondences have been clearly demonstrated by the ability to characterize precise cross-hemispheric cortical maps (Jo et al., 2012).

In the present study, we aimed to explore two intrinsic architectures of brain function in patients with PD. To this end, we adopted AI to estimate cerebral specialization, and developed a novel index of inter-hemispheric cooperation involving the connectivity between functionally homotopic voxels (CFH). The functional homotopic region of a given voxel was defined as the point with the largest FC value in the contralateral hemisphere. Regions with higher CFH values indicated more communication across hemispheres.

2. Materials And Methods

2.1 Participants

This study included 70 idiopathic PD patients recruited from the First Affiliated Hospital of Anhui Medical University. The inclusion criteria were as follows: 1) a diagnosis of idiopathic PD according to the United Kingdom Brain Bank Criteria, 2) ages between 42 and 80 years, and 3) a Hoehn and Yahr (H-Y) disease stage ≤ 3 . Exclusion criteria included: 1) a history of head injury or addiction, 2) psychiatric or neurological disease other than PD, and 3) head motion exceeding 3 mm in translation or 3° in rotation during the fMRI scanning. All patients underwent neurological assessment by a clinician, which consisted of the Unified Parkinson's Disease Rating Scale III (UPDRS-III) and the H-Y stage. Symptoms of 67 patients were assessed after medication withdrawal for at least 12 h ("OFF" state); the other three patients were assessed without medication withdrawal ("ON" state). Moreover, 70 age-, sex-, education-, and cognitive function-matched healthy controls (HCs) with no psychiatric and neurological history were enrolled from the local community (Table 1). This study protocol was reviewed and approved by the Medical Ethics Committee of Anhui Medical University. Written informed consent was obtained from all participants after full explanation of the procedures involved.

Table 1
Demographic and clinical features

	PD	HC	Statistics	p value
Sample size (M/F)	35/35	33/37	0.11	0.74 ^a
Age (years)	59.1 ± 8.26	60.6 ± 8.36	NA	0.39 ^b
Education (years)	8.6 ± 4.39	9.7 ± 3.91	1.47	0.14 ^c
MoCA	24.5 ± 4.15	24.6 ± 2.95	NA	0.53 ^b
Duration (years)	4.4 ± 3.36	NA	NA	NA
UPDRS-III	30.5 ± 10.46	NA	NA	NA
H-Y	1.7 ± 0.56	NA	NA	NA
Data are expressed as the mean ± SD.				
^a Chi-square test; ^b Mann-Whitney test; ^c two-sample <i>t</i> -test.				
Abbreviations: F = female; HC = healthy control; H-Y = Hoehn and Yahr stage; M = male; MoCA = Montreal Cognitive Assessment; NA = not available; PD = Parkinson's Disease; UPDRS = Unified Parkinson's Disease Rating Scale.				

2.2 MRI data acquisition

All functional and structural MRI datasets were obtained at the University of Science and Technology of China with a 3-T scanner (Discovery 750; GE Healthcare, Milwaukee, WI, USA). Foam padding and

headphones were used to attenuate scanner noise and restrain head motion. During resting-state fMRI scanning, participants were instructed to lie quietly with their eyes closed and without falling asleep. Functional images (217 volumes) were acquired using an echo-planar imaging sequence (repetition/echo time: 2,400/30 ms; flip angle: 90°). Images of 46 transverse slices (field of view: 192 mm × 192 mm²; matrix: 64 × 64; slice thickness, 3 mm with no inter-slice gap; voxel size, 3 mm × 3 mm × 3 mm) parallel to the anteroposterior commissure line were acquired. Subsequently, high spatial resolution T1-weighted anatomic images were acquired with the following parameters: (repetition/echo time: 8.16/3.18 ms; flip angle: 12°; field of view: 256 × 256 mm²; matrix: 256 × 256; slice thickness: 1 mm, with no inter-slice gap; and voxel size: 1 × 1 × 1 mm³; 188 slices).

2.3 RS-fMRI data preprocessing

Functional images were preprocessed using DPARSF (Chao-Gan and Yu-Feng, 2010), REST (Song et al., 2011), and SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>). The first five volumes were deleted to exclude the influence of unstable longitudinal magnetization. The remaining steps were as follows: slice timing, realignment; co-registering T1 to functional images; normalizing T1 to the MNI space and segmenting it into gray matter, white matter, and cerebrospinal fluid by Diffeomorphic Anatomical Registrations through Exponentiated Lie Algebra (Ashburner, 2007); smoothing functional images with a 4-mm full width at half-maximum isotropic Gaussian kernel; regressing out nuisance signals including 24 head-motion parameters, mean signals in the whole brain, white matter, and CSF; and filtering temporal bandpass (0.01–0.1 Hz). Acquisitions were discarded if their head motion exceeded 3 mm of translation or 3° of rotation during the fMRI scanning.

2.4 AI calculation

The AI [15] was calculated in the whole brain according to the following equation:

$$AI = Ni/Hi - Nc/Hc$$

The Ni and Nc are the numbers of voxels significantly correlated with a given voxel ($r > 0.25$, $p < 0.001$) in the ipsilateral and contralateral hemispheres, respectively. Hi and Hc are the total number of voxels in the ipsilateral and contralateral hemispheres, respectively. Ultimately, the AI map was obtained for each participant and used for the following analyses.

2.5 CFH computation

To overcome the flaws of traditional inter-hemispheric connectivity based on structurally symmetric regions, we computed the connectivity between functionally homotopic regions. Briefly, there were two steps: 1) Define homotopic regions. For a given voxel, we performed seed to whole brain functional connectivity analysis and averaged the result maps across all participants. The voxel with the maximal connectivity value in the contralateral hemisphere was defined as the homotopic voxel of the seed voxel. 2) Compute homotopic connectivity maps. The CFH value of each voxel was defined as its Pearson's

correlations with homotopic voxels in the contralateral hemisphere. The CFH map was finally divided by the mean value of the whole brain to improve the normality.

2.6 Statistical analysis

The demographic and clinical characteristics of the PD and HCs groups were compared using the two-sample *t*-test or Mann-Whitney U test according to the normality of data distribution.

To identify differences in cerebral specialization and inter-hemispheric cooperation, we compared AI and CFH maps between PD and HC groups within a grey matter mask (probability threshold > 0.2, from SPM12). The permutation test was performed in the comparison using the toolbox in SPM12, Statistic Non-Parametric Mapping (SnPM13) (Nichols and Holmes, 2002) with age, sex, and education as covariates. To control the family-wise error in multiple comparisons, we first set a voxel level threshold of $P < 0.001$. Then, only clusters larger than 29 voxels (AI analysis) and 17 voxels (CFH analysis) were reported as having survived the cluster-level correction, $P_{corr} < 0.05$.

AI and CFH of the clusters showing significant differences between PD and HCs groups were extracted to test their relationships with clinical variables (UPDRS-III score, disease duration, H-Y stage, and MoCA). Pearson's or Spearman's correlation was performed according to the normality of data distribution. A value of $P < 0.05$ was considered to be statistically significant.

3. Results

3.1 Demographic and clinical features

The demographic and clinical characteristics of the PD and HCs groups are summarized in Table 1. No significant group differences were observed in sex, age, MoCA scores, and level of education.

3.2 Differences in cerebral specialization

Functional specialization maps revealed similar patterns in patients and HCs (Fig. 1A and B). However, PD patients showed a statistically stronger AI in the left angular gyrus (AG) than HCs (Fig. 1C, peak *t*-value = 5.48, MNI coordinates = [-51, -63, 18], cluster size = 91 voxels). To show the connectivity change of left AG in detail, we further compared its whole brain functional connectivity between groups. Specifically, the seed was defined as a sphere centered at the left AG cluster, with a 6 mm radius. The resulting correlation coefficients were converted to z-scores using Fisher's z-transformation. The statistical method was the same as Sect. 2.6. Clusters larger than 37 voxels were reported as having survived the cluster-level correction, $P_{corr} < 0.05$. Although functional connectivity maps revealed similar patterns in patients and HCs (Fig. 2A and 2B), PD patients showed increased FC in the left middle orbitofrontal gyrus (MOFG), left middle frontal gyrus (MFG), left supplementary area (SMA), and decreased FC in the right supramarginal gyrus (SMG), left precentral gyrus (PreCG), and left postcentral gyrus (PostCG)(Fig. 2C, Table 2).

Table 2
Functional connectivity difference between the PD and HCs groups

Brain regions	MNI coordinates	Brodmann area	Voxel number	Peak t value
MOFG L	-39,45,-3	10/11	55	5.26
MFG L	-36,24,45	8	50	4.81
SMA L	-6,21,57	6/8	65	4.23
SMG R	45,-30,27	40	127	-4.76
PreCG L/PostCG L	-39,-24,66	6/4/3	38	-4.20
MFG L = left middle frontal gyrus; MNI = Montreal Neurological Institute; MOFG L = left middle orbitofrontal gyrus; PostCG L = left postcentral gyrus; PreCG L = left precentral gyrus; SMA L = left supplementary area; SMG R = right supramarginal gyrus				

3.3 Differences in inter-hemispheric cooperation

Inter-hemispheric cooperation maps showed a similar spatial distribution in the two groups (Fig. 3A and 3B). As compared to HCs, the PD group showed decreased CFH in the right sensorimotor region (Fig. 3C, peak t -value = 4.98, MNI coordinates = [42, -21, 51], cluster size = 21 voxels). The functional homotopic area of this cluster was in the left sensorimotor area (see Supplementary Materials for a detailed description).

3.4 Left- vs. right-dominant groups

To exclude the confounder of symptom lateralization, we used right- and left-side sub-scores from the UPDRS-III to divide the PD patients into two groups (including tremor, rigidity, finger taps, and leg agility) involving the left-dominant group (N = 27) (LD) and right-dominant group (N = 35) (RD). The sex, age, MoCA score, and level of education were matched between the two groups. No significant difference in AI or CFH was found between the groups.

3.5 Correlation with clinical variables

The AI in the left AG was negatively correlated with MoCA score in HCs ($r = -0.24$, $p = 0.04$) while it was not in the PD patients ($p = 0.20$, $p = 0.10$) and the z-test found significant differences in the correlation coefficient between the two groups ($z = 2.58$, $p = 0.01$).

The FC between the left AG with the left MOFG ($p = 0.28$, $p = 0.019$) and SMA ($p = 0.37$, $p = 0.0015$) were positively correlated with MoCA score in PD patients respectively, but not in HCs ($r = -0.21$, $p = 0.08$ for the left MOFG; $r = -0.10$, $p = 0.41$ for the left SMA) (Fig. 2D and 2E). In addition, the z-test found significant differences between the correlation coefficient in the two groups ($z = 2.9$, $p = 0.004$ for the left MOFG; $z = 2.83$, $p = 0.005$ for the left SMA).

Other results of PD versus HCs comparisons in AI and CFH were not related to any clinical variables, including UPDRSIII score, disease duration, H-Y stage, and MoCA ($p > 0.05$, see statistics in Supplementary Material Table S1)

4. Discussion

This study aimed to investigate cerebral specialization and inter-hemispheric cooperation in PD patients using two novel methods involving the AI and CFH, derived from rs-fMRI data. First, we found PD patients exhibited abnormally increased specialization in the left AG, when compared with HCs. Specifically, this alteration in specialization resulted from increased ipsilateral FC (e.g., the left SMA), and decreased contralateral FC (e.g., the right SMG). Second, we identified disrupted cooperation between the right sensorimotor region and its functionally homotopic area in PD patients. Overall, these findings revealed specific alterations of basic brain functional architecture in PD, which were important for understanding the pathophysiology mechanism of this disease.

4.1 Increased cerebral specialization

Cerebral specialization is a fundamental feature of the human brain. Both imaging and neuropathology have shown that the left nigrostriatal system was more susceptible to early degeneration in PD than the right side (Claassen et al., 2016; Prakash et al., 2012; Scherfler et al., 2012). In the present study, abnormal specialization was also found in the left hemisphere. The increased AI in the left AG was mainly caused by increased within-hemispheric connectivity and reduced cross-hemispheric connectivity. It suggested that information processing in the left AG was mainly within the hemisphere. AG is a multimodal association area involved in multiple mental processes. Dysfunction of the left AG may cause deficits in semantic processing (Price et al., 2015) and memory (Thakral et al., 2017), which are two common nonmotor symptoms of PD (Aarsland et al., 2017; Dashtipour et al., 2018). Previous studies have demonstrated that noninvasive brain stimulation techniques targeting the left AG and left parietal cortex could promote associative memory and semantic integration, respectively, in healthy subjects (Bjekić et al., 2019; Price et al., 2016; Wang et al., 2014b). The memory improvement was positively correlated to the FC increasing between the hippocampus and the stimulation target in the left AG (Wang et al., 2014b). Taken together, these findings suggested increased specialization of the left AG as a compensatory alteration after PD. Future studies may adopt the left AG as a potential target for promoting nonmotor symptoms of PD.

4.2 Decreased inter-hemispheric cooperation

Inter-hemispheric cooperation is an intrinsic functional architecture regulating precise performance. In the present study, we found abnormal decreased cooperation between the left and right sensorimotor areas. This is consistent to our previous meta-analysis suggesting the dysfunction of sensorimotor areas as a core pathological change in PD patients (Ji et al., 2018). Sensorimotor cortex is associated with numerous motor functions, such as motor imagery, movement preparation and planning, and execution. Its dysfunction in inter-hemispheric coordination has also been reported in other movement disorders, such

as stroke, and hemiparkinsonism(Wu et al., 2020). In studies developing novel therapies, the sensorimotor area has been identified as one of the most effective targets in repetitive transcranial magnetic stimulation (rTMS) treatment for alleviating motor symptoms of PD patients (Brys et al., 2016; Gonzalez-Garcia et al., 2011). Specifically, high frequency (usually elevating the cortical excitability) is recommended in these treatment protocols. However, the mechanism of rTMS in PD is still largely unknown. In the future, it would be interesting to determine whether inter-hemispheric cooperation will change the improvement of motor symptoms after rTMS treatment.

4.3 Limitations

There were some limitations in our work. First, although the MRI scanning and clinical examinations were conducted after withdrawing medicine overnight in most patients, the long-term effect of years of medicine consumption was unavoidable. In the future, changes of functional specialization and cooperation could be investigated in drug-naïve PD patients and in different stages of the disease. Second, although a relatively large sample population was included, this cross-sectional study could not causally relate our findings to the symptoms of PD. To address this issue, future studies should be designed in a longitudinal manner. Third, rs-fMRI signal is mixed with psychological noise. Regressing out average signal in white matter and CSF is a common way to elevate the signal-noise ratio. In our lab, global signal regression is a routine processing for resting-state functional connectivity analysis (Bai et al., 2019; Chen et al., 2019; Ji et al., 2019; Ji et al., 2020; Ji et al., 2017). However, it should be noted that there was no significant between-group difference in either AI or CFH, if we did not regress out average signals from white matter, CSF, and the whole brain in preprocessing.

5. Conclusions

This study demonstrated alterations of cerebral specialization and inter-hemispheric cooperation in PD patients using rs-fMRI. We found increased specialization in the left AG and decreased cooperation between bilateral sensorimotor regions in PD patients as compared to controls. Future magnetic stimulation studies may adopt the left AG as a potential target to promote nonmotor symptoms and the right sensorimotor region as a potential target to alleviate motor symptoms in PD. In summary, these findings provided new insights to clarify the pathological mechanism of PD, as well as suggesting potential therapeutic targets for future studies.

Declarations

Acknowledgements

The authors thank the participants for taking part in this study and thank Information Science Laboratory Center of USTC for the measurement services.

Author's contributions

All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, J.M.S., G.J.J., P.P.H., and K.W.; Data Acquisition, J.M.S., X.R.G., Q.H., R.R.D., P.P.L. and T.T.L.; Methodology, J.M.S., and G.J.J.; Writing – Original Draft, J.M.S.; Writing – Review & Editing, G.J.J., P.P.H. and K.W.; Formal Analysis, G.J.J.; Funding Acquisition, G.J.J., P.P.H., and K.W.; Resources, P.P.H., and K.W.; Supervision, J.Y.Y. and B.S.Q.

Funding

This study was funded by the National Natural Science Foundation of China, Grant/Award Numbers: 31970979, 81971689, 91432301, 81671354, 31571149, 91232717, and 81771456; the Doctoral Foundation of Anhui Medical University, Grant/Award Number XJ201532; the National Basic Research Program of China, Grant/Award Number 2015CB856405; the National Key R&D Plan of China, Grant/Award Number: 2016YFC1300604; the Collaborative Innovation Center of Neuropsychiatric Disorders and Mental Health of Anhui Province; and the Youth Top-notch Talent Support Program of Anhui Medical University.

Compliance with Ethical Standards

Ethical approval

This study protocol was reviewed and approved by the Medical Ethics Committee of Anhui Medical University.

Consent to Participate

The research protocol was performed according to the Helsinki Declaration of 1975 and approved by the Medical Ethics Committee of Anhui Medical University. Written informed consent was obtained from all participants after full explanation of the procedures involved.

Consent to publish

This manuscript has not been published elsewhere and the authors agree to publication in the journal.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Aarsland, D., Creese, B., Politis, M., Chaudhuri, K.R., Ffytche, D.H., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson disease. *Nat Rev Neurol*, 13, 217-231.
2. Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage*, 38, 95-113.
3. Bai, T., Wei, Q., Xie, W., Wang, A., Wang, J., Ji, G.J., Wang, K., & Tian, Y. (2019). Hippocampal-subregion functional alterations associated with antidepressant effects and cognitive impairments of electroconvulsive therapy. *Psychol Med*, 49, 1357-1364.
4. Beaulé, V., Tremblay, S., & Théoret, H. (2012). Interhemispheric control of unilateral movement. *Neural Plast*, 2012, 627816.
5. Beeman, M.J., Bowden, E.M., & Gernsbacher, M.A. (2000). Right and left hemisphere cooperation for drawing predictive and coherence inferences during normal story comprehension. *Brain Lang*, 71, 310-336.
6. Bjekić, J., Vulić, K., Živanović, M., Vujičić, J., Ljubisavljević, M., & Filipović, S.R. (2019). The immediate and delayed effects of single tDCS session over posterior parietal cortex on face-word associative memory. *Behav Brain Res*, 366, 88-95.
7. Brys, M., Fox, M.D., Agarwal, S., Biagioni, M., Dacpano, G., Kumar, P., Pirraglia, E., Chen, R., Wu, A., Fernandez, H., Wagle Shukla, A., Lou, J.S., Gray, Z., Simon, D.K., Di Rocco, A., & Pascual-Leone, A. (2016). Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease: A randomized trial. *Neurology*, 87, 1907-1915.
8. Chao-Gan, Y., & Yu-Feng, Z. (2010). DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. *Front Syst Neurosci*, 4, 13.
9. Chen, X., Ji, G.J., Zhu, C., Bai, X., Wang, L., He, K., Gao, Y., Tao, L., Yu, F., Tian, Y., & Wang, K. (2019). Neural Correlates of Auditory Verbal Hallucinations in Schizophrenia and the Therapeutic Response to Theta-Burst Transcranial Magnetic Stimulation. *Schizophr Bull*, 45, 474-483.
10. Chi, J.G., Dooling, E.C., & Gilles, F.H. (1977). Left-right asymmetries of the temporal speech areas of the human fetus. *Arch Neurol*, 34, 346-348.
11. Claassen, D.O., McDonnell, K.E., Donahue, M., Rawal, S., Wylie, S.A., Neimat, J.S., Kang, H., Hedera, P., Zald, D., Landman, B., Dawant, B., & Rane, S. (2016). Cortical asymmetry in Parkinson's disease: early susceptibility of the left hemisphere. *Brain Behav*, 6, e00573.
12. Cronin-Golomb, A. (2010). Parkinson's disease as a disconnection syndrome. *Neuropsychol Rev*, 20, 191-208.
13. Dashtipour, K., Tafreshi, A., Lee, J., & Crawley, B. (2018). Speech disorders in Parkinson's disease: pathophysiology, medical management and surgical approaches. *Neurodegener Dis Manag*, 8, 337-348.
14. Davis, S.W., & Cabeza, R. (2015). Cross-hemispheric collaboration and segregation associated with task difficulty as revealed by structural and functional connectivity. *J Neurosci*, 35, 8191-8200.
15. Gazzaniga, M.S. (2000). Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? *Brain*, 123 (Pt 7), 1293-1326.

16. Gonzalez-Garcia, N., Armony, J.L., Soto, J., Trejo, D., Alegria, M.A., & Drucker-Colin, R. (2011). Effects of rTMS on Parkinson's disease: a longitudinal fMRI study. *J Neurol*, 258, 1268-1280.
17. Hornykiewicz, O. (2006). The discovery of dopamine deficiency in the parkinsonian brain. *J Neural Transm Suppl*, 9-15.
18. Ji, G.J., Chen, X., Bai, T., Wang, L., Wei, Q., Gao, Y., Tao, L., He, K., Li, D., Dong, Y., Hu, P., Yu, F., Zhu, C., Tian, Y., Yu, Y., & Wang, K. (2019). Classification of schizophrenia by intersubject correlation in functional connectome. *Hum Brain Mapp*, 40, 2347-2357.
19. Ji, G.J., Hu, P., Liu, T.T., Li, Y., Chen, X., Zhu, C., Tian, Y., Chen, X., & Wang, K. (2018). Functional Connectivity of the Corticobasal Ganglia-Thalamocortical Network in Parkinson Disease: A Systematic Review and Meta-Analysis with Cross-Validation. *Radiology*, 287, 973-982.
20. Ji, G.J., Sun, J., Liu, P., Wei, J., Li, D., Wu, X., Zhang, L., Yu, F., Bai, T., Zhu, C., Tian, Y., & Wang, K. (2020). Predicting Long-Term After-Effects of Theta-Burst Stimulation on Supplementary Motor Network Through One-Session Response. *Front Neurosci*, 14, 237.
21. Ji, G.J., Yu, F., Liao, W., & Wang, K. (2017). Dynamic aftereffects in supplementary motor network following inhibitory transcranial magnetic stimulation protocols. *Neuroimage*, 149, 285-294.
22. Jo, H.J., Saad, Z.S., Gotts, S.J., Martin, A., & Cox, R.W. (2012). Quantifying agreement between anatomical and functional interhemispheric correspondences in the resting brain. *PLoS One*, 7, e48847.
23. Kempster, P.A., Gibb, W.R., Stern, G.M., & Lees, A.J. (1989). Asymmetry of substantia nigra neuronal loss in Parkinson's disease and its relevance to the mechanism of levodopa related motor fluctuations. *J Neurol Neurosurg Psychiatry*, 52, 72-76.
24. LeMay, M. (1976). Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann N Y Acad Sci*, 280, 349-366.
25. Li, J., Yuan, Y., Wang, M., Zhang, J., Zhang, L., Jiang, S., Wang, X., Ding, J., & Zhang, K. (2018). Decreased interhemispheric homotopic connectivity in Parkinson's disease patients with freezing of gait: A resting state fMRI study. *Parkinsonism Relat Disord*, 52, 30-36.
26. Li, P., Ensink, E., Lang, S., Marshall, L., Schilthuis, M., Lamp, J., Vega, I., & Labrie, V. (2020). Hemispheric asymmetry in the human brain and in Parkinson's disease is linked to divergent epigenetic patterns in neurons. *Genome Biol*, 21, 61.
27. Moorman, S., & Nicol, A.U. (2015). Memory-related brain lateralisation in birds and humans. *Neurosci Biobehav Rev*, 50, 86-102.
28. Mueller, S., Wang, D., Pan, R., Holt, D.J., & Liu, H. (2015). Abnormalities in hemispheric specialization of caudate nucleus connectivity in schizophrenia. *JAMA Psychiatry*, 72, 552-560.
29. Nichols, T.E., & Holmes, A.P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*, 15, 1-25.
30. Prakash, B.D., Sitoh, Y.Y., Tan, L.C., & Au, W.L. (2012). Asymmetrical diffusion tensor imaging indices of the rostral substantia nigra in Parkinson's disease. *Parkinsonism Relat Disord*, 18, 1029-1033.

31. Price, A.R., Bonner, M.F., Peelle, J.E., & Grossman, M. (2015). Converging evidence for the neuroanatomic basis of combinatorial semantics in the angular gyrus. *J Neurosci*, 35, 3276-3284.
32. Price, A.R., Peelle, J.E., Bonner, M.F., Grossman, M., & Hamilton, R.H. (2016). Causal Evidence for a Mechanism of Semantic Integration in the Angular Gyrus as Revealed by High-Definition Transcranial Direct Current Stimulation. *J Neurosci*, 36, 3829-3838.
33. Scherfler, C., Seppi, K., Mair, K.J., Donnemiller, E., Virgolini, I., Wenning, G.K., & Poewe, W. (2012). Left hemispheric predominance of nigrostriatal dysfunction in Parkinson's disease. *Brain*, 135, 3348-3354.
34. Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., He, Y., Yan, C.G., & Zang, Y.F. (2011). REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS One*, 6, e25031.
35. Stark, D.E., Margulies, D.S., Shehzad, Z.E., Reiss, P., Kelly, A.M., Uddin, L.Q., Gee, D.G., Roy, A.K., Banich, M.T., Castellanos, F.X., & Milham, M.P. (2008). Regional variation in interhemispheric coordination of intrinsic hemodynamic fluctuations. *J Neurosci*, 28, 13754-13764.
36. Thakral, P.P., Madore, K.P., & Schacter, D.L. (2017). A Role for the Left Angular Gyrus in Episodic Simulation and Memory. *Journal of Neuroscience*, 37, 8142-8149.
37. Toga, A.W., & Thompson, P.M. (2003). Mapping brain asymmetry. *Nat Rev Neurosci*, 4, 37-48.
38. Wang, D., Buckner, R.L., & Liu, H. (2014a). Functional specialization in the human brain estimated by intrinsic hemispheric interaction. *J Neurosci*, 34, 12341-12352.
39. Wang, J.X., Rogers, L.M., Gross, E.Z., Ryals, A.J., Dokucu, M.E., Brandstatt, K.L., Hermiller, M.S., & Voss, J.L. (2014b). Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science*, 345, 1054-1057.
40. Wu, J., Guo, T., Zhou, C., Gao, T., Guan, X., Xuan, M., Gu, Q., Huang, P., Song, Z., Xu, X., & Zhang, M. (2020). Disrupted interhemispheric coordination with unaffected lateralization of global eigenvector centrality characterizes hemiparkinsonism. *Brain Res*, 1742, 146888.
41. Zuo, X.N., Kelly, C., Di Martino, A., Mennes, M., Margulies, D.S., Bangaru, S., Grzadzinski, R., Evans, A.C., Zang, Y.F., Castellanos, F.X., & Milham, M.P. (2010). Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *J Neurosci*, 30, 15034-15043.

Figures

Figure 1

Cerebral specialization patterns in the Parkinson's disease (PD) (A) and healthy control groups (B). Increased autonomy index values in patients with PD were detected in the left angular gyrus (C).

Figure 2

Functional connectivity (FC) patterns in Parkinson's disease (PD) patients (A) and healthy control (HC) groups (B). The FC was calculated with the seed located at the left angular gyrus. Regions showing significant differences in FC between PD patients and controls (C). The cold color indicates regions with decreased FC values in PD patients. The warm color indicates regions with increased FC values in PD patients. There was a significant relationship between FC of the left middle orbitofrontal gyrus and supplementary area with Montreal Cognitive Assessment score in PD patients (D) but not in HCs (E).

Figure 3

Inter-hemispheric cooperation patterns in Parkinson's disease (PD) patients (A) and healthy control (HC) groups (B). The functionally homotopic voxel values were significantly decreased in the right sensorimotor region in PD patients compared with HCs (C). The functional homotopic region of the significant cluster is in the left sensorimotor area (D).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [BIBChecklist.docx](#)
- [SupplementaryMaterial0514.docx](#)