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RESEARCH ARTICLE

Resting-state functional magnetic resonance imaging in patients with Parkinson's disease with and without constipation: a prospective study

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Abstract

Purpose The etiology of constipation in Parkinson's disease is largely unknown. The aim of this study was to explore changes in regional neural activity and functional connections associated with constipation in a large cohort of individuals with Parkinson's disease.

Methods We prospectively recruited 106 patients with Parkinson's disease with constipation and 73 patients with Parkinson's disease without constipation. We used resting-state functional magnetic resonance imaging for the first time to measure differences in regional neural activity and functional connections between the two patient groups.

Results Patients with constipation showed significantly higher amplitude of low-frequency fluctuation than patients without constipation in the right dorsal pons extending into the cerebellum and in the right insula. The two types of patients also showed substantial differences in functional connections linking the superior temporal gyrus, particularly the right superior temporal gyrus, with multiple brain regions.

Conclusion Regional neural activity and functional connectivity in the brain differ substantially between patients with Parkinson's disease with or without constipation. These findings provide a foundation for understanding the involvement of constipation in this disease and for identifying therapeutic targets.

Keywords Parkinson's disease · Constipation · fMRI · Pons · Insula

Introduction

Constipation is a common non-motor symptom of Parkinson's disease (PD) and can precede the extrapyramidal clinical symptoms by many years [1]. Constipation causes discomfort, challenging the daily life of patients, and it can lead to serious and potentially life-threatening complications, such as intestinal pseudo-obstruction, volvulus, megacolon, and bowel perforation [2].

The etiology of constipation in PD remains largely unknown. It may be caused by intestinal or brain dysfunction due to the accumulation of pathological alpha-synuclein in either or both organs [3–5]. Resting-state functional magnetic resonance imaging (fMRI) has been widely used to non-invasively assess motor and non-motor symptoms, including autonomic symptoms, in patients with PD [6–10]. These studies have detected impairment of a complex central network that modulates resting-state parasympathetic outflow in the early stages of PD [11], as well as disruptions in

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the executive control network, dorsal attention network [9], and thalamo-striato-hypothalamic functional connectivity [10] in PD patients with autonomic dysfunction. However, we are unaware that fMRI has ever been applied to analyses of constipation in PD.

In this study, we used resting-state fMRI in a large cohort of PD patients to compare regional neural activity and functional connections between those with or without constipation. Specifically, we measured the amplitude of low-frequency fluctuation (ALFF) of the blood oxygen level-dependent signal as an index of neural activity [12], while we performed functional connectivity analysis to explore the brain's intrinsic functional networks [13].

Methods

Patients

Patients with idiopathic PD were prospectively recruited at Henan Provincial People's Hospital between February 2019 and January 2020. The inclusion criteria for patients were as follows: (1) clinically established PD according to the Movement Disorder Society Clinical Diagnostic Criteria for PD [14], (2) no family history of PD in first-degree relatives, (3) no MRI evidence of structural lesions related to other neurological disorders, (4) no serious cognitive impairment that may affect the patient's evaluation, and (5) no head movement artifacts during the MRI session.

Patients were excluded if they were diagnosed with multiple system atrophy, progressive supranuclear palsy, or secondary Parkinsonism. Patients were also excluded if their constipation symptoms disappeared after taking anti-constipation drugs. Such patients would otherwise have been assigned to the non-constipation group, where they might have confounded our analysis. Patients whose constipation symptoms did not completely disappear after taking anti-constipation drugs, regardless of whether the symptoms were alleviated, were assigned to the constipation group.

This study was approved by the Ethics Committee of Henan Provincial People's Hospital, and written informed consent was obtained from all participants.

Clinical assessment

Clinicodemographic data were collected on age, sex, disease duration, and use of medications including drugs against constipation, drugs that can cause constipation, and dopaminergic drugs. Constipation was defined according to item 5 of the Non-motor Symptoms Questionnaire (NMSQ) [15] as fewer than three bowel movements a week or having to strain to pass stool. Medications currently taken by the patients were calculated in terms of the levodopa equivalent daily dose (LEDD) according to an established formula [16]. PD severity was assessed using Part III of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) [17].

Resting-state fMRI

Images were acquired using a Siemens MAGNETOM Prisma 3-T scanner with a 64-channel head coil. Patients were asked to lie still, relax, and keep their eyes open throughout the scanning. Functional images were obtained using axial echo-planar imaging with the following parameters: TR = 2000 ms, TE = 35 ms, flip angle = 80°, FOV = 240 × 240 mm, matrix size = 94 × 94, voxel dimensions 2.20 × 2.20 × 2.20 mm, slice thickness = 2.2 mm, number of slices = 75, and number of time points = 180.

Statistical Parametric Mapping version 12b (SPM12b; www.fil.ion.ucl.ac.uk/spm) and the CONN functional connectivity toolbox version 18_b [18] (http://www.nitrc.org/projects/conn) were used to preprocess images and analyze resting-state fMRI data. Preprocessing of data from all functional sequences involved the following steps: (1) functional slice-timing correction, (2) functional realignment and unwarping (subject motion estimation and correction), (3) functional outlier detection using an artifact detection tool (www.nitrc.org/projects/artifact_detect/) and scrubbing, (4) structural centering to (0,0,0) (translation), (5) functional direct normalization based on the Montreal Neurological Institute space, and (6) functional smoothing (spatial convolution with Gaussian kernel). Functional images were resliced at a resolution of $2 \times 2 \times 2$ mm^3 and smoothed using a Gaussian kernel (full width at half maximum, 8 mm). Subjects were excluded if their head motion exceeded 2 mm in displacement or 2° in rotation in a single image. White matter, cerebrospinal fluid, and head motion were regressed in the denoising step. Low-frequency drift and high-frequency physiological noise were removed using bandpass filtering ($0.01 < \text{frequency} < 0.08$ Hz), while systematic shifts were removed using detrending.

First-level analysis of the CONN pipeline was conducted to generate individual ALFF maps in order to evaluate regional neural activity. Data were standardized across subjects by dividing the ALFF of each voxel by the global mean ALFF for all patients using DPABI toolbox (version 4.0) [19].

To evaluate functional connectivity in the brain, we analyzed neurological activity among 132 regions, comprising 91 cortical and 15 subcortical regions of interest (ROIs) from the FSL Harvard–Oxford Atlas, as well as 26 cerebellar ROIs from the Anatomical Automatic Labeling Atlas in the CONN functional connectivity toolbox (version 18_b). Potential correlations were identified by applying a general linear model and performing bivariate

correlation analysis, which was weighted according to the hemodynamic response function based on first-level analysis of the CONN pipeline.

Statistical analysis

Differences in demographic and clinical characteristics between the two groups were assessed for significance using Student's t test and the χ^2 test. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 22.0; IBM Corp., Armonk, NY, USA). Differences were considered significant if they were associated with $P < 0.05$.

To evaluate differences in regional neural activity between the two groups, we analyzed ALFF from the individual standardized ALFF maps using the SPM12b software package. Age, sex, disease duration, and MDS-UPDRS-III score were entered as covariates to exclude their potential influence on ALFF. The significance threshold was defined as an uncorrected $P = 0.001$ at the initial voxel level, and as a false discovery rate-adjusted $P = 0.05$ at the cluster level in order to correct for multiple comparisons.

To evaluate changes in ROI-to-ROI functional connectivity between the two groups, differences from the second-level analysis of the CONN pipeline were assessed using two-sample t tests. The significance threshold was defined as a false discovery rate-adjusted $P = 0.05$ at the seed level in order to correct for multiple comparisons.

Results

Demographic and clinical features of the participants

Of the 236 patients initially considered for enrollment, 57 were excluded according to the inclusion criteria and exclusion criteria. Among those excluded were four patients whose constipation symptoms completely disappeared after taking medicine; we did not want them to confound our analysis of other patients in the non-constipation group. In the end, the final analysis included 179 PD patients, who were divided into those with constipation (106), 37 of whom took anti-constipation drugs, and those without constipation (73) (Table 1). Only 13 patients in our constipation group reported that their symptoms had improved after medication. Those with constipation were less likely to be male and were older and had higher MDS-UPDRS-III scores. The two groups did not differ significantly in disease duration, frequency of any dopaminergic drug use, or total LEDD. Similar proportions of patients with or without constipation were taking trihexyphenidyl (34.9% vs. 41.1%), and no patients were taking any other drugs known to cause constipation.

ALFF analysis

When we included age, sex, disease duration, and MDS-UPDRS-III score as covariates, the two-sample t test showed that patients with constipation had a significantly higher ALFF value in the right dorsal pons extending into the cerebellum and in the right insula (Table 2 and Fig. 1).

Table 1 Clinicodemographic information about PD patients with or without constipation

Characteristic	PD with constipation	PD without constipation	*P* value
n	106	73	–
Male	55 (51.9)	53 (72.6)	0.005
Age at MRI scan, years	63.2 ± 6.2	60.7 ± 7.4	0.016
PD duration, years	7.0 ± 4.2	5.9 ± 4.2	0.072
MDS-UPDRS-III score	42.5 ± 18.7	36.4 ± 17.7	0.029
Trihexyphenidyl	37 (34.9)	30 (41.1)	0.400
Amantadine	15 (14.2)	15 (20.5)	0.260
Levodopa	93 (87.7)	59 (80.8)	0.204
Dopamine receptor agonist	44 (41.5)	35 (47.9)	0.394
MAO-B inhibitor	2 (1.9)	5 (6.8)	0.092
COMT inhibitor	5 (4.7)	3 (4.1)	1.000
LEDD	462.3 ± 297.1	433.7 ± 343.7	0.554

Values are *n*, *n* (%), or mean ± SD, unless otherwise noted

COMT catechol-*O*-methyltransferase, *LEDD* levodopa equivalent daily dose, *MAO-B* monoamine oxidase B, *MDS-UPDRS-III* Part III of Movement Disorder Society Unified Parkinson's Disease Rating Scale, *PD* Parkinson's disease

Table 2 Brain regions showing higher ALFF in PD patients with constipation than in those without constipation

Region	Cluster size	Montreal Neurological Institute coordinates (*x*, *y*, *z*)			T score*
Right dorsal pons extending into the cerebellum	247	18	−36	−24	4.92
Right insula	135	32	−18	14	4.95

ALFF amplitude of low-frequency fluctuation, *PD* Parkinson's disease

*Corrected for a cluster-level false discovery rate (single voxel $P < 0.001$, cluster size ≥ 135 voxels)

Functional connectivity analysis

Compared to patients without constipation, those with constipation showed significantly weaker resting-state functional connections between the superior temporal gyrus (STG) and the following three brain regions (Table 3 and Fig. 2): frontal lobe (frontal medial cortex, inferior frontal gyrus, middle frontal gyrus), temporal lobe (middle temporal gyrus, inferior temporal gyrus), and limbic lobe (hippocampus, parahippocampal gyrus). Patients with constipation also showed significantly weaker resting-state functional connections between the lateral occipital cortex (LOC) and the lingual gyrus, as well as between the middle temporal gyrus and the inferior temporal gyrus.

Conversely, patients with constipation showed significantly stronger resting-state functional connections between the STG and cerebellum (cerebellum_3, cerebellum_4_5, Vermis_4_5, Vermis_6), as well as between the LOC and both the planum polare and thalamus.

Discussion

In this study, we explored changes in neural activity associated with constipation in a large cohort of individuals with PD. Our study appears to be the first to apply resting-state fMRI to measure regional neural activity and functional connections in PD patients with or without constipation. We found significantly higher ALFF values in the right dorsal pons extending into the cerebellum and in the right insula in patients with constipation compared to those without constipation. Additionally, we found that the STG, especially the right STG, showed altered functional connectivity with multiple brain regions in PD patients with constipation.

Both the insula and the locus coeruleus and parabrachial nucleus in the dorsal pons are involved in autonomic control [20, 21]. The locus coeruleus contains the pontine center for micturition and defecation [21]: norepinephrine in the locus coeruleus facilitates colonic motility in rats [22], vascular

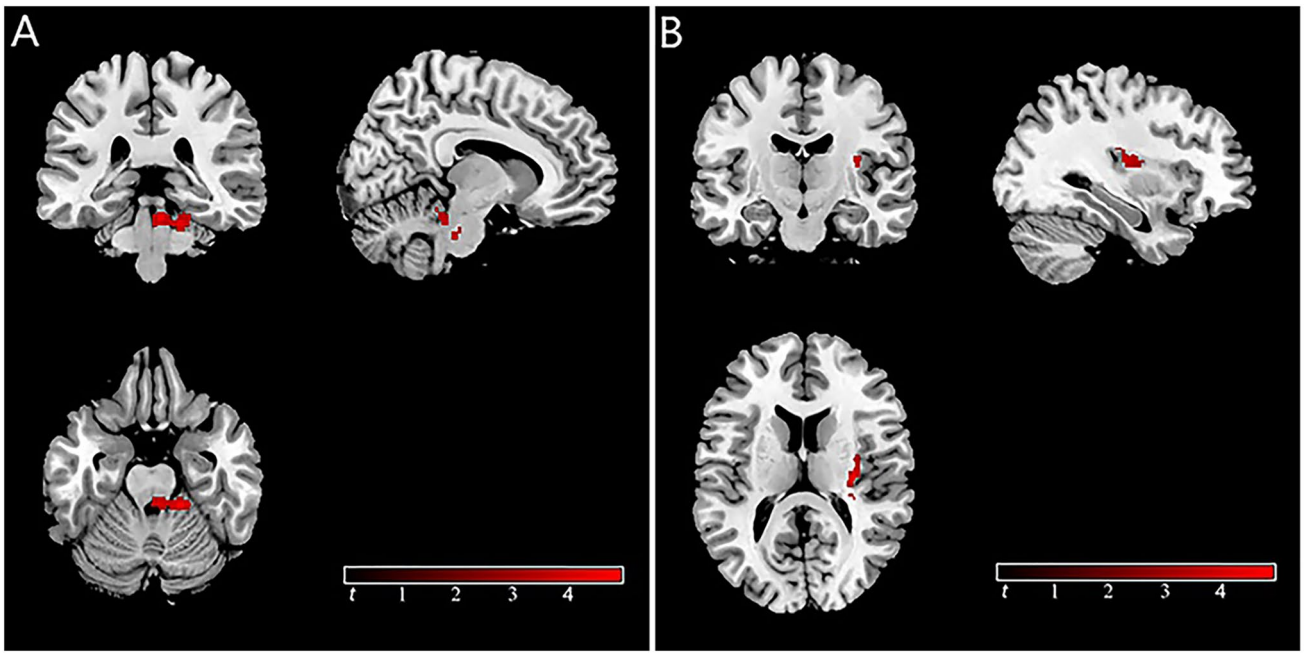

Fig. 1 Analysis of the amplitude of low-frequency fluctuations in patients with Parkinson's disease. Standard brain showing higher amplitude of low-frequency fluctuations in patients with constipation than in patients without constipation. The right dorsal pons extending into the cerebellum (**a**) and the right insula (**b**) are highlighted in red. More detailed information can be found in Table 2

Table 3 Functional connection differences in PD patients with or without constipation

Connection	*T* value	FDR-corrected *P*
aSTG_l—MedFC	−4.16	0.003
aSTG_l—pMTG_r	−3.64	0.040
aSTG_r—MedFC	−3.55	0.022
pSTG_l—MedFC	−4.78	0.001
pSTG_l—Hippocampus_l	−4.14	0.004
pSTG_l—aMTG_r	−3.89	0.004
pSTG_l—pMTG_l	−3.86	0.004
pSTG_l—pMTG_r	−3.64	0.007
pSTG_l—pPaHC_l	−3.61	0.008
pSTG_l—aMTG_l	−3.38	0.010
pSTG_l—pITG_l	−3.27	0.013
pSTG_l—pITG_r	−3.04	0.024
pSTG_l—IFG_tri_l	−3.04	0.024
pSTG_l—MidFG_l	−2.89	0.035
pSTG_l—aITG_l	−2.78	0.044
pSTG_l—aPaHC_l	−2.78	0.044
pSTG_r—pMTG_r	−3.37	0.040
pSTG_l—Cereb3_r	3.98	0.004
pSTG_l—Cereb3_l	3.56	0.008
pSTG_l—Cereb45_r	3.49	0.009
pSTG_l—Ver6	3.43	0.010
pSTG_l—Ver45	3.40	0.010
iLOC_r—PP_r	4.23	0.004
iLOC_r—Thalamus_r	3.87	0.010
iLOC_l—Thalamus_r	4.19	0.006
iLOC_l—PP_r	3.87	0.010
sLOC_l—LG_r	−3.80	0.026
toMTG_l—pITG_r	−3.83	0.024

aITG anterior division of the inferior temporal gyrus, *aMTG* anterior division of the middle temporal gyrus, *aPaHC* anterior division of parahippocampal gyrus, *aSTG* anterior division of the superior temporal gyrus, *Cereb3* cerebellum_3, *Cereb45* cerebellum_4_5, *FDR* false discovery rate, *IFG_tri* pars triangularis of inferior frontal gyrus, *iLOC* inferior division of lateral occipital cortex, *l* left, *LG* lingual gyrus, *MedFC* frontal medial cortex, *MidFG* middle frontal gyrus, *PD* Parkinson's disease, *pITG* posterior division of inferior temporal gyrus, *pMTG* posterior division of the middle temporal gyrus, *PP* planum polare, *pPaHC* posterior division of parahippocampal gyrus, *pSTG* posterior division of the superior temporal gyrus, *r* right, *sLOC* superior division of lateral occipital cortex, *toMTG* temporo-occipital part of middle temporal gyrus, *Ver45* Vermis_4_5, *Ver6* Vermis_6

lesions at this site cause constipation in humans [23], and Lewy bodies at this site have been associated with infrequent bowel movements [24]. The parabrachial nucleus receives input from the nucleus of the solitary tract and relays this information to certain cortical sites including the insular cortex and amygdala [25, 26]. Electrical and chemical stimulation of the parabrachial nucleus alters respiration and arterial pressure [27]. In fact, fMRI has shown that various visceral tasks, such as isometric hand-gripping, maximal inspiration, and the Valsalva maneuver, can activate the parabrachial nucleus [28]. Similarly, maximal inspiration and breath-holding activate the insular cortex in a pattern that correlates with the activity of sympathetic muscle nerves [29]. Electrical stimulation of the neck area overlying the vagus nerve can activate classic vagal afferent projections, including the nucleus of the solitary tract, the parabrachial area, the primary sensory areas, and the insula [30]. These observations strongly link the parabrachial nucleus and the insula to autonomic control, and the present study implicates these brain regions in PD-associated constipation, which has also been attributed to autonomic dysfunction [31].

The STG is an important locus in PD and plays a role in the disease's manifestations of theory of mind, apathy, dementia, depressive symptoms, freezing of gait and frequent falling [7, 32–36]. Nevertheless, we did not detect significant differences in spontaneous STG activity between patients with or without constipation, although we did find that the STG, especially the right STG, differed in its functional connections with multiple brain regions between the two types of patients. Patients with constipation showed stronger functional connections between the STG and cerebellum, but weaker connections between the STG and other cerebral lobes. Interestingly, fMRI has linked the cerebellum to regulation of autonomic function [29, 37, 38]. Our functional connectivity analysis suggests that the STG may be part of an important brain network contributing to constipation in PD.

Our results may not be specific to PD, since our study did not include healthy controls or individuals with constipation from the general population. In fact, at least some of our findings may be relevant to constipation in the general population. For example, spontaneous activity in the insula appears to be higher among individuals in the general population with functional constipation than among healthy controls [39]. Further study with appropriate comparison groups should examine whether the associations between constipation and altered functional connectivity in PD also occur in the general population.

In the general population, functional constipation is generally more prevalent among women than men [40]. A similar sex bias for constipation has been observed among PD patients [41, 42], which we observed in the present study as well. Risk of constipation among PD patients may also depend on PD severity, with risk increasing as the disease progresses [43, 44]. We also observed that PD patients with constipation had a higher motor symptom score than PD patients without constipation.

It is important to acknowledge the limitations of our study. Since no definitive criteria exist for the diagnosis of constipation in PD [1], we applied commonly used diagnostic criteria [15]. In addition, we excluded patients whose

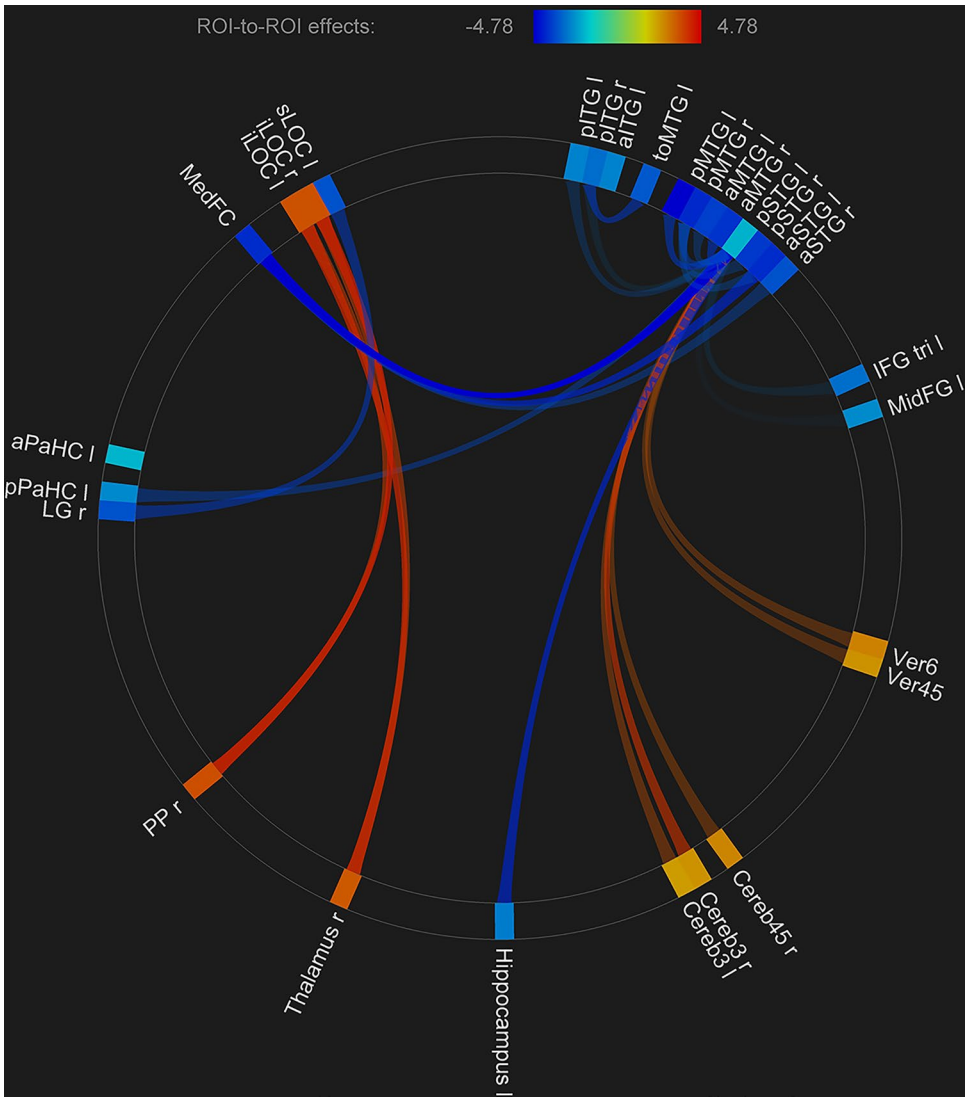

Fig. 2 Functional connectivity analysis. Differences in functional connectivity between regions of interest in PD patients with or without constipation. Red and blue indicate, respectively, stronger or weaker connectivity in patients with constipation. Abbreviated names of regions of interest are defined in Table 3

constipation symptoms disappeared after taking anti-constipation drugs. Both these factors may limit the generalizability of our results to other patient populations. We did not assess severity of constipation, so it remains unclear whether the observed alterations in brain activity and connectivity correlate with constipation severity. Lastly, we did not collect data on other autonomic symptoms such as orthostatic hypotension, excess salivation, urinary symptoms, sexual symptoms, or thermoregulatory symptoms. As autonomic symptoms often cluster together, this may confound our results [45]. Nevertheless, we did treat PD duration and disease severity as covariates in our analysis, and both these variables are associated with autonomic symptoms [45]. Thus, our analysis may have reduced the impact of such confounding.

Future work should address these limitations and seek to verify and extend our findings, which suggest substantial differences in brain activity and functional connectivity between PD patients with or without constipation. Our study may advance the understanding of how constipation occurs in PD and what treatments may be effective against it.

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Data availability Anonymized data that were analyzed in this report are available upon request from the corresponding authors.

Declarations

Conflict of interest The authors declare that they do not have any conflicts of interest.

Ethical statement This study was approved by the Ethics Committee of Henan Provincial People's Hospital and conducted in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants.

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