Received: 13 August 2022 | Revised: 11 October 2022 | Accepted: 23 October 2022

DOI: 10.1002/hbm.26139

RESEARCH ARTICLE

WILEY

Common and unique dysconnectivity profiles of dorsal and median raphe in Parkinson's disease

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 82071423

Abstract

The serotonergic (5-HT) system, which undergoes degeneration in Parkinson's disease (PD), is involved in the pathogenesis of motor and nonmotor symptoms. The dorsal raphe (DR) and median raphe (MR) nuclei are the main source of 5-HT neurons, however, brain connectivity changes in these two nuclei have not been delineated in PD. Here we used resting-state fMRI (rs-fMRI) to characterize functional connectivity profiles of DR and MR and further examine the associations between dysconnectivity of raphe nuclei and clinical phenotypes of PD. We found that DR and MR commonly hypo-connected with the sensorimotor, temporal, and occipital cortex, limbic system, left thalamus, putamen, and cerebellum in PD. DR had unique decreased connectivity with the bilateral prefrontal and cingulate cortices, while MR had lower connectivity with the pons. Moreover, reduced connectivity of DR correlated with depression, drowsiness, and anxiety, whereas dysconnectivity of MR correlated with depression, cognitive deficits, sleep disturbances, and pain. Our findings highlight the complex roles of raphe nuclei in motor and nonmotor symptoms, providing novel insights into the neurophysiological mechanisms underlying pathogenesis of PD.

KEYWORDS
functional connectivity, functional MRI, Parkinson's disease, raphe nuclei, resting state

1 | INTRODUCTION

Parkinson's disease (PD) is characterized by degeneration of nigrostriatal dopaminergic neurons associated with the formation of intracellular inclusion (Lewy body) containing aggregates of α-synuclein (Goedert et al., 2013; Poewe, 2008). As the disease progresses, Lewy bodies are progressively identified in the midbrain, subcortex, and neocortex, which leads to defects in dopaminergic as well as nondopaminergic neurotransmitters, especially the serotonergic (5-HT) system (Buddhala et al., 2015). Serotonergic innervation in the cortical, subcortical (limbic system, basal ganglia) areas, and cerebellum is mainly derived from the dorsal (DR) and median (MR) raphe nuclei (Charnay & Leger, 2010; Commons, 2016).

Previous studies often used positron emission tomography (PET) technique to investigate serotonergic dysfunction in PD. These studies revealed that serotonergic dysfunction was associated with both motor (dyskinesia, tremor) and nonmotor symptoms (NMS) (cognitive impairment, mood disorders, and sleep disorders; Huot et al., 2011; Maillet et al., 2021; Wilson et al., 2018). However, these studies only focused on altered regional serotonergic levels, it remains unclear

how serotonergic deficits of raphe nuclei inducing brain functional alterations in PD. Only two small sample studies (approximately 20 patients) have examined functional connectivity (FC) changes of the raphe nuclei in PD. These studies observed a significant decrease in FC between raphe nuclei and frontal lobe and cingulate cortices in PD with pain (Shen et al., 2022) or with frozen of gait (Lv et al., 2022) compared to the healthy controls (HC). However, these studies considered the raphe nuclei as a whole structure and did not explore the similarities and differences in the altered connectivity patterns of DR and MR. Therefore, how functional abnormalities of DR and MR contribute to the pathophysiology of diverse motor symptom and NMS in PD has not been investigated.

Here, we used resting-state fMRI (rs-fMRI) to characterize functional connectivity of DR and MR in PD and examine the associations between dysconnectivity of raphe nuclei and clinical phenotypes of PD. DR and MR have common and distinct serotonergic circuitries, specifically DR prefers to project to cortical, subcortical (limbic system, basal ganglia) regions, whereas MR tends to project to subcortical, midbrain regions, and cerebellum (Commons, 2016). Thus, we explored the similarities and differences between DR and MR in terms of both functional abnormalities and their roles in phenotypes of PD.

2 | MATERIALS AND METHODS

2.1 | Participants

A total of 156 participants were enrolled in this study. Nine patients with PD and seven healthy controls (HCs) were excluded due to excessive head movements. Therefore, we finally enrolled 140 participants (PD: 70, HC: 70). All patients were recruited from June 2017 to May 2021 from the Department of Neurology, Xuanwu Hospital Capital Medical University. Notably, to reduce the effects of dopamine drugs on brain activity, we only included patients who were in the "OFF medication" state (at least 12 h dopaminergic drug withdrawal) during MRI scans. This study was approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University. All participants provided written informed consent before inclusion. Patients with PD were diagnosed according to the Movement Disorders Society (MDS) Clinical Diagnostic Criteria (Postuma et al., 2015). The HCs were recruited from the community. The exclusion criteria were left-handed, confounding neurological diseases, unsafe MRI acquisition, excessive head movement during scanning, and poor quality of space standardization.

2.2 | Clinical and behavioral assessments

All participants underwent clinical assessment of motor symptoms and NMS in the "OFF medication" state. Motor symptoms were evaluated using the MDS Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III). The dosage of antiparkinsonian drugs was calculated using the levodopa equivalent daily dose (LEDD). Olfactory function was assessed using the Brief Smell Identification Test (BSIT). Cognitive ability was evaluated using the Montreal Cognitive Assessment (MOCA). The presence of depression, anxiety, apathy, and pain was measured using the Hamilton Depression Scale (HAMD), State-Trait Anxiety Inventory (STAI), and Apathy Evaluation Scale self-rated version (AES-S), and MDS-UPDRS I-1.9, respectively. Sleep disturbances were measured using the Rapid Eye Movement Sleep Behavior Disorder Questionnaire (RBDQ-HK) and Epworth Sleepiness Scale (ESS) (Table 1).

2.3 | MRI acquisition and preprocessing

During MRI scanning, participants were instructed to keep eyes closed, stay awake, and not think of anything. All the patients were scanned in the "OFF medication" state. The MRI data were acquired using a Siemens Magnetom Skyra 3T scanner (Erlangen, Germany). Rs-fMRI images were obtained using a single-shot spin-echo echo-planar imaging (SE-EPI) sequence with following parameters: repetition time (TR), 2000 ms; echo time (TE), 30 ms; field of view (FOV), 22×22 cm^2; flip angle, 90°; voxel size, $3.4 \times 3.4 \times 3$ mm^2; 35 slices, no gap; 176 repetitions; scanning time, 5 min 52 s. T1-weighted anatomic images were scanned using a magnetization-prepared 3D rapid gradient echo (MPRAGE) sequence. The image parameters were as follows: TR/TE/flip angle, 2530 ms/2.98 ms/7°; FOV, 25.6×25.6 cm^2; voxel size $1 \times 1 \times 1$ mm^2; 192 slices, no gap. The acquisition time was 5 min 13 s.

Imaging data were preprocessed and analyzed using DPABI (version 6.0; http://www.rfmri.org/dpabi), including removal of the first 10 volumes, slice timing correction, head motion correction, tissue segmentation, spatial normalization into Montreal Neurological Institute (MNI) space and resampling into 3-mm isotropic voxels. Considering that, the raphe nuclei are in the brainstem and susceptible to interference from physiological noises, independent component analysis (ICA) was used to correct the fMRI signal for respiratory and cardiac noise (Griffanti et al., 2017). FSL's tool MELODIC (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) was used to perform ICA to denoise the whole-brain fMRI data for all subjects. Briefly, single-subject fMRI data are first decomposed into a collection of independent components (ICs) across the time domain (time series) and spatial domain (maps). Then, the signal and noise are manually identified, and the ICs of the noise are labeled and removed (Griffanti et al., 2017). The characteristics of the signal and noise were summarized in Table S1. Examples of signal and noise components are shown in Figures S1–S3. Subsequently, spatial smoothing with a full width at half maximum of 6 mm Gaussian kernel, and temporal bandpass filtering at 0.01–0.08 Hz were performed using DPABI. Notably, participants were excluded if their mean framewise displacement (FD) was >0.3 mm, or if the translational/rotational movements were >3 mm or 3°.

TABLE 1 Demographic and clinical information of the participants

Characteristics	PD group	HC group	*p*-value
Age, years	61.70 ± 8.47	59.94 ± 8.65	.226
Gender, male/female	34/36	30/40	.141
Education, years	11.21 ± 3.65	12.13 ± 3.68	.611
Motor symptoms			
Disease duration, years	4.50 ± 4.11	—	—
Hoehn–Yahr stage	1.73 ± 0.58	—	—
MDS-UPDRS III	27.63 ± 11.99	—	—
LEDD, mg	384.13 ± 294.33	—	—
Nonmotor symptoms			
BSIT	6.80 ± 2.74	8.91 ± 2.64	**.000**
MoCA	22.99 ± 3.81	25.84 ± 2.96	**.000**
RBD-HK	21.69 ± 16.55	9.80 ± 7.17	**.000**
Epworth sleepiness scale	5.44 ± 4.46	4.39 ± 2.92	.099
HAMD	6.74 ± 4.81	0.89 ± 1.80	**.000**
STAI	71.29 ± 18.52	54.01 ± 7.89	**.000**
AES-S	13.33 ± 8.86	4.73 ± 4.80	**.000**
Pain (UPDRS I-1.9)	0.60 ± 0.89	0.19 ± 0.40[a]	**.007**

Note: Values are presented as mean ± standard deviation (SD). Bold values indicate significant differences between two groups.

Abbreviations: AES-S, Apathy Evaluation Scale self-rated version; BSIT, Brief Smell Identification Test; HAMD, Hamilton Depression Scale; HC, healthy controls; LEDD, levodopa-equivalent daily dose; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; RBD-HK, Rapid eye movement sleep Behavior Disorder Questionnaire (Hong Kong version); STAI, State-Trait Anxiety Inventory.

[a]16 HC rated MDS UPDRS I and II. Values were derived from 16 HC.

2.4 | Functional connectivity analysis of raphe nuclei

The whole-brain FC patterns were measured with DR and MR as region of interest (ROI). The ROI for DR or MR is defined as a sphere with a radius of 4 mm. The center of position for DR is $x = 2$, $y = -26$, $z = -18$, and for MR is $x = 0$, $y = -34$, $z = -20$ (MNI space; Bar et al., 2020; Beliveau et al., 2015). For each ROI, a whole-brain FC map was obtained for each participant by calculating Pearson's correlation coefficients between the mean time series of all voxels in the ROI and the time series of every voxel within the gray matter (GM). The correlation coefficients were converted to *z*-scores using Fisher's *r*–*z* transformation to improve the normality. Two *z*-scored FC maps were generated for each participant.

2.5 | Statistical analysis

Statistical analyses for demographic and clinical features were performed using SPSS 22.0 (IBM, NY). Two-sample *t*-tests were used to determine demographic, and clinical differences between the two groups (chi-square test for sex difference). For the FC maps of DR and MR, we first applied one-sample t-tests to the PD and HC groups to determine the connectivity profile of each ROI. The significant level for the within-group test was set at a family-wise error (FWE) corrected $p < .05$ at voxel-level with a cluster size ≥10 voxels. An FC mask was then generated as the union of the within-group results from both groups for each ROI. Between-group differences in FC maps for each ROI were then measured using the general linear model within this mask, with age, sex, and head movements as covariates, and the significant level was FDR corrected $p < .01$ at the voxel level with a cluster size ≥10 voxels.

Pearson or spearman correlations (depending on data were normally or non-normally distributed) were used to calculate the relationship between brain and behavior. First, FC values of the PD group were extracted from the clusters that exhibit significant group differences, then FC values within each cluster were averaged. Correlation was performed between the mean FC values in each cluster and clinical variables. Correlation values were Bonferroni-corrected for two tests, that is, significance threshold was $p < .025$ (0.05/2).

3 | RESULTS

3.1 | Characteristics of demographic, and clinical measures

Seventy patients with PD and 70 HCs were finally included in this study. No significant differences were found in age, sex, and education between the PD and HC groups. Patients with PD had

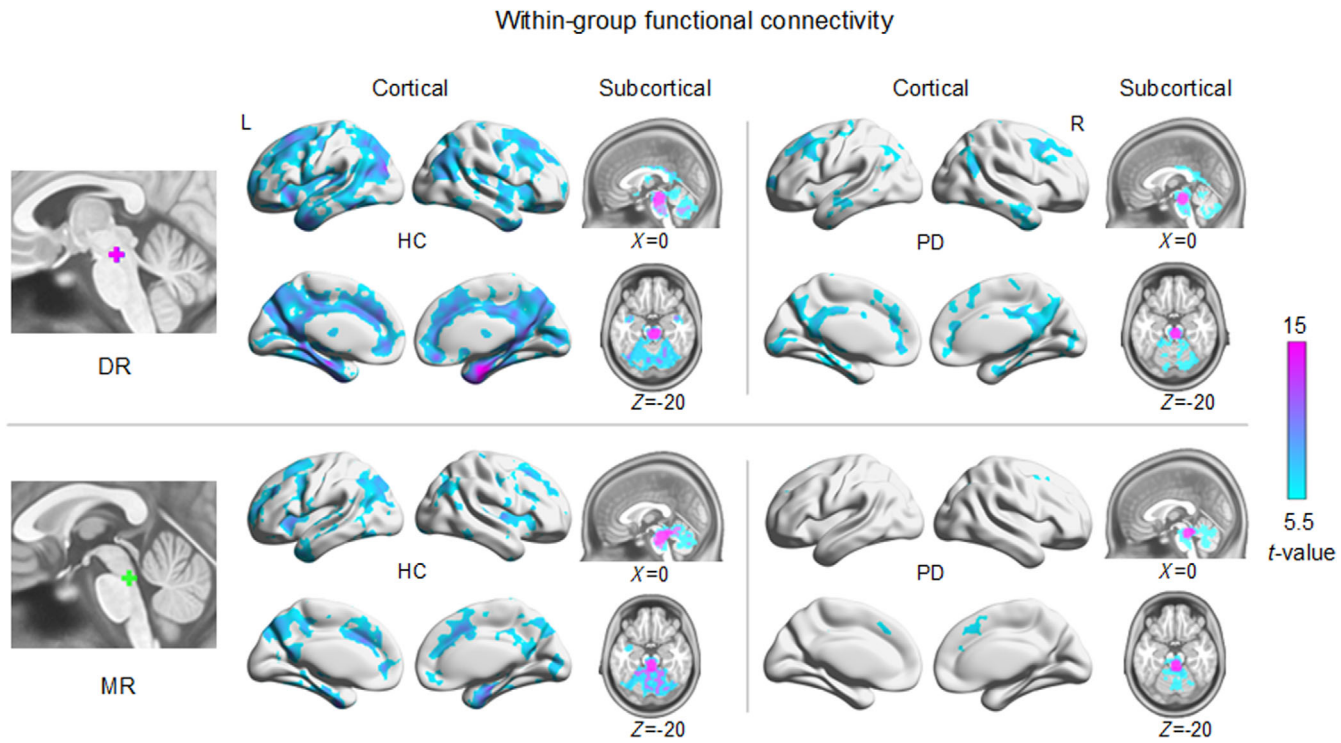

FIGURE 1 Within-group functional connectivity (FC) of raphe nuclei. Results are thresholded at FWE-corrected voxel-level $p < .05$ (cluster size ≥10 voxels).

significantly lower average UPSIT and MoCA scores but higher sleep, emotional, and pain scores than the HCs (all $p < .007$, Table 1). Daytime sleepiness did not differ between the two groups.

3.2 | Functional connectivity of raphe nuclei in PD

3.2.1 | Within-group functional connectivity profiles

Within-group functional connectivity analysis showed that the DR and MR shared a large amount of common positive connectivity in HC group, including the bilateral prefrontal cortex (PFC), medial and lateral temporal cortices, occipital cortex, limbic system including cingulated cortex, insula, amygdala, and hippocampus, as well as subcortical structures including basal ganglia, thalamus, brainstem, and cerebellum (Figure 1). These nuclei also exhibited differential connections, with DR having more extensive connections with the cerebral cortex and basal ganglia and MR having more intense connections with the brainstem and cerebellum.

3.2.2 | Between-group functional connectivity profiles

Statistical between-group comparisons showed that compared to HC, patients with PD demonstrated widespread dysconnectivity of DR and MR (Figure 2a). Commonly decreased FC of these nuclei in PD were found with the sensorimotor cortex (superior and inferior frontal gyri [SFG/IFG], postcentral gyrus [PoCG]), temporal cortex (inferior and middle temporal gyri [ITG/MTG], temporal pole [TP]), occipital cortex, limbic system (hippocampus, parahippocampus, amygdala, insula), left thalamus, putamen, and cerebellum. Distinct PD-related dysconnectivity patterns were also observed for each ROI. DR had lower functional connectivity with the bilateral ventral medial PFC (vmPFC), orbital frontal gyrus (OFC), anterior and middle cingulate cortices (ACC/MCC), and right thalamus, while MR had lower connectivity with the pons in patients with PD compared to HCs (FDR-corrected voxel-level $p < .01$, cluster size ≥10 voxels; Figure 2b and Table S2).

3.3 | Associations between raphe nuclei connectivity and clinical variables in PD

Correlation analyses showed that reduced connectivity between the DR and limbic system, occipital, and somatosensory cortex was associated with NMS in PD, whereas reduced connectivity between MR and the frontal and temporal lobes, limbic system, and cerebellum was associated with both motor symptoms and NMS (Table 2). Specifically, in DR, reduced connectivity with the left amygdala, left postcentral gyrus, and bilateral cingulate cortices was associated with depression, daytime sleepiness, and anxiety, respectively. In MR, decreased connectivity with the left cerebellum and bilateral pons was associated with motor deficits, and reduced connectivity with the left cerebellum, insula, and IFG was associated with disease severity. Reduced connectivity of MR with the left thalamus, cerebellum, IFG and insula, and

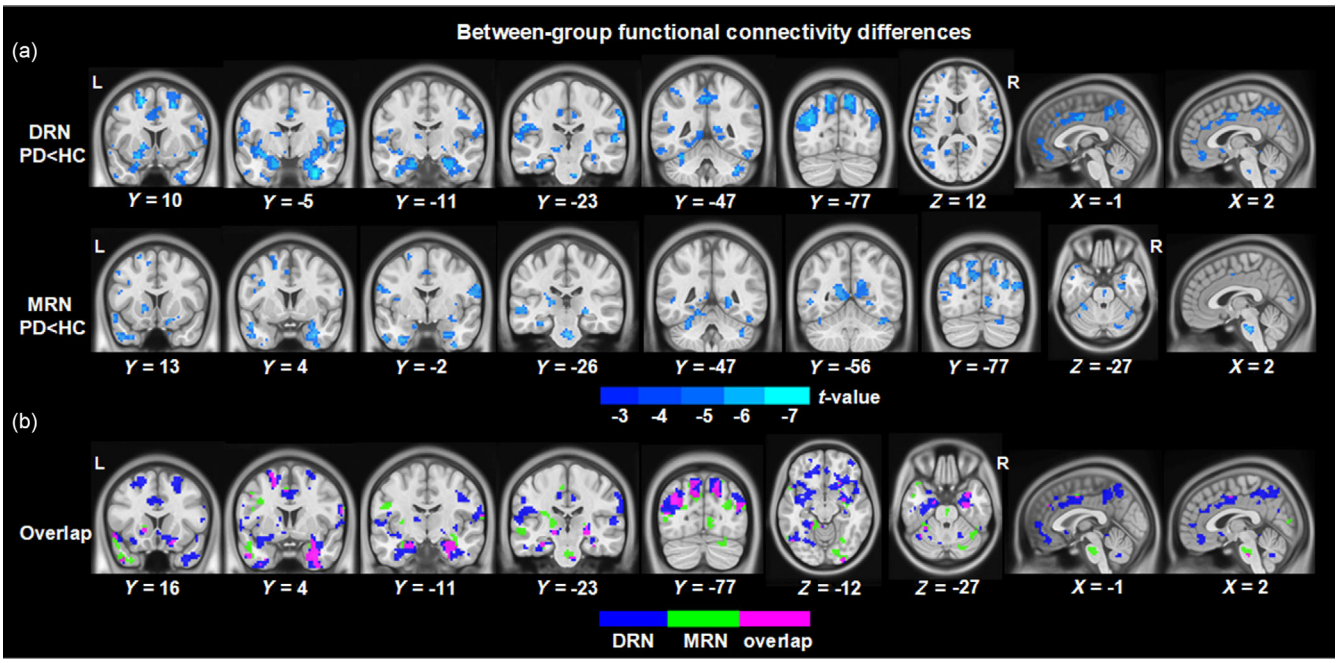

FIGURE 2 Differences in functional connectivity of the raphe nuclei between the PD and HC groups. (a) Significant group differences in FC for dorsal raphe nucleus (DRN) and median raphe nucleus (MRN). Group difference FC maps are thresholded at FDR-corrected voxel-level $p < .01$ (MNI152 space, cluster size ≥10 voxels). (b) Spatial similarities and differences of FC maps between DR and MR. The brain areas with blue are unique to DR, those with green are specific to MR, and those with purple are common to both.

TABLE 2 Decreased connectivity with raphe nuclei correlates with motor and nonmotor symptoms in PD

Clinical variables	Regions with decreased FC	Correlation	*p*-value
Dorsal raphe			
Depression (HAMD score)	Left amygdala	−0.331	.005
Daytime sleepiness (ESS score)	Left postcentral gyrus	−0.323	.006
Anxiety (STAI score)	Bilateral cingulate cortex	−0.296	.013
Median raphe			
Motor impairment	Bilateral pons	−0.363	.002
(MDS-UPDRS III score)	Left cerebellum	−0.268	.025
Disease severity	Left cerebellum	−0.357	.002
(Hoehn–Yahr stage)	Left inferior frontal gyrus	−0.309	.009
	Left insula	−0.309	.009
Depression (HAMD score)	Left thalamus	−0.343	.004
Cognition (MoCA score)	Left cerebellum	0.362	.002
Sleep disorder (RBDQ-HK score)	Left inferior frontal gyrus	−0.326	.006
	Left insula	−0.326	.006
Pain (UPDRS I-1.9)	Left superior frontal gyrus	−0.301	.011

SFG was associated with depression, cognitive impairment, sleep disturbances, and pain.

4 | DISCUSSION

In this study, we investigated FC abnormalities of the raphe nuclei in PD and further linked these FC profiles to the motor and NMS features of PD using correlation analysis. We identified for the first time, PD-related common and unique dysconnectivity profiles of DR and MR in a large dataset. Overlapping hypoconnectivity with these nuclei were observed in the sensorimotor cortex, temporal cortex, occipital cortex, and subcortical areas including the left thalamus, putamen, and cerebellum. Unique hypoconnectivity with DR was found in the PFC and cingulate cortices, whereas unique hypoconnectivity with MR was found in the pons. Dysconnectivity of these raphe

nuclei was commonly associated with depression. In addition, DR hypofunction was uniquely associated with anxiety and sleepiness, while MR hypofunction was uniquely associated with motor deficit, cognitive deficit, RBD, and pain.

4.1 | Altered spatial patterns of FC in the raphe nuclei in PD

Based on a relatively large sample, our results revealed that in the HC group, DR, and MR shared common positive connectivity with widespread cerebral cortex as well as subcortical regions such as basal ganglia, thalamus, brainstem, and cerebellum (Figure 1). Differential connectivity was also observed, with DR having more extensive connectivity with the cerebral cortex and basal ganglia and MR having more intense connectivity with the brainstem and cerebellum, which is consistent with the FC results reported by Beliveau et al. (2015). Previous fiber tracing studies also found overlapping and differential projections from DR and MR (Azmitia & Segal, 1978), with extensive 5-HT projections from both nuclei to the PFC, cingulate cortex, basal ganglia, amygdala, hippocampus, and thalamus. The projections from DR prefer more laterally located regions (cerebral cortex, striatum, etc.), whereas MR prefer more medially located regions (hippocampus, septum, and brainstem; Charnay & Leger, 2010; Commons, 2016). Our findings of connectivity patterns in the HCs are consistent with those 5-HT projections, thus suggesting that fMRI may provide an effective in vivo measurement of 5-HT-related brain function.

Differences between groups reveal that DR and MR share common hypo-connectivity in PD in the following aspects: (1) both two raphe nuclei are hypo-connected with the sensorimotor network (SMN), such as the sensorimotor cortex, left thalamus, and putamen. Functional impairment of the SMN has been reportedly associated with impaired sensory integration and motor deficit in PD (Caspers et al., 2021; Hou et al., 2021). (2) Both two nuclei also showed hypo-connectivity with the salience network (SN), including the insula, amygdala, and thalamus. Less engagement with the SN has been implicated in reward, emotion disturbances, and cognitive impairment (Chang et al., 2017; Christopher et al., 2015; Navalpotro-Gomez et al., 2020). (3) The cerebellum is thought to be associated with motor deficits and NMS such as hyposmia and cognitive impairment in PD (Riou et al., 2021; Wu & Hallett, 2013). Dysconnectivity between both raphe nuclei and cerebellum may lead to a range of symptoms mentioned above. (4) Both two nuclei exhibit decreased connectivity with the occipital cortex, which is a hub of memory development (Rosen et al., 2018; Yin et al., 2020). Sawyer and Kuo (2018) also observed that hypometabolism in the occipital regions was associated with dementia.

Despite the common dysconnectivity, there is also differential dysconnectivity between DR and MR in PD. Specifically, DR had unique hypo-connectivity with the bilateral vmPFC, OFC, ACC, and MCC. These hypo-connected areas are collectively referred to as the default mode network (DMN; Raichle, 2015). Decreases in DMN activity have been reportedly associated with olfactory impairment (Karunanayaka et al., 2017; Lu et al., 2019), depression (Xiao et al., 2022), cognitive impairment (Ruppert et al., 2021), sleep problem (Hong, Fallon, & Friston, 2021), and pain (Alshelh et al., 2018). Additionally, MR had decreased connectivity with the pons, which may lead to dysfunction of the cortico-ponto-cerebellar loops and impaired sensory-motor control (Glickstein, 1998; Kamali et al., 2010; Palesi et al., 2017).

Notably, the ROIs of the DR and MR used in this study are very small and located in the brainstem, which makes them challenging to accurately normalize from raw space to the MNI152 template space. In this study, the following steps were done to improve the accuracy of normalization. First, the origin of individual raw structural and functional image was manually adjusted to the origin of the MNI152 template (anterior commissure) using SPM12. Second, the functional images normalized to MNI152 space were superimposed on the MNI152 T1 template to check the accuracy of normalization (Figure S4).

4.2 | Common and unique roles of raphe nuclei dysconnectivity in PD

Not surprisingly, common and unique roles of DR and MR on motor symptoms and NMS are observed. Particularly, hypo-connectivity of DR with the left amygdala and MR with the left thalamus are jointly associated with depression. Previous studies also found structural and functional alterations in the amygdala and thalamus in depression (Hong, Li, et al., 2021; Miller et al., 2017; Sibille et al., 2009; Williams, 2017), thus dysconnectivity of the raphe nuclei with the amygdala and thalamus may be one of the mechanisms of depression in PD.

In addition, unique roles of DR in PD are as follows (Table 2): (1) hypo-connectivity with the left postcentral gyrus is negatively correlated with daytime sleepiness. Modulating role of serotonin in sleep–wake behavior has been widely reported (Monti, 2011; Vaseghi et al., 2022), thus, impaired connectivity between DR and sensory cortex may be a reason for daytime sleepiness. (2) Hypo-connectivity with the bilateral ACC/MCC is associated with anxiety. ACC is an important emotional processing hub and is involved in social anxiety (Duval et al., 2013). In addition, Li et al. (2021) found that serotonergic circuit from DR to ACC regulates emotion and sociability. Our findings suggest that anxiety may be associated with abnormalities of the serotonergic neural circuitry between DR and ACC.

Moreover, unique roles of MR in PD were also observed (Table 2). First, we found that decreased connectivity with the left cerebellum and bilateral pons was negatively correlated with the severity of motor impairment (MDS-UPDRS III scores and H&Y stage), suggesting that disrupted connectivity of the cortico-ponto-cerebellar loop may be a reason of motor deficits. Next, we observed that reduced connectivity with the left cerebellum was positively correlated with MoCA scores. As mentioned earlier, cerebellum is a hub of cognition (Jacobi et al., 2021), working memory and executive tasks are accompanied by activation of bilateral cerebellum (Guell

et al., 2018). Cerebellar lesions can lead to cognitive deficits (Argyropoulos et al., 2020). Therefore, reduced connectivity between MR and cerebellum could be related to cognitive impairment in PD. Besides, dysconnectivity between MR and the left insula was related to RBD. The insula has strong connection with wake and sleep-promoting regions such as hypothalamus and brainstem, and regulates sleep and wake activity (Chen et al., 2016). Therefore, impaired 5HT projection from MR to the insula may promote the development of RBD symptom. Finally, hypo-connectivity between MR and the left superior frontal gyrus was associated with pain. The superior frontal gyrus is located at the superior part of the PFC. 5-HT has been reported to play a crucial role in pain modulation, and 5-HT receptors is widely distributed in the PFC, making the PFC important in pain processing (Liu et al., 2020; Ong et al., 2019).

4.3 | Limitations

Our study highlights a common and unique clinical-functional relationship between DR and MR in PD. However, some important limitations should be considered when interpreting these findings. First, ROIs of DR and MR used in this study are very small and located in the brainstem, which makes them sensitive to motion and physiological noise (Beliveau et al., 2015). Although we have set strict head movement inclusion criteria and applied ICA to physiological noise correction to minimize these confounding effects, physiological noise might be still existed and represented as a potential confounder. Moreover, our study did not assess the serotonergic contribution to raphe FC changes, and future studies could combine serotonergic PET to directly examine the relationship between serotonergic deficits and raphe nuclei related network changes in PD. Third, dynamic connectivity could capture and explain the diversity of neural states, which may reflect the interplay of neuromodulation (Sporns, 2022). Measuring the dynamic connectivity of raphe nuclei may lead to a more comprehensive understanding of the functional abnormalities of raphe nuclei in PD and may reveal the possibility of the raphe nuclei as a neuromodulatory target. Future studies are needed to use dynamic functional connectivity to further reveal dysconnectivity profiles of DR and MR in PD.

5 | CONCLUSION

In conclusion, we revealed significant disorganization of the connectome in the raphe nuclei in PD. In addition, DR and MR of raphe nuclei have common, as well as unique roles in motor deficit and NMS in PD. Overall, our study provides novel insights into the neurophysiological mechanisms of motor deficit and NMS in PD.

AUTHOR CONTRIBUTIONS

Junling Wang: Conceptualization, methodology, software, formal analysis, writing-original draft, writing-review and editing. Junyan Sun, Linlin Gao, Dongling Zhang, and Lili Chen: Methodology, software, writing-review and editing. Tao Wu: Conceptualization, methodology, writing-review and editing, supervision, funding acquisition. All authors read and approved the final manuscript.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (82071423).

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Anyone interested in the study can contact the corresponding author for data availability. The software (DPABI, FSL) used in the study are open sources and links have been included in the article.

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REFERENCES

Alshelh, Z., Marciszewski, K. K., Akhter, R., di Pietro, F., Mills, E. P., Vickers, E. R., Peck, C. C., Murray, G. M., & Henderson, L. A. (2018). Disruption of default mode network dynamics in acute and chronic pain states. *NeuroImage: Clinical*, *17*, 222–231.

Argyropoulos, G. P. D., van Dun, K., Adamaszek, M., Leggio, M., Manto, M., Masciullo, M., Molinari, M., Stoodley, C. J., van Overwalle, F., Ivry, R. B., & Schmahmann, J. D. (2020). The cerebellar cognitive affective/Schmahmann Syndrome: A task force paper. *Cerebellum*, *19*(1), 102–125.

Azmitia, E. C., & Segal, M. (1978). An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. *The Journal of Comparative Neurology*, *179*(3), 641–667.

Bar, K. J., Kohler, S., Cruz, F., Schumann, A., Zepf, F. D., & Wagner, G. (2020). Functional consequences of acute tryptophan depletion on raphe nuclei connectivity and network organization in healthy women. *NeuroImage*, *207*, 116362.

Beliveau, V., Svarer, C., Frokjaer, V. G., Knudsen, G. M., Greve, D. N., & Fisher, P. M. (2015). Functional connectivity of the dorsal and median raphe nuclei at rest. *NeuroImage*, *116*, 187–195.

Buddhala, C., Loftin, S. K., Kuley, B. M., Cairns, N. J., Campbell, M. C., Perlmutter, J. S., & Kotzbauer, P. T. (2015). Dopaminergic, serotonergic, and noradrenergic deficits in Parkinson disease. *Annals of Clinical Translational Neurology*, *2*(10), 949–959.

Caspers, J., Rubbert, C., Eickhoff, S. B., Hoffstaedter, F., Südmeyer, M., Hartmann, C. J., Sigl, B., Teichert, N., Aissa, J., Turowski, B., Schnitzler, A., & Mathys, C. (2021). Within- and across-network alterations of the sensorimotor network in Parkinson's disease. *Neuroradiology*, *63*(12), 2073–2085.

Chang, Y. T., et al. (2017). Salience network and depressive severities in Parkinson's disease with mild cognitive impairment: A structural covariance network analysis. *Frontiers in Aging Neuroscience*, *9*, 417.

Charnay, Y., & Leger, L. (2010). Brain serotonergic circuitries. *Dialogues in Clinical Neuroscience*, *12*(4), 471–487.

Chen, M. C., Chiang, W. Y., Yugay, T., Patxot, M., Özçivit, İ. B., Hu, K., & Lu, J. (2016). Anterior insula regulates multiscale temporal organization

of sleep and wake activity. *Journal of Biological Rhythms*, *31*(2), 182–193.

Christopher, L., Duff-Canning, S., Koshimori, Y., Segura, B., Boileau, I., Chen, R., Lang, A. E., Houle, S., Rusjan, P., & Strafella, A. P. (2015). Salience network and parahippocampal dopamine dysfunction in memory-impaired Parkinson disease. *Annals of Neurology*, *77*(2), 269–280.

Commons, K. G. (2016). Ascending serotonin neuron diversity under two umbrellas. *Brain Structure & Function*, *221*(7), 3347–3360.

Duval, E. R., Hale, L. R., Liberzon, I., Lepping, R., N. Powell, J., Filion, D. L., & Savage, C. R. (2013). Anterior cingulate cortex involvement in subclinical social anxiety. *Psychiatry Research*, *214*(3), 459–461.

Glickstein, M. (1998). Cerebellum and the sensory guidance of movement. *Novartis Foundation Symposium*, *218*, 252–266 discussion 266–271, 332–333.

Goedert, M., Spillantini, M. G., del Tredici, K., & Braak, H. (2013). 100 years of Lewy pathology. *Nature Reviews. Neurology*, *9*(1), 13–24.

Griffanti, L., Douaud, G., Bijsterbosch, J., Evangelisti, S., Alfaro-Almagro, F., Glasser, M. F., Duff, E. P., Fitzgibbon, S., Westphal, R., Carone, D., Beckmann, C. F., & Smith, S. M. (2017). Hand classification of fMRI ICA noise components. *NeuroImage*, *154*, 188–205.

Guell, X., Gabrieli, J. D. E., & Schmahmann, J. D. (2018). Triple representation of language, working memory, social and emotion processing in the cerebellum: Convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *NeuroImage*, *172*, 437–449.

Hong, C. C., Fallon, J. H., & Friston, K. J. (2021). fMRI evidence for default mode network deactivation associated with rapid eye movements in sleep. *Brain Sciences*, *11*(11), 1528.

Hong, W., Li, M., Liu, Z., Li, X., Huai, H., Jia, D., Jin, W., Zhao, Z., Liu, L., Li, J., Sun, F., Xu, R., & Zhao, Z. (2021). Heterogeneous alterations in thalamic subfields in major depression disorder. *Journal of Affective Disorders*, *295*, 1079–1086.

Hou, Y., Wei, Q., Ou, R., Zhang, L., Yuan, X., Gong, Q., & Shang, H. (2021). Different resting-state network disruptions in newly diagnosed drug-naive Parkinson's disease patients with mild cognitive impairment. *BMC Neurology*, *21*(1), 327.

Huot, P., Fox, S. H., & Brotchie, J. M. (2011). The serotonergic system in Parkinson's disease. *Progress in Neurobiology*, *95*(2), 163–212.

Jacobi, H., Faber, J., Timmann, D., & Klockgether, T. (2021). Update cerebellum and cognition. *Journal of Neurology*, *268*(10), 3921–3925.

Kamali, A., Kramer, L. A., Frye, R. E., Butler, I. J., & Hasan, K. M. (2010). Diffusion tensor tractography of the human brain cortico-pontocerebellar pathways: A quantitative preliminary study. *Journal of Magnetic Resonance Imaging*, *32*(4), 809–817.

Karunanayaka, P. R., Wilson, D. A., Tobia, M. J., Martinez, B. E., Meadowcroft, M. D., Eslinger, P. J., & Yang, Q. X. (2017). Default mode network deactivation during odor-visual association. *Human Brain Mapping*, *38*(3), 1125–1139.

Li, L., et al. (2021). Dorsal raphe nucleus to anterior cingulate cortex 5-HTergic neural circuit modulates consolation and sociability. *eLife*, *10*, e67638.

Liu, Q. Q., Yao, X. X., Gao, S. H., Li, R., Li, B. J., Yang, W., & Cui, R. J. (2020). Role of 5-HT receptors in neuropathic pain: Potential therapeutic implications. *Pharmacological Research*, *159*, 104949.

Lu, J., et al. (2019). Disruptions of the olfactory and default mode networks in Alzheimer's disease. *Brain and Behavior: A Cognitive Neuroscience Perspective*, *9*(7), e01296.

Lv, L., Zhang, H., Tan, X., Long, Z., Qin, L., Bai, R., Xiao, Q., Wu, Z., Hu, S., Tan, C., Liao, H., Yan, W., Tang, B., Ren, F., & Wang, C. (2022). Associated factors and abnormal dorsal raphe nucleus connectivity patterns of freezing of gait in Parkinson's disease. *Journal of Neurology*, *269*(12), 6452–6466.

Maillet, A., Météreau, E., Tremblay, L., Favre, E., Klinger, H., Lhommée, E., le Bars, D., Castrioto, A., Prange, S., Sgambato, V., Broussolle, E., Krack, P., & Thobois, S. (2021). Serotonergic and dopaminergic lesions underlying Parkinsonian neuropsychiatric signs. *Movement Disorders*, *36*(12), 2888–2900.

Miller, O. H., Bruns, A., Ben Ammar, I., Mueggler, T., & Hall, B. J. (2017). Synaptic regulation of a thalamocortical circuit controls depression-related behavior. *Cell Reports*, *20*(8), 1867–1880.

Monti, J. M. (2011). Serotonin control of sleep-wake behavior. *Sleep Medicine Reviews*, *15*(4), 269–281.

Navalpotro-Gomez, I., Kim, J., Paz-Alonso, P. M., Delgado-Alvarado, M., Quiroga-Varela, A., Jimenez-Urbieta, H., Carreiras, M., Strafella, A. P., & Rodriguez-Oroz, M. C. (2020). Disrupted salience network dynamics in Parkinson's disease patients with impulse control disorders. *Parkinsonism & Related Disorders*, *70*, 74–81.

Ong, W. Y., Stohler, C. S., & Herr, D. R. (2019). Role of the prefrontal cortex in pain processing. *Molecular Neurobiology*, *56*(2), 1137–1166.

Palesi, F., de Rinaldis, A., Castellazzi, G., Calamante, F., Muhlert, N., Chard, D., Tournier, J. D., Magenes, G., D'Angelo, E., & Gandini Wheeler-Kingshott, C. A. M. (2017). Contralateral cortico-ponto-cerebellar pathways reconstruction in humans in vivo: Implications for reciprocal cerebro-cerebellar structural connectivity in motor and non-motor areas. *Scientific Reports*, *7*(1), 12841.

Poewe, W. (2008). Non-motor symptoms in Parkinson's disease. *European Journal of Neurology*, *15*(Suppl 1), 14–20.

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disorders*, *30*(12), 1591–1601.

Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience*, *38*, 433–447.

Riou, A., Houvenaghel, J. F., Dondaine, T., Drapier, S., Sauleau, P., Drapier, D., Duprez, J., Guillery, M., le Jeune, F., Verin, M., & Robert, G. (2021). Functional role of the cerebellum in Parkinson disease: A PET Study. *Neurology*, *96*(23), e2874–e2884.

Rosen, M. L., Sheridan, M. A., Sambrook, K. A., Peverill, M. R., Meltzoff, A. N., & McLaughlin, K. A. (2018). The role of visual association cortex in associative memory formation across development. *Journal of Cognitive Neuroscience*, *30*(3), 365–380.

Ruppert, M. C., Greuel, A., Freigang, J., Tahmasian, M., Maier, F., Hammes, J., Eimeren, T., Timmermann, L., Tittgemeyer, M., Drzezga, A., & Eggers, C. (2021). The default mode network and cognition in Parkinson's disease: A multimodal resting-state network approach. *Human Brain Mapping*, *42*(8), 2623–2641.

Sawyer, D. M., & Kuo, P. H. (2018). "occipital tunnel" sign on FDG PET for differentiating dementias. *Clinical Nuclear Medicine*, *43*(2), e59–e61.

Shen, Y., Wang, J., Peng, J., Wu, X., Chen, X., Liu, J., Wei, M., Zou, D., Han, Y., Wang, A., & Cheng, O. (2022). Abnormal connectivity model of raphe nuclei with sensory-associated cortex in Parkinson's disease with chronic pain. *Neurological Sciences*, *43*(5), 3175–3185.

Sibille, E., et al. (2009). A molecular signature of depression in the amygdala. *The American Journal of Psychiatry*, *166*(9), 1011–1024.

Sporns, O. (2022). The complex brain: Connectivity, dynamics, information. *Trends in Cognitive Sciences*, *1364–6613*(22), 00183–00188.

Vaseghi, S., Arjmandi-Rad, S., Eskandari, M., Ebrahimnejad, M., Kholghi, G., & Zarrindast, M. R. (2022). Modulating role of serotonergic signaling in sleep and memory. *Pharmacological Reports*, *74*(1), 1–26.

Williams, L. M. (2017). Amygdala-guided neurofeedback for major depression. *The American Journal of Psychiatry*, *174*(8), 717–718.

Wilson, H., Giordano, B., Turkheimer, F. E., Chaudhuri, K. R., & Politis, M. (2018). Serotonergic dysregulation is linked to sleep problems in Parkinson's disease. *NeuroImage: Clinical*, *18*, 630–637.

Wu, T., & Hallett, M. (2013). The cerebellum in Parkinson's disease. *Brain*, *136*(Pt 3), 696–709.

Xiao, Y., Wang, D., Tan, Z., Luo, H., Wang, Y., Pan, C., Lan, Z., Kuai, C., & Xue, S. W. (2022). Charting the dorsal-medial functional gradient of the default mode network in major depressive disorder. *Journal of Psychiatric Research*, *153*, 1–10.

Yin, Q., Johnson, E. L., Tang, L., Auguste, K. I., Knight, R. T., Asano, E., & Ofen, N. (2020). Direct brain recordings reveal occipital cortex involvement in memory development. *Neuropsychologia*, *148*, 107625.

SUPPORTING INFORMATION

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

How to cite this article: Wang, J., Sun, J., Gao, L., Zhang, D., Chen, L., & Wu, T. (2023). Common and unique dysconnectivity profiles of dorsal and median raphe in Parkinson's disease. *Human Brain Mapping*, *44*(3), 1070–1078. https://doi.org/10.1002/hbm.26139