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ORIGINAL ARTICLE

Functional neural networks stratify Parkinson's disease patients across the spectrum of cognitive impairment

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Abstract

Introduction: Cognitive impairment (CI) is a significant non-motor symptoms in Parkinson's disease (PD) that often precedes the emergence of motor symptoms by several years. Patients with PD hypothetically progress from stages without CI (PD-normal cognition [NC]) to stages with Mild CI (PD-MCI) and PD dementia (PDD). CI symptoms in PD are linked to different brain regions and neural pathways, in addition to being the result of dysfunctional subcortical regions. However, it is still unknown how functional dysregulation correlates to progression during the CI. Neuroimaging techniques hold promise in discriminating CI stages of PD and further contribute to the biomarker formation of CI in PD. In this study, we explore disparities in the clinical assessments and resting-state functional connectivity (FC) among three CI stages of PD.

Methods: We enrolled 88 patients with PD and 26 healthy controls (HC) for a cross sectional clinical study and performed intra- and inter-network FC analysis in conjunction with comprehensive clinical cognitive assessment.

Results: Our findings underscore the significance of several neural networks, namely, the default mode network (DMN), frontoparietal network (FPN), dorsal attention network, and visual network (VN) and their inter–intra-network FC in differentiating between PD-MCI and PDD. Additionally, our results showed the importance of sensory motor network, VN, DMN, and salience network (SN) in the discriminating PD-NC from PDD. Finally, in comparison to HC, we found DMN, FPN, VN, and SN as pivotal networks for further differential diagnosis of CI stages of PD.

Conclusion: We propose that resting-state networks (RSN) can be a discriminating factor in distinguishing the CI stages of PD and progressing from PD-NC to MCI or PDD. The integration of clinical and neuroimaging data may enhance the early detection of PD in clinical settings and potentially prevent the disease from advancing to more severe stages.

KEYWORDS
cognitive impairment, dementia, fMRI, MCI, Parkinson's disease, resting-state

1 | INTRODUCTION

Parkinson's disease (PD) is a common chronic and progressive neurodegenerative disease characterized by the loss of dopaminergic neurons in the substantia nigra and α-synucleinopathy (Aarsland & Kramberger, 2015; Göttlich et al., 2013). The dysfunctional cortico-striatal-thalamic-cortical loop in PD causes cardinal motor symptoms such as tremor, akinesia, and rigidity (Jankovic, 2008). Moreover, multiple neurotransmitter deficiencies result in heterogeneity in the clinical phenotype, associating with a wide spectrum of motor and non-motor clinical symptoms (Aarsland & Kramberger, 2015; Lee et al., 2022). The symptoms and progression of PD vary greatly from person to person (Fereshtehnejad et al., 2017), in addition to the important role of clinical phenotypes, age of onset, disease severity, or neuropathological changes in PD progression (Krüger et al., 2017). On the other hand, alterations in many functional brain networks are one of the potential underlying mechanisms in the relationship between neuropathology and behavioral outcomes in PD (Gratton et al., 2019). The widespread symptoms and functional neuropathology in PD emphasize the need to study PD functional neural networks and their alterations in relation to each other (Filippi et al., 2018).

Non-motor symptoms have recently been shown to play an increasingly important role in the clinical heterogeneity of PD (Mu et al., 2017). One of the major non-motor symptoms is cognitive impairment (CI), which includes working memory deficits, planning, visuospatial, and set-shifting problems (Khoo et al., 2013). CI can start years before the motor manifestations in PD patients (Aarsland et al., 2017). Importantly, the presence of mild CI (MCI) in PD (PD-MCI) is a transitional state between PD with normal cognition (PD-NC) and PD with dementia (PDD) and has been introduced as an independent predictor for PDD (Aarsland & Kurz, 2010). Therefore, early detection of the CI and consequently the PD-MCI would play an integral role in the course of PD diagnosis and treatment. Of note, the symptoms of CI in PD are linked to changes in a number of different brain regions via neural pathways, in addition to being the result of dysfunctional subcortical regions (Suo et al., 2022). However, it is still unknown how functional dysregulation correlates to disease progression (Filippi et al., 2021).

Recently, advanced neuroimaging techniques have been instrumented in identifying the alterations in functional connections associated with PD and providing a deeper understanding of the disease (Caspers et al., 2021). There is emerging evidence for using the functional magnetic resonance imaging (fMRI) findings as biomarkers of CI (i.e., PD-NC, PD-MCI, and PDD) in PD (Hou & Shang, 2022; Rektorova et al., 2014). Resting-state fMRI (rs-fMRI) is a relatively new technique for assessing spontaneous or intrinsic neural activity, which measures slow oscillations in the blood-oxygen-level dependent (BOLD) signal, whereas subjects are awake and not performing any specific task (Tahmasian et al., 2017). The rs-fMRI enables identification of brain networks associated with symptoms of the disease (Filippi et al., 2021) and can be a critical tool for investigating the causal factors of CI in PD and in the process of diagnosis (Li et al., 2018). The altered functional connectivity (FC) of the default mode (DMN), dorsal attention (DAN), frontoparietal (FPN), salience (SN), and related visual networks (VN) are among the previously reported rs-fMRI hallmarks in PD patients with CI (Filippi et al., 2018). Furthermore, the rs-fMRI findings in studies of CI stages of PD (i.e., patients with PD-NC, PD-MCI, and PDD) based on the predefined cognitive levels have shown differences in the FC, but there is not a clear consensus over differentiating neural correlates across the spectrum of PD-CI (Wolters et al., 2019). In this context, there are only a few studies that have included all three clinically predefined CI stages of PD (i.e., patients with PD-NC, PD-MCI, and PDD) in their analysis, and specifically, the number of PDD patients included in these studies is relatively low. Additionally, due to the heterogeneity of the analysis methods used to investigate brain FC, the need to implement methods that can be further used in clinical diagnosis and individualized medicine and also distinguish different stages of

CI in the progression of PD is highly warranted in recent years. Therefore, there is a need for studies that include all three CI stages of PD cognitive phenotypes, specifically patients with PDD, to better understand the FC and clinical differences between the CI stages of PD. To address these problems, we investigated the differences in the clinical outcomes and the resting-state FC of all three CI stages of PD and compared them among each other and also with healthy control (HC). We hypothesized that FC shifts in association with CI progression in PD and includes the discriminatory factors for diagnosing and predicting CI stages in PD. The purpose of this study was to investigate clinical and inter- and intra-network differences in the CI stages of PD by reporting the differences between three CI stages and better defining the characteristics of the PD-MCI and PDD stages, and showing the transition between CI stages. This paper shows how the three CI stages of PD differ from each other in terms of clinical outcomes and resting-state FC, as well as how they differ from HC. We show that the results of rs-fMRI networks, in conjunction with clinical factors related to cognitive outcomes, can be useful in distinguishing between CI stages of PD. This can hopefully highlight the treatment plans based on the differences between the CI stages of PD.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

The ethics committee of the Istanbul Medipol University approved this study with authorization number 10840098-604.01.01-E.3958. We used a cross sectional study design. We first assessed 138 participants for their eligibility in the study. PD patients were recruited in the neurology clinic at the Istanbul Medipol University Medipol Mega Hospital (Bagcilar, Istanbul). We screened these participants based on the inclusion and exclusion criteria (see below) and included 94 PD patients and 26 HC participants in the initial evaluation. All participants gave their informed consent in accordance with the principles of the Declaration of Helsinki. We completed the data collection between 2018 and 2022. An experienced neurologist (coauthor LH) evaluated the patients and gave the clinical diagnosis of PD within the framework of brain bank criteria (Gelb et al., 1999) and based on the most up-to-date Movement Disorders Society (MDS) diagnostic criteria (Postuma et al., 2015). The clinical diagnosis of CI in PD was after the neuropsychometric assessment and clinical criteria as PD-MCI (Litvan et al., 2012) and PDD (Emre et al., 2007). The diagnosis of the groups was according to the MDS guidelines as Level II for PD-MCI and "Probable PD-Dementia" for PDD. We included the patients with clinical dementia rating (CDR) global score of 1 and 2 in the PDD group. Due to the difficulty of conducting evaluations such as fMRI in patients with CDR 3, we excluded patients with the CDR global score of 3. Some patients with PDD were taking acetylcholinesterase inhibitors. However, we ensured that there was no treatment change in the 2-week period prior to enrollment, and the fMRI scans for these patients took place at a stable dose.

2.2 | Inclusion criteria

Inclusion criteria for the PD patients were the diagnosis of PD, receiving stable anti-parkinsonian medication for at least 1 month and aged between 45 and 90 years old.

2.3 | Exclusion criteria

Exclusion criteria were the history of unstable medical treatment, pyramidal findings, cerebellar involvement, gaze palsy, and autonomic dysfunction, receiving device-assisted therapy, and contraindications for MRI scanning.

2.4 | Clinical evaluation

We performed the comprehensive neuropsychological testing and fMRI scans for all the participants. Besides screening tests for PD patients, including the Hoehn and Yahr test, the unified PD rating scale-motor (UPDRS-III), and demographic screening, we performed a precise cognitive assessment by means of a neuropsychological test battery. A multidisciplinary team of neurologists, neuropsychologists, and physical therapists conducted the overall assessment of the patients.

2.5 | Cognitive assessment

We used the mini-mental state examination (MMSE) to assess global cognition (Güngen et al., 2002). We used the digit span test to evaluate attention functions (Kurt et al., 2011). We then used the Wechsler Memory Scale (WMS) to evaluate memory functions including the WMS visual reproduction and recognition test (immediate and delayed) (Karakaş et al., 1999), and Oktem Verbal Memory Process Test (Turkish Verbal Memory Test: SBST) (Bosgelmez et al., 2015). We evaluated the language skills by the Boston Naming Test (Soylu & Cangöz, 2018). We evaluated visual and perceptual functions by judgment of the line orientation test (Spencer et al., 2013) and Benton Facial Recognition Test (Schretlen et al., 2001). Finally, we evaluated executive functions by Stroop test (Karakaş et al., 1999) and the clock drawing test (Shulman, 2000). We used the Turkish versions of the memory, language, and executive functions tests.

2.6 | Functional magnetic resonance imaging protocol

2.6.1 | Data acquisition

We conducted structural and functional MRI scans at the Istanbul Medipol University Medipol Mega University Hospital in the

Radiology clinic (Bagcilar, Istanbul). To conduct rs-fMRI, we used a 32-channel head coil using standard sequences. We explained the nature of the MR environment to all participants and trained them to act accordingly, with regard to the safety of patients with movement disorders (Van Dijk et al., 2012). Similar to our previous studies in patients with neurodegenerative diseases (Budak et al., 2022; Hajebrahimi et al., 2022), to get the benefit of the highest level of participants' alertness was planned the functional scan as the earliest in the imaging queue, just after the localizer protocol: (1) localizer, (2) rs-fMRI, (3) fieldmap, (4) T1 weighted structural, and (5) T2 weighted structural scans. We scanned the patients during their "ON" period. We asked the participants to fix their gaze on a spot inside the scanner, during resting-state data acquisitions, while keeping their eyes open and not thinking about anything particular or rhythmic (praying, counting, tapping, etc.), and instructed to stay still as much as possible. We suggested the participants close their eyes and rest during the structural scans. To minimize movement artifacts, we stabilized the patients' heads with spongy pads inserted between the sides of the head and the MR coil. The imaging process took approximately 30 min to complete, including preparation time.

We acquired the structural T1 and T2 images in the sagittal plane (TR/TE: 8.1/3.7), FOV (field-of-view) 256 × 256 × 190 mm^3 (FH [foot-to-head] × AP [anteior-to-posterior] × RL [right-to-left]), with the voxel size of 1 × 1 × 1 mm^3. The functional scan parameters were 300 volumes (TR/TE: 2230/30 ms, FA 77°), FOV 240 × 240 × 140 mm^3 (RL × AP × FH), voxel size of 3 × 3 × 4 mm^3, and 35 slices. These parameters, including scanning protocols and their order, were the same in all participants except for a difference in TR and volume of functional scans due to a scanner upgrade, whereas the study was in progress (TR: 2000 ms, number of volumes: 341). To eliminate the effects of this difference in the group comparisons and network analysis, we included covariates of no interest in the GLM (General Linear Model) design during the analysis steps. Additionally, we included age, brain volume (in mm^3-normalized to [MNI]), and L-dopa equivalent daily dose (LEDD) as covariates of no interest in the GLM design (Tahmasian et al., 2017).

2.7 | Analysis

2.7.1 | fMRI data analysis

We used FMRIB FSL software package for data preprocessing and subsequent functional network analysis (Jenkinson et al., 2002; RRID: SCR_002823). We first convert DICOM files into NIFTI format using the dcm2niix tool (Li et al., 2016; RRID: SCR_023517). Next, we used the fsl_anat script for brain extraction from the NIFTI images. After brain extraction, we used the tools supplied in the FSL FEAT interface for motion correction and smoothing with a Gaussian kernel of 5 mm full width at half maximum (FWHM) in each voxel. To filter the functional data, we used a 150 s high-pass filter. We used the FSL MCFLIRT algorithm to correct the head motions between dynamic scans (Jenkinson et al., 2002). We spatially normalized the functional and anatomical data to MNI152 for group comparisons; in three steps using the FSL FLIRT and FNIRT linear and nonlinear registration tools, respectively. Using limited transformations, we first matched the functional brain images to the participants' own high-resolution anatomical images (6 DOF). Next, we matched the participants' high-resolution anatomical images with MNI152 standard brain images, utilizing 12 DOFs and nonlinear transformations in the second step. The distortion resolution was 10 mm. In the third step, using matrices from previous transformations, we mapped low-resolution functional images to the MNI152 brain. In a separate step, we processed each participant's functional data in the native space into an exploratory independent component analysis (ICA) using the FSL MELODIC tool to determine movement, physiological (heart, respiration, etc.), and other imaging artifacts. By inspecting signal features of ICA components such as spatial distribution, frequency spectrum, and temporal fluctuation, we manually hand-classified the components and filtered those compatible with the noise from the functional data using the fsl_regfilt command (Griffanti et al., 2017). We then transformed the functional data into the standard space after artifact removal in the native space.

2.8 | Independent component analysis and dual regression

We reported the analysis pipeline in Figure 1. For group comparison, we also utilized the FSL MELODIC tool to perform a group-level ICA. For this reason, we used a temporal concatenation approach in FSL MELODIC to perform group-ICA with 20 components on the preprocessed artifact-free data (Beckmann & Smith, 2004). Afterward, we evaluated each component's spatial correlation with RSNs and labeled the components consistent with the RSNs explained elsewhere (Smith et al., 2009). Next, we used FSL dual regression to first regress the group-level ICs into all subjects' data and extract timeseries of each of the 20 components and in the second regression, regressing timeseries into the same resting-state data of the participants to calculate the subject-specific spatial maps of each ICs (Beckmann et al., 2009; Nickerson et al., 2017). We finally calculated z-stat images for each of the subject-specific spatial maps. For the group comparisons, we designed a GLM for a one-way analysis of variance (ANOVA) (4 groups × 1 time). We included TR, volume, age, brain volume (MNI), and LEDD as covariates of no interest in our group-level GLM design. We used the FSL randomize tool for nonparametric inference with 5000 random permutations to examine the significance of the differences. We corrected multiple comparisons using cluster-based threshold-free cluster enhancement (TFCE) and considered the results significant at $p < .05$ (Smith & Nichols, 2009; Winkler et al., 2014).

2.9 | Network connectivity analysis

We reported the analysis pipeline in Figure 1. We used the tools implemented in FSLNets (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets) for inter-network connectivity analysis. For this reason and to better compare the results of network analysis with the literature, we

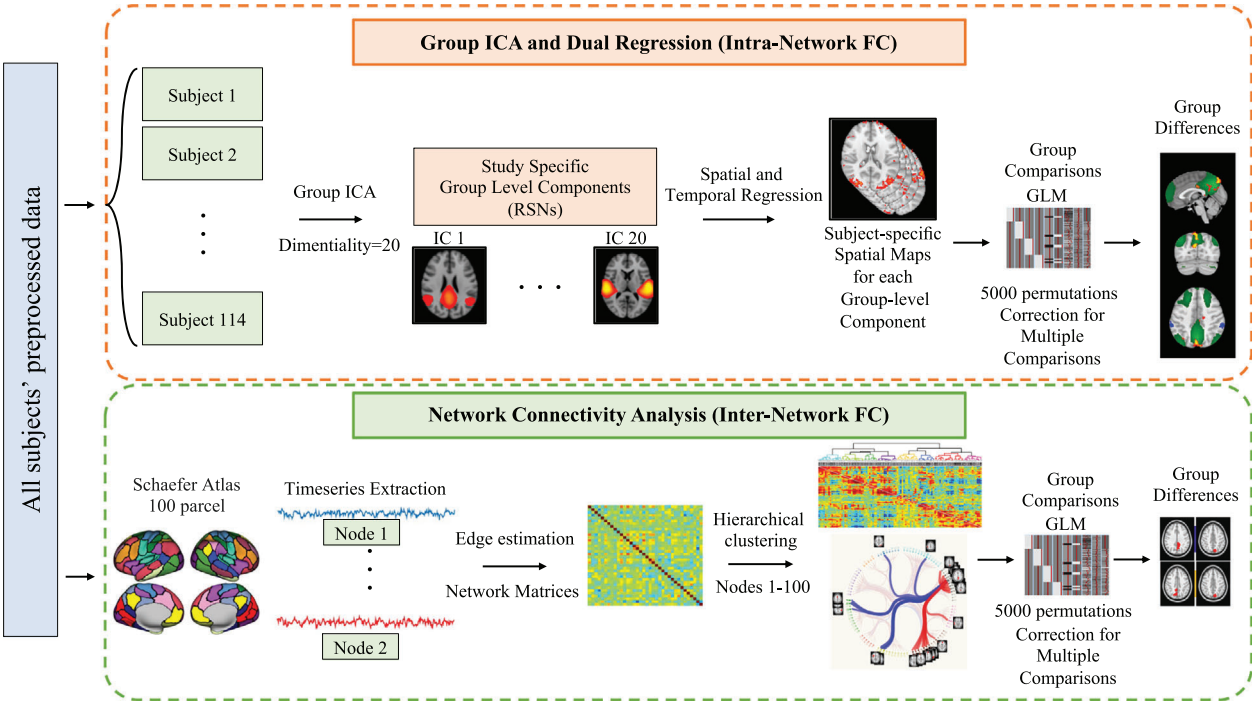

FIGURE 1 Analysis pipeline.

performed the network analysis utilizing a functional atlas. To evaluate the inter-network connectivity and the differences in network organization, we used the Schaefer2018 with 100 parcellations (Schaefer et al., 2018). These parcellations are generated from the rs-fMRI data of 1489 subjects by using a gradient weighted Markov random field approach and are registered using surface-based alignment. Different versions of parcellations from 100 to 1000 parcels are available and can be utilized based on the nature of the studies. Each parcel in the Schaefer parcellations is matched to a corresponding network in the 7 and 17 network parcellations by Yeo et al. (2011). For our inter-network connectivity comparisons in the current study, we used 100 parcellations that are projected to MNI space and match to 17 networks parcellations by Yeo et al.(2011) More information can be found at Schaefer et al. (2018) and https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal. Afterward, we extracted subject-specific time series using the first stage of dual regression to shape the inter-network connectivity matrices. We calculated full and partial correlations between 100 nodes. Although full correlation can demonstrate indirect connections between two specific nodes, in partial correlation, other nodes are controlled to calculate the correlation between two specific nodes, which therefore may provide better information regarding the direct connectivity (Bijsterbosch et al., 2017). After obtaining the full and partial correlation matrices across all subjects, we extracted the full and partial correlation matrices of each group separately. Consequently, we prepared the hierarchical clustering for each of the described groups by utilizing the nets_hierarchy tool in MATLAB (a total of four hierarchical clustering dendrograms as HC, PD-NC, PD-MCI, and PDD). Next, we used the partial and full correlation matrices in all four groups to create a connectome to compare the results with hierarchical clusterings. Finally, we used the same GLM design explained above to compare the groups regarding inter-network connectivity. Here, we fed 100 nodes into the GLM design and included previously described covariates (i.e., TR, number of volumes, age, brain volume, and LEDD) in the GLM design as covariates of no interest. The cross-subject GLM on the partial correlation netmats (FSL-randomize with 5000 permutations) gave uncorrected and corrected *p*-values as output (i.e., corrected for multiple comparisons with TFCE across the 100 × 100 netmat elements). We extracted the corrected *p*-values to report the differences in the network organization between groups. Furthermore, we reported contrasts and their related significant nodes. To better visualize the differences between groups related to the inter-network connectivity, we compared the connectograms of groups and showed multiple significant nodes with their connections (here, partial connections) to the entire network. Of note, we used those nodes that were significant more than once (at least 2) in the group comparison to visualize the difference. Finally, to better conceptualize how our results explain the CI progression across the cognitive spectrum of the PD, we prepared an overall continuum map to better show the transition among different CI stages of the disease, merging all the results coming out of the group-level ICA and network FC comparison.

2.10 | Statistical analysis

We used IBM SPSS (Statistical Package for Social Science) version 25.0 for statistical analysis. We presented the mean, standard deviation, and

TABLE 1 Distribution of demographic data.

		HC ($n = 26$)	PD-NC ($n = 25$)	PD-MCI ($n = 32$)	PDD ($n = 31$)	Between group differences
Age (M ± SD)		58.2 ± 8.1	67.8 ± 9.0	67.9 ± 9.9	71.8 ± 8.9	$F_3 = 11.19, p < .001$*
Sex	Female (*n*/%)	17/65.4	6/24	16/50	17/54.8	$X_3 = 9.48, p = .024$*
	Male (*n*/%)	9/34.6	19/76	16/50	14/45.2	
Years of education (M ± SD) (years)		9.9 ± 5.2	6.5 ± 3.9	4.1 ± 4.2	10.2 ± 11.4	$F_3 = 5.15, p = .002$*
Dominant hand	Right (*n*/%)	26/100	25/100	32/100	31/100	- -
	Left (*n*/%)	0/0	0/0	0/0	0/0	
Duration of disease (M ± SD) (months)		0/0	47.8 ± 32.1	69.2 ± 48.4	101.9 ± 45.2	$F_3 = 33.76, p < .001$*
LEDD		–	649.0 ± 393.8	750.2 ± 253.9	832.1 ± 425.1	$F_2 = 1.77, p = .177$
UPDRS-III (M ± SD)		0/0	24.0 ± 18.6	29.7 ± 13.9	49.3 ± 20.3	$F_3 = 47.05, p < .001$*
Hoehn–Yahr scale (M ± SD)		0.0 ± 0.0	2.1 ± 0.8	1.8 ± 0.8	2.7 ± 0.9	$F_3 = 64.34, p < .001$*

Abbreviations: HC, healthy control; LEDD, L-dopa equivalent daily dose; M, mean; PD, Parkinson's disease; PD-NC, PD-normal cognition; PD-MCI, PD-mild cognitive impairment; PDD, PD dementia; SD, standard deviation; UPDRS, unified Parkinson's disease rating scale.
*$p < .05$.

percentage values in the descriptive statistics of the data. We measured the normal distribution of the variables with the Kolmogorov–Smirnov test. Next, we evaluated the nominal data of the independent variables with the chi-square test, and the numerical data with the one-way ANOVA test. The significance value was accepted as $p < .05$.

2.11 | Sample size

The sample size was determined using the "G*power sample size calculator" (Faul et al., 2007). The sample size was calculated as 112 subjects using "ANCOVA: Fixed effects, main effects, and interaction" design for four groups with a power of 95% ($\alpha = .05, \beta = .95, \lambda = 17.92, F = 2.68$) and an effect size of 0.40.

3 | RESULTS

From the included participants, six PD patients refused to complete the study and were excluded. We included 88 patients with PD in the study and allocated them into three groups as the PD-NC Group ($n = 25$), the PD-Mild CI (PD-MCI) Group ($n = 32$), and the PDD Group ($n = 31$). We also included 26 HC in the study (Figure 2).

3.1 | Cognitive assessment results

The demographic and clinical variables and their statistical comparisons are shown in Table 1. Overall, 49% (56/114) of the participants were female. Patients with PDD were significantly older (71.8 ± 8.9), had a longer duration of the disease (101.9 ± 45.2, months), had higher LEDD, and worse UPDRS-III compared with the PD-NC, PD-MCI, and HC groups ($p < .05$). Between-group cognitive status is shown in Table 2. There were statistically significant differences in all parameters between groups ($p < .05$). As expected, the PDD group performed worse in cognitive assessments when compared to PD-NC, PD-MCI, and HC groups. We found statistically significant and gradual deterioration from HC to PDD in the neuropsychometric cognitive assessments including attention, executive functions, memory, language, visual spatial functions, and general cognition ($p < .001$). In all clinical outcomes, there was a significant gradual decrease in scores from HC to PD-NC, from PD-NC to PD-MCI, and from PD-MCI to PDD ($p < .001$). Post hoc findings between groups are shown in Supplementary File 1.

3.2 | Functional neuroimaging results

3.2.1 | Group comparison with dual regression

We conducted the final analysis with the data from 114 participants (88 PD patients and 26 HC), divided into four groups. We labeled 12 out of the 20 components as components of interest regarding their representative networks (Smith et al., 2009). Significant between-group differences in the network components and representative maps are given in Figure 3 ($p < .05$; corrected for multiple comparisons with TFCE). We showed the comparison between groups as FC differences in each of the components, considering the transition of the disease continuum from HC to PD-NC, PD-MCI, and PDD. Additionally, the number of voxels in the significant contrasts with minimum *p*-values, *t*-values, peak MNI152 coordinates, and their labels on the Harvard-Oxford Atlas are shown in Table 3. In general, our Dual Regression results showed that patients with PD-NC and PD-MCI had reduced FC in the left FPN compared to HCs. Additionally, decreased FC of DMN, left FPN, and SN and increased FC of sensory motor network (SMN) and VN were observed in PDD patients compared to HC. Briefly, compared to HCs, FC in the LFPN decreases in all three CI stages. Contrastingly, the PDD patients showed an additional decrease in the FC in

TABLE 2 Clinical between groups findings.

		HC ($n = 26$)	PD-NC ($n = 25$)	PD-MCI ($n = 32$)	PDD ($n = 31$)	
		M ± SD	M ± SD	M ± SD	M ± SD	Between group differences
Attention	Digit span forward	6.6 ± 2.3	5.3 ± 0.8	5.0 ± 0.8	4.2 ± 0.9	$F_3 = 18.06, p < .001$*
	Digit span backward	3.6 ± 1.0	3.6 ± 1.2	3.0 ± 1.0	2.1 ± 1.0	$F_3 = 14.12, p < .001$*
Executive functions	Stroop spontaneous correction	1.4 ± 1.7	1.7 ± 2.2	4.0 ± 3.9	2.6 ± 1.3	$F_3 = 5.47, p < .001$*
	Stroop false answers	0.9 ± 2.4	3.0 ± 3.8	6.2 ± 9.8	10.7 ± 11.8	$F_3 = 13.23, p < .001$*
	Stroop time difference	51.3 ± 21.4	128.1 ± 235.3	160.7 ± 155.7	296.3 ± 173.0	$F_3 = 5.78, p < .001$*
	Clock drawing	3.7 ± 0.9	2.2 ± 1.6	2.9 ± 1.7	1.5 ± 1.2	$F_3 = 18.21, p < .001$*
Memory	Visual immediate recall	9.6 ± 2.4	6.1 ± 3.1	5.2 ± 3.5	2.9 ± 2.2	$F_3 = 28.10, p < .001$*
	Visual delayed recall	7.7 ± 3.4	4.4 ± 2.9	4.3 ± 3.6	1.4 ± 1.8	$F_3 = 22.55, p < .001$*
	Visual recognition	2.8 ± 1.1	2.1 ± 1.1	1.8 ± 1.0	1.1 ± 1.0	$F_3 = 11.40, p < .001$*
	VMPT immediate recall	5.6 ± 2.2	3.8 ± 1.4	3.2 ± 1.3	2.3 ± 1.1	$F_3 = 21.89, p < .001$*
	VMPT delayed recall	11.4 ± 2.2	6.4 ± 3.0	6.1 ± 2.8	3.5 ± 3.3	$F_3 = 87.94, p < .001$*
	VMPT recognition	3.4 ± 1.9	3.9 ± 1.6	6.6 ± 3.3	4.3 ± 3.3	$F_3 = 7.76, p < .001$*
	VMPT total	14.9 ± 0.3	13.1 ± 2.2	11.8 ± 1.2	8.6 ± 3.5	$F_3 = 34.03, p < .001$*
Language	Boston naming test	27.0 ± 3.4	22.6 ± 6.3	21.6 ± 7.4	18.2 ± 6.3	$F_3 = 8.70, p < .001$*
Visual spatial functions	Benton face recognition	43.5 ± 5.5	42.4 ± 4.1	38.2 ± 8.6	36.8 ± 6.6	$F_3 = 6.52, p < .001$*
	Line orientation	35.2 ± 15.0	21.6 ± 4.9	10.7 ± 8.6	10.5 ± 9.9	$F_3 = 42.49, p < .001$*
General cognition	MMSE	27.6 ± 1.9	26.2 ± 2.2	23.6 ± 3.3	19.1 ± 3.4	$F_3 = 50.21, p < .001$*

Abbreviations: HC, healthy control; M, mean; MMSE, mini-mental standard examination test; PD, Parkinson's disease; PDD, PD dementia; PD-MCI, PD-mild cognitive impairment; PD-NC, PD-normal cognition; SD, standard deviation; VMPT, verbal memory process test.

*$p < .05$.

TABLE 3 Between groups comparisons, results of dual-regression corrected for multiple comparisons with threshold-free cluster enhancement (TFCE, *p*-value <.05).

Group-ICA network	Contrast	Number of voxels	Min *p* value	*t* Value	Peak MNI152 coordinate	Brain regions, Harvard-Oxford Atlas and Cerebellar Atals in MNI152 space
a-DMN	**HC > PDD**	1186	.0052	4.607	4 −58 −6	Cerebellum right V
	PD-NC > PDD	210	.0266	3.899	16 −76 −24	Cerebellum right crus I
p-DMN	**HC > PDD**	207	.015	4.510	−10 −66 26	Precuneus cortex
	PD-MCI > PDD	797	.003	4.425	−10 −62 32	Precuneus cortex
	PDD > PD-MCI	36	.023	5.152	−46 −38 24	Parietal operculum cortex
LFPN	**HC > PD-MCI**	82	.012	4.781	18 10 −8	Right thalamus
	HC > PDD	129	.027	4.432	6 −30 60	Precentral gyrus
	HC > PD-NC	434	.015	4.407	−10 −14 12	Left thalamus
m-VN	**PD-MCI > PDD**	73	.013	5.284	−38 −88 −18	Lateral Inferior occipital cortex
l-VN	**PDD > HC**	198	.027	3.740	32 −98 14	Occipital pole
	PDD > PD-NC	91	.01	5.690	52 −14 42	Posterior inferior temporal gyrus
	PDD > PD-MCI	1508	.011	4.532	−22 −84 −24	Occipital fusiform gyrus
SMN	**PDD > HC**	1213	.017	3.738	−12 −52 70	Superior parietal lobule
	PDD > PD-NC	2009	.017	3.705	20 −44 74	Postcentral gyrus
SN	**HC > PDD**	85	.022	4.631	52 −24 42	Supramarginal gyrus
TPN	**PD-MCI > PDD**	2	.05	4.415	26 −54 −18	Temporal occipital fusiform cortex

Abbreviations: a-DMN, anterior default mode network; HC, healthy control; lVN, lateral visual network; LFPN, left frontoparietal network; mVN, medial visual network; PD, Parkinson's disease; PDD, PD-dementia; PD-NC, PD-normal cognition; PD-MCI, PD-mild cognitive impairment; p-DMN, posterior default mode network; SMN, sensory-motor network; SN, salience network; TPN, temporoparietal network.

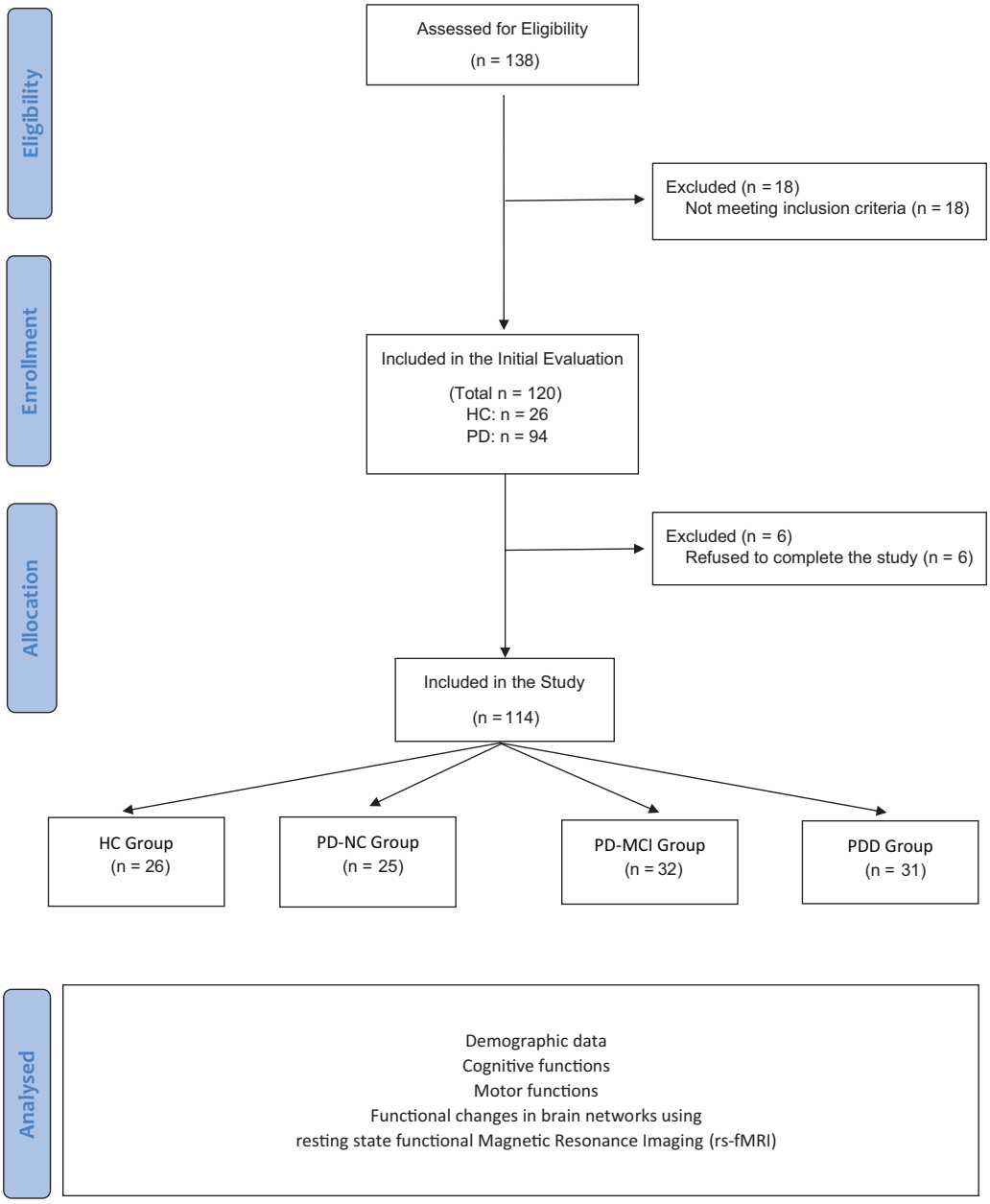

FIGURE 2 Flowchart of the study.

the DMN and SN, whereas these patients had increased FC in the VN and SMN compared to HC. This increase in FC in SMN and VN was also seen in the comparison of PDD versus PD-NC. In comparison of PDD versus PD-MCI, we found decreased FC of the DMN, temporoparietal network, and VN and increased FC of DMN and VN. Therefore, different nodes of DMN and VN in PDD showed both increased and decreased FC when compared to PD-MCI.

3.3 | Network connectivity with FSLNets

Four hierarchical clustering dendrograms were calculated and presented as HC, PD-NC, PD-MCI, and PDD (Supplementary File 2). These dendrograms can show the progression of sparseness from HC toward PD and among CI stages, from PD-NC to PD-MCI and PDD. Group comparisons regarding network connectivity based on Schaefer parcellation (accepted as significant at $p < .05$, FWE-corrected) revealed significant differences in various contrasts between 10 pairs of nodes. The edges between these significant nodes and related violin plots showing edge strength differences between groups are shown in Table 4 and Figure 4. Nodes that were significant more than once (at least 2) were used to visualize the difference between the groups regarding the inter-network connectivity. Nodes 35 (left precuneus), 39 (left posterior cingulate cortex), 91 (right posterior cingulate cortex), and 27 (right medial posterior prefrontal cortex) were significant more than once, and their connection in the connectogram is used

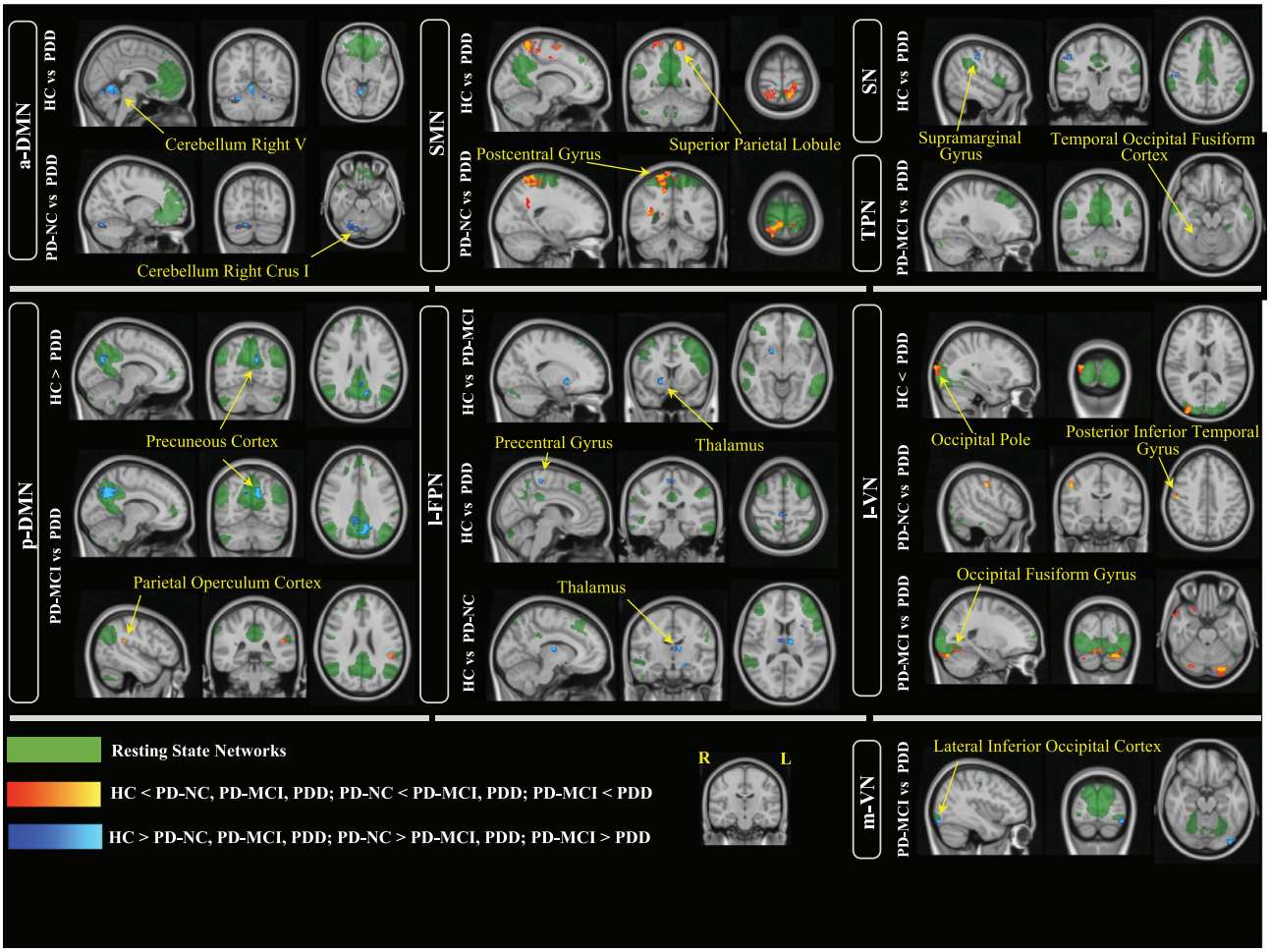

FIGURE 3 Significant DR analysis between Parkinson's disease (PD)-normal cognition (NC), PD-Mild cognitive impairment (MCI), PD-dementia (PDD), and healthy control (HC). $p < .05$; corrected for multiple comparisons with threshold-free cluster enhancement (TFCE). Resting-state networks are shown in green. Pairwise comparisons show the functional connectivity (FC) differences in the transitions between stages. Peak regions are shown with arrows. More information on cluster sizes and their anatomical locations is given in Table 3. All images are shown in the radiological convention. a-DMN, anterior default mode network; l-FPN, left frontoparietal network; l-VN, lateral visual network; m-VN, medial visual network; p-DMN, posterior default mode network; SMN, sensory-motor network; SN, salience network; TPN, temporoparietal network.

for visualization purposes in the inter-network comparisons (Figure 5). Finally, in Figure 6, the continuum of the disease was shown to better represent the differences between groups and show the transition in the CI stages of PD. Overall, our network analysis with FSLNETS revealed that, compared to HC, FC between nodes of the DMN-VN in PD-MCI increased, whereas FC between nodes of the DMN in PDD decreased. In addition, increased FC of SN-DMN was observed in PD-MCI compared to PD-NC. Importantly, decreased FC of FPN and DMN (both correlation and anticorrelation) was observed in their own nodes and also in communication with each other in PDD compared to PD-MCI. These results admitted the positive and negative synchronizations in PDD compared to the PD-MCI. Finally, these altered synchronizations were accompanied by a decreased FC of VN-DAN in PDD compared to PD-MCI.

4 | DISCUSSION

Using clinical behavioral data and rs-fMRI data of patients with PD, we showed the differences between three stages of PD related to the cognitive phenotype, including PD-NC, PD-MCI, and PDD, and compared them with HC. Our results showed the importance of DMN, FPN, DAN, and VN in distinguishing the PD-MCI from PDD; SMN, VN, DMN, and SN in distinguishing the PD-NC from PDD; and DMN, FPN, VN, and SN in in distinguishing the CI stages of PD from HC. Hypothetically, PD progresses from stages without CI to MCI and to dementia. PD-MCI is a transitional stage that comes after PD-NC and before PDD and can be a sign of dementia in people with PD (Yu & Wu, 2022). More challenges with daily living arise for PD patients as the disease progresses from PD-NC to PD-MCI or PDD (Leroi et al., 2012). Discovering the biomarkers linked to various cognitive PD phenotypes and,

TABLE 4 Intra-network differences between groups, Schaefer2018 with 100 parcellation.

Contrast	Parcellation name	Yeo 17 networks
PD-MCI > HC	Right dorsal prefrontal cortex	Default B
	Right extra-striate superior	Visual peripheral
HC > PDD	Left inferior parietal lobule	Default B
	Left precuneus posterior cingulate cortex	Default A
PD-MCI > PD-NC	Left dorsal prefrontal cortex	Default B
	Left medial posterior prefrontal cortex	Salience ventral attention B
	Right dorsal prefrontal cortex	Default B
	Left medial posterior prefrontal cortex	Salience ventral attention B
PD-MCI > PDD	Left precuneus posterior cingulate cortex	Default A
	Left precuneus	Frontoparietal control C
	Right precuneus	Frontoparietal control C
	Left precuneus	Frontoparietal control C
	Right precuneus posterior cingulate cortex	Default A
	Left precuneus	Frontoparietal control C
	Right retrosplenial	Default C
	Left precuneus	Frontoparietal control C
	Right precuneus posterior cingulate cortex	Default A
	Left precuneus posterior cingulate cortex	Default A
	Right frontal eye fields	Dorsal attention B
	Right temporal occipital	Dorsal attention A

Note: Results of nonparametric tests using 5000 random permutations (FWE-corrected, $p < .05$).
Abbreviation: HC, healthy control; PD, Parkinson's disease; PDD, PD-dementia; MCI, mild cognitive impairment; NC, normal cognition.

later, classifying PD patients into the accurate CI stage of PD will be crucial for planning the necessary pharmacological, rehabilitative, or neuromodulatory treatment plans. Particularly, neuroimaging results would play a pivotal role in separating out the various CI stages of PD (Devignes et al., 2022; Martín-Bastida et al., 2021). Labrador-Espinosa et al. (2023) interestingly reported that degeneration in the cholinergic basal forebrain, which is the main cholinergic source of the brain, and cognitive decline detected by Montreal Cognitive Assessment scores were associated with cortical thinning in the medial superior and lateral frontal areas, lateral temporoparietal areas, entorhinal cortex, cuneus, precuneus, and posterior cingulate cortex (PCC) in patients with de novo PD that were followed longitudinally. These areas are largely similar to the brain regions associated with the networks that we found to be affected in CI in our study. In a comprehensive review by Wolters et al. (2019), from 17 studies included, comparing the rs-fMRI results only two studies have reported differences between four groups. In one of the studies, only six participants with PDD were included (Gorges et al., 2015) who were evaluated together with other patients with CI in the same group; therefore, the results could not be distinguished between PD-MCI and PDD. In the other study with 27 PD patients, only 9 PDD patients are included in the study, and the whole hypothesis has been made on the PCC (Zhan et al., 2018). The conclusion of this review paper has been reported according to the evaluation of both the PD-MCI and PDD populations as one population of patients with CI. Furthermore, in an important study by Fiorenzato et al. (2019), three stages of PD have been investigated to show the differences in brain network connectivity only by utilizing the temporal dynamic changes. Here, our results demonstrate clinical and neuroimaging differences between CI stages of PD. We discuss the differences between each of the CI stages with HC and further review the differences between the CI stages of PD with each other.

4.1 | CI Stages of PD versus HC

Although defined as cognitively normal, a subtle CI is also reported in the PD-NC population without the diagnosis of PD-MCI (Chua et al., 2021). Compared to HC, PD-NC has both increased and decreased FC, including decreased FC of FPN with DMN, VN, and DAN (Klobušiaková et al., 2019) and increased FC of VN-LFPN with a reduction in visuospatial processing by demonstrating a crucial decline in working memory (Wei et al., 2022). In an important study by Peraza et al. (2017), both decreased and increased FC in PD-NC and increased FC in PD-MCI compared to HC, as well as increased between-network FC of basal and motor networks, are reported. The increased FC/hyperconnectivity in the DMN, left and right FPN, SN, motor, basal ganglia-thalamic, and brainstem in patients without CI is interpreted as a compensation for the neuronal loss due to the pathophysiology of the PD. On the other hand, this hyperconnectivity has changed to hypoconnectivity in PD patients with PD-MCI mostly seen in the DMN, motor, and DAN.

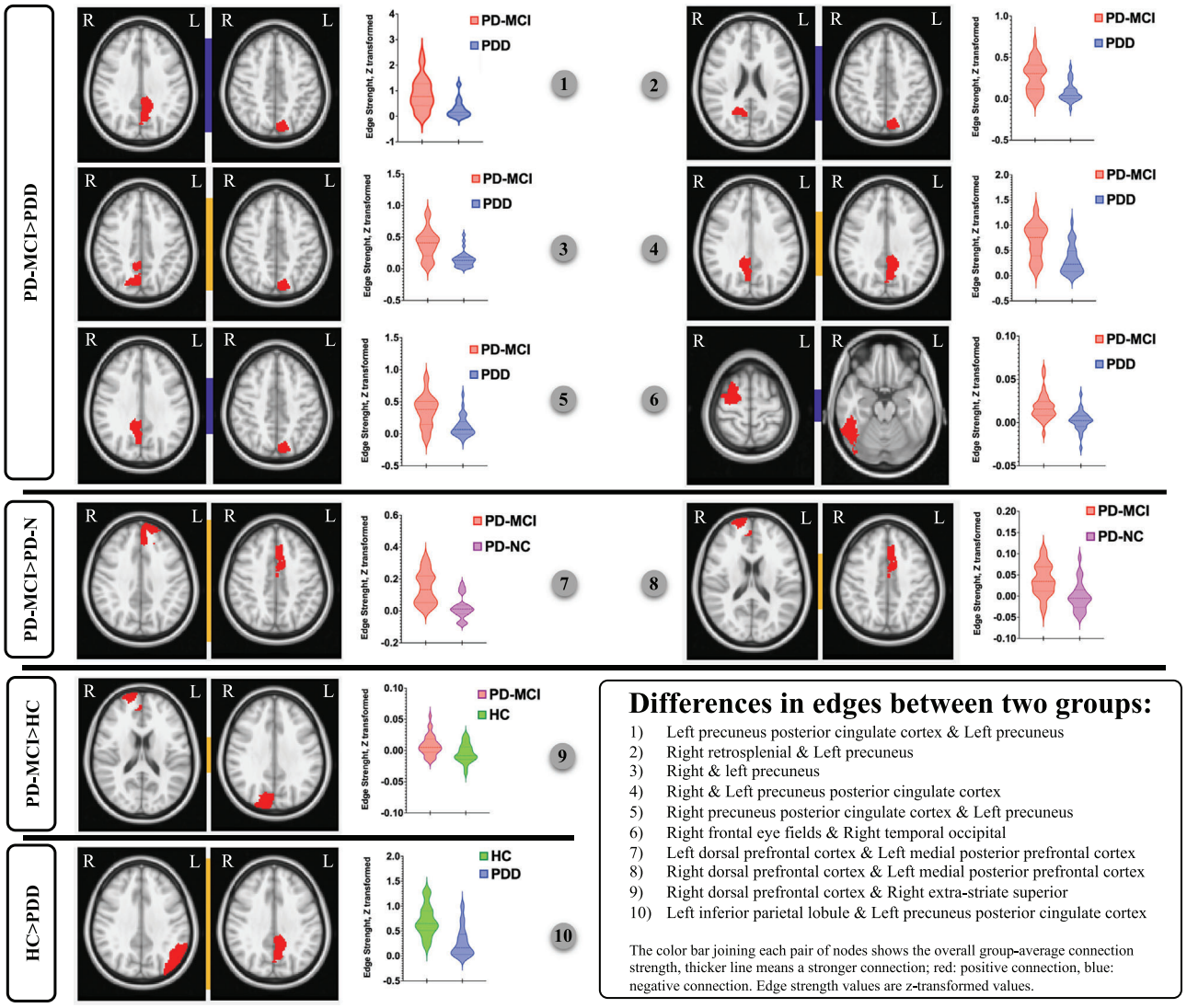

FIGURE 4 Significant differences in edge strength (Z transformed) across every two groups based on Schaefer2018 with 100 parcellation, showing significant differences in the connectivity between two nodes and related violin plots ($p < .05$, FWE-corrected). More information on the anatomical locations is given in Table 4.

Therefore, although there can be both a preserved and increased FC of DMN in the early stages of the disease preceding PD-MCI, the introduction of CI may lead to the loosening of connections specifically at nodes of DMN (Gorges et al., 2015). The above-described changes in FC can show heterogeneity in study results. As the disease progresses to the severe stages from PD-MCI to PDD, the FC and clinical outcomes continue to deteriorate. Over the course of a 3-year follow-up, PD patients show a progressive loss of FC in several brain regions, as confirmed by longitudinal studies (Dubbelink et al., 2014). FPN and DMN are two important networks associated with CI in PD. The integrations of cognitive and emotional processing, as well as mind-wandering, are considered to be regulated by the DMN. On the other hand, FPN is associated with higher cognitive skills such as actively preserving and processing information in working memory, problem solving and executive control, and making decisions in the context of goal-directed behavior (Grady et al., 2016). The impaired cognitive functions of PD, such as attention, executive functions, memory, and visuospatial abilities, can be associated with altered FC in related networks such as DMN and FPN due to the progressive neurodegenerative effect of the disease (Baggio et al., 2015; Dubbelink et al., 2014; Gorges et al., 2015; Mak et al., 2015). Compared to HC, decreased FC of DMN was reported in PD-NC and PD-MCI, and decreased FC of FPN with bilateral prefrontal cortex (PFC) was reported in PD-MCI (Amboni et al., 2015). In advanced levels of the disease, subjects with PD-MCI and PDD demonstrate impaired FC in the FPN and its associated networks, even when controlled for dopaminergic medications (Borroni et al., 2015; Rektorova et al., 2012). Moreover, PDD patients have shown decreased FC of DMN and VN compared to HC in a previous study using 1.5 T scanning (Rektorova et al., 2012).

We discovered decreased FC of the FPN in all three stages compared to HC. FPN is an important neurocognitive network that can play a role in all CI stages of PD. Altered FC of FPN in our study can be

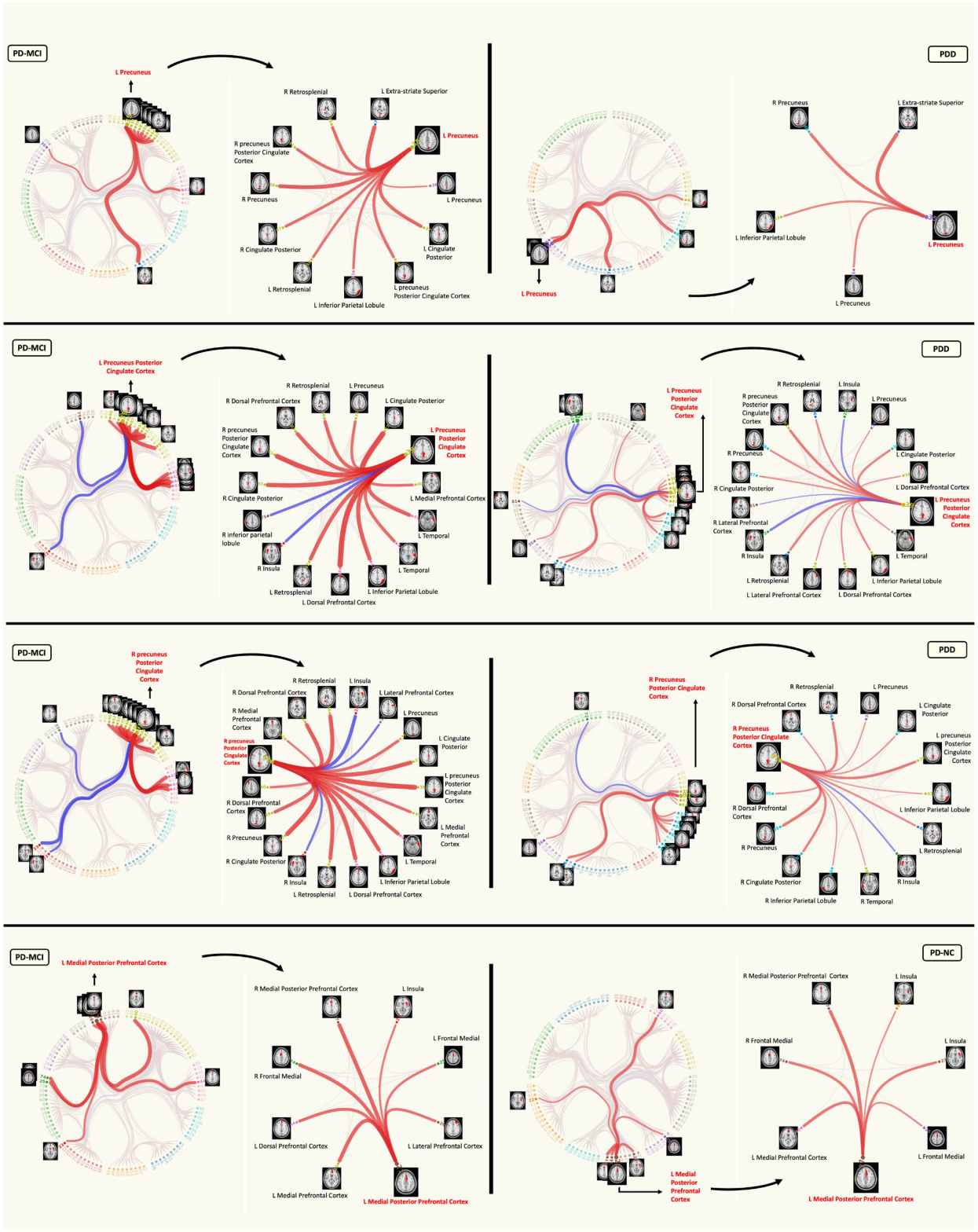

FIGURE 5 Differences between edge-bundling connectograms in the inter-network comparisons. Only four nodes are compared here as example. All connections (edges) of the selected node on the connectograms (e.g., L precuneus) are shown in the inset maps right to the connectograms. Positions of the nodes on the connectograms are according to their hierarchical clustering (Supplementary file 2). Red connections show positive correlations, and blue connections show anticorrelations. Darker and thicker lines indicate stronger connections. The interactive connectograms can be reached at https://osf.io/f4avz/.

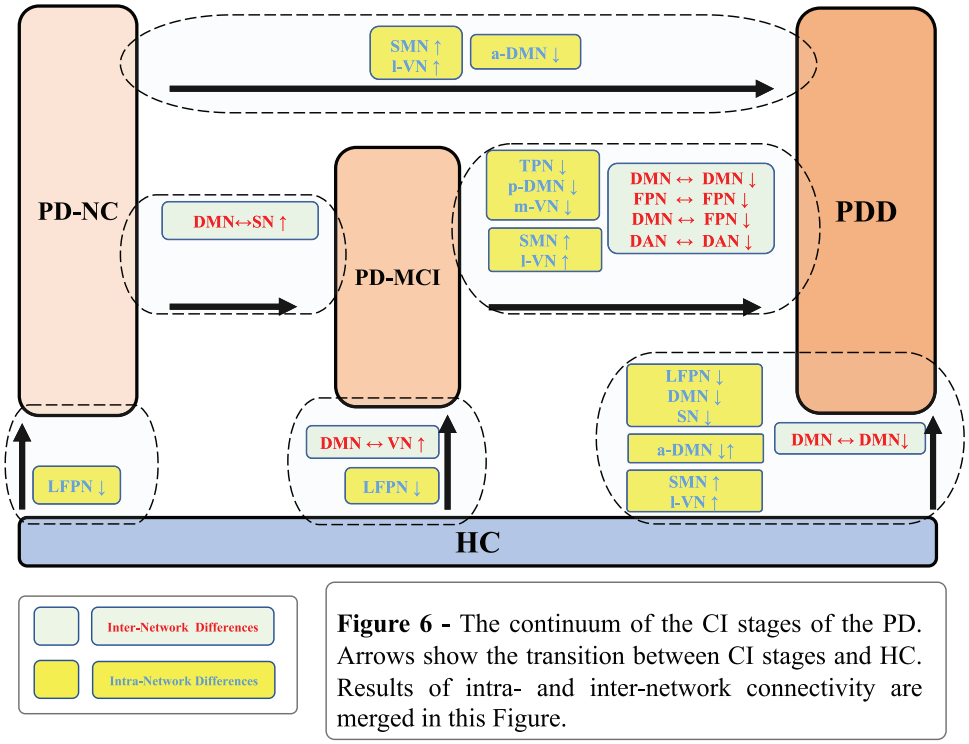

Figure 6 - The continuum of the CI stages of the PD. Arrows show the transition between CI stages and HC. Results of intra- and inter-network connectivity are merged in this Figure.

FIGURE 6 The continuum of the cognitive impairment (CI) stages of Parkinson's disease (PD).

interpreted as deteriorated clinical outcomes in all three groups, such as executive functions, memory, and visuospatial functions. Substantially, our DR results in the PD-NC and PD-MCI groups were significant in the FC of the left FPN with thalamus. Reduced FC of the mediodorsal thalamus with the paracingulate gyrus has previously been linked to CI in PD (Owens-Walton et al., 2021). In our results, the decreased FC of FPN extended beyond the network (in the thalamus) and can be interpreted as decreased communication of FPN with the thalamus. Although the FPN network is crucial for the cognitive abilities of PD patients, its association with the thalamus, one of the primary subcortical brain regions, can be significant. Additionally, our results showed decreased FC of the supramarginal gyrus in PDD versus HC. The results of an important neuroimaging meta-analysis by Tahmasian et al. (2017) have shown the importance of the supramarginal gyrus in PD patients compared to HC, which is affected by the role of dopamine replacement therapy, and highlight the importance of this region in the neuropathology of PD. Our results emphasize the importance of this region also in the advanced stages of the CI levels. Our results in the PDD group compared to HC also showed reduced FC of FPN, DMN, and SN and increased FC of SMN and VN. This was admitted by our network analysis results as decreased interconnection in the posterior nodes of DMN was found in PDD compared to HC, whereas communication was increased in the FC of VN and DMN in PD-MCI compared to HC. This can acknowledge the fact that the gradual decreased FC of neurocognitive networks in the progression of CI in PD results in worse cognitive functions, but in the advanced stages of CI, the load on motor and VNs may increase to compensate for this cognitive decline. Additionally, PD-MCI patients may try to increase the coupling between posterior-frontal regions of the brain (DLPFC and superior extrastriate cortex) that may be an indicator of a strategy in PD-MCI patients that try to rely on their imagery visualization to preserve their memory. Of note, differences between HC versus PD-MCI and PDD in our study may contribute to the previous knowledge in the literature that PD-MCI is more associated with the fronto-striatal dopaminergic dysfunction, which embraces clinical problems in executive functions and working memory, whereas PDD is associated with posterior cholinergic dysfunction that is involved in visuospatial dysfunctions and can be a predictor of worse cognitive progression (Kehagia et al., 2013).

4.2 | PD-NC versus PD-MCI and PDD

The most targeted intervention and care should be used to prevent PD patients from progressing to advanced CI. Therefore, comparing CI stages of PD with each other and investigating their progression from PD-NC is important. Many studies have shown decreased inter and intra-network FC in various networks in the progression from PD-NC to PD-MCI, predicting the CI (Amboni et al., 2015; Gorges et al., 2015; Lopes et al., 2017; Peraza et al., 2017), as well as a reduction in normal anticorrelation in DMN-DAN (Baggio et al., 2015). Like in comparisons to HC explained above, increased FC in the preceding stage before progression of the CI has given its place to hypoconnectivity in patients with CI, specifically MCI (Gratton et al., 2019). A recent longitudinal study showed that decreased FC between two nodes of the DMN (mPFC and PCC) can be a predictive factor in the conversion from PD-NC to PD-MCI (Zarifkar et al., 2021). Additionally, with the

progression of the PD, FC within SMN and the interconnection between DAN and FPN decreases and progressive decline in the DAN-FPN FC is associated with the CI in PD that can further be used as a marker in assessing the progression into PDD (Campbell et al., 2020).

However, some studies have also shown increased FC in the progression from PD-NC. Increased FC in cerebellar and insular networks (Peraza et al., 2017) and hyperconnectivity of PCC with several frontal and posterior regions are reported in PD-MCI compared to PD-NC (Zhan et al., 2018). Results of a graph theory study showed decreased long range connectivity but increased local interconnectedness in PD-MCI compared to PD-NC which was linked to visuospatial and memory functions (Baggio et al., 2014). In two studies by Aracil-Bolaños et al. (2019, 2022), stronger functional coupling between nodes of the normally anticorrelated DMN and central executive network, as well as increased SN-DMN FC, are reported in PD-MCI compared to PD-NC. With the deterioration of cognition in the progression of PD, FC changes as well. Reduced FC of DMN in the right inferior frontal gyrus in PDD compared to PD-NC has been shown in a previous study using 1.5 T scanning (Rektorova et al., 2012). The anterior cingulate cortex, caudate nucleus, medial and dorsolateral prefrontal cortices, and left precentral gyrus are recruited more strongly in PDD and PD-MCI patients than in PD-NC patients during working memory or executive function tasks (Nagano-Saito et al., 2014).

Our clinical and network analysis can admit the worse visuospatial functions in PDD and PD-MCI compared to PD-NC. Moreover, our results supported the increased FC between DMN and SN, as close nodes in the frontal regions of the brain showed increased FC in PD-MCI compared to PD-NC. Although less is reported about the comparisons between PD-NC and PDD in the literature, we observed increased FC in SMN and VN, probably as a compensation mechanism, with regard to decreases in the FC of the neurocognitive networks in PDD compared to PD-NC. Therefore, from PD-NC to PD-MCI and PDD, communication between close regions of the brain increases with the communication between DMN and SN in PD-MCI, and later in the PDD level that the decline in neurocognitive networks is settled, the terminal load is seen on SMN and VN to compensate the functional loss associated with PDD. Further studies may be needed to support this hypothesis that from PD-NC to MCI or PDD, the increased FC between neurocognitive networks such as DMN-SN can be a predictor of PD-MCI but increased FC in the SMN and VN can be a predictor of the PDD commence, therefore needed for emergent action. All this information should be supported by the clinical neuropsychological data.

4.3 | PD-MCI versus PDD

Differentiating between PD-MCI and PDD can be the most critical step in differentiating the CI stages of PD, as dementia can have debilitating effects on patients with an increased hospitalization rate and related life difficulties. Therefore, when possible, early detection and the application of effective interventions can be highly beneficial for patients with PD (Biundo et al., 2016). Longitudinal studies have shown a progressive age-independent decrease in FC in posterior brain regions-parietotemporal that may predict the CI toward PDD in patients with PD-MCI (Dubbelink et al., 2014). Previous studies have also shown that the FC between the frontal cortex and the corticostriatal cortex is disrupted in PDD, which leads to cognitive decline (Rektorova et al., 2012; Seibert et al., 2012). From PD-MCI to PDD, a decrease in FC of PCC is found with subcortical nuclei including the left caudate and right thalamus, as well as cortical regions including the precuneus, middle frontal, and right angular gyri in PDD compared to PD-MCI. Additionally, a compensatory loop connection is introduced between the cerebellum and FPNs in PD with CI (Zhan et al., 2018). Increased FC in the left middle and superior frontal gyri remains the same when comparing PDD to PD-NC. However, the FC between the PCC and anterior cingulate and paracingulate gyri changes to hypoconnectivity in PDD compared to PD-NC (Zhan et al., 2018). It is important to note that the described work by Zahn et al. was performed with only nine participants in each group. It can be inferred from this study that PCC, which is one of the main hubs in DMN, plays a key role in the progressive CI from PD-NC to PDD, as its FC increases from NC to MCI and then decreases from MCI to PDD. Similarly, two nodes of the DMN, PCC, and middle prefrontal cortex, showed increased FC in the absence of CI (PD-NC) and in the PDD (Chen et al., 2015). Regarding clinical symptoms, although memory performance is a significant determinant of the development of PDD, other cognitive processes like attention, executive function, visuospatial function, and language also play an important role in PDD development (Galtier et al., 2016). Biundo et al. concluded that language and executive functions, together with visuospatial and visuo-perceptual abilities, demonstrated the best sensitivity in detecting PDD (Rektorova et al., 2014). Our clinical data showed significant impairments in terms of attention, executive function, memory, and general cognition in PDD versus PD-MCI. Patients with PDD had more significant CIs than PD-MCI patients, particularly in the frontal/executive and memory domains. These findings may have consequences for cognitive prognosis. Our results showed that moving from PD-MCI to PDD can lead to decrease in DMN-FPN and DAN-VN functional connections. Importantly, our results were most dominant in the DMN-FPN. Therefore, it can be inferred that not only is the connectivity within the DMN and FPN important in differentiating the dementia levels of PD patients, but also how these two networks communicate with each other is also important in describing the progression from PD-MCI to PDD. We also found both increased and decreased FC in DMN and VN of PDD compared to PD-MCI. Therefore, we can propose that DMN and VN can show different changes in FC with other brain regions when transitioning from PD-MCI to PDD. This can further be supported by the decreased FC inside DMN, FPN, and DAN (the intra-network communications inside these networks decrease) and also between each other (both DMN and FPN communicate less with each other). Although decreased and increased FC of DMN and VN can be seen in the transition from PD-MCI to PDD, how DMN communicates in its own nodes and especially with FPN, and whether there is a hypofunction in the nodes of DAN, can be a classifier in further studies to capture PDD after PD-MCI.

4.4 | Limitations

Our study has some limitations. First, our results do not contain any longitudinal information, and the results presented in thus paper are related to the cross-sectional comparisons of the subgroups of PD in different CI stages. As PD is a progressive disease, evaluating the longitudinal data from the same population would give more overwhelming information regarding the progression of the disease and continuum of CI. Second, there were statistically significant differences in demographic parameters, and although we tried to match the patient groups with HC and included age as a covariate of no interest in our data analysis, patients were significantly older than the HCs. Third, the results of our study may reflect the general process of the degeneration ion PD. Further studies are needed with correlating specific cognitive functions with differences in the FC in studying the CI stages of PD.

5 | CONCLUSION

Our results showed the importance of DMN, FPN, DAN, and VN and their inter/intra-network FC in distinguishing the difference between PD-MCI and PDD. Additionally, our results showed the importance of SMN, VN, DMN, and SN in the progression from PD-NC to PDD. In comparison to HC, we found DMN, FPN, VN, and SN as important networks for further differential diagnosis of CI stages of PD. With emergence and progression of the diseases, patients with PD rely on different strategies in several networks to compensate for the loss in FC of neurocognitive networks, specially DMN and FPN. We propose that, if approved with clinical data, from PD-NC to MCI or PDD, the increased functional coupling between neurocognitive networks such as DMN-SN can be a predictor of PD-MCI, but increased FC in the VN and SMN can be a predictor of the PDD. We further propose that although decreased and increased in DMN and VN can be seen in transition from PD-MCI to PDD, but how DMN behaves in the inter- and intra-network level specially with FPN, and a hypofunction in nodes of DAN can be a predictor factor in further studies to capture PDD after PD-MCI. All these results were in line with clinical changes in cognitive functions. Utilizing clinical and neuroimaging data can contribute to capture early stages of PD in clinical settings, better plan the interventions in PD and consequently prevent progression of PD to more advanced levels of the disease.

AUTHOR CONTRIBUTIONS

Farzin Hajebrahimi and Miray Budak contributed to the writing of the original draft. Farzin Hajebrahimi, Mevhibe Saricaoglu, Zeynep Temel, and Tugce Kahraman Demir contributed to the data collection. Zubeyir Bayraktaroglu, Farzin Hajebrahimi, and Miray Budak conducted data curation. Farzin Hajebrahimi, Miray Budak, Mevhibe Saricaoglu, and Zubeyir Bayraktaroglu contributed to the formal analysis. Suleyman Yildirim and Lutfu Hanoglu acquired funding. Farzin Hajebrahimi, Miray Budak, and Zubeyir Bayraktaroglu contributed to the methodology. Lutfu Hanoglu, Suleyman Yildirim, and Zubeyir Bayraktaroglu contributed to the resources and supervision. All authors read and revised the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The interactive connectograms of the inter-network connectivity analysis of this study can be reached at https://osf.io/f4avz/.

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PEER REVIEW

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