scientific reports

Check for updates

OPEN

Changes in brain functional connectivity between on and off states and their relationship with cognitive impairment in Parkinson's disease

Kaoru Kinugawa[1], Tomoo Mano[1,2]✉ & Kazuma Sugie[1]

Parkinson's disease (PD) is characterized by motor and non-motor symptoms. Cognitive decline is crucial in disease progression and affect quality of life; however, their underlying mechanisms in PD remain unclear. We explored the relationship between cognitive impairment and functional connectivity (FC) using resting-state functional magnetic resonance imaging in 26 patients with sporadic PD, focusing on the changes in FC between on and off states. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) score. The correlation between MMSE scores and changes in FC values during on and off states was assessed using Pearson's correlation coefficient. The correlation between changes in FC during the on and off periods and cognitive function differed for each cognitive function item. MMSE memory scores were positively correlated with FC between the brainstem and the left cerebral hemisphere. MMSE attention scores were positively correlated with FC between the bilateral thalamus and frontal lobes and negatively correlated with FC between the left cerebral hemispheres. These findings may facilitate our understanding of the neural correlates underlying cognitive impairment in PD and help develop treatment strategies to preserve cognitive function.

Keywords Parkinson's disease (PD), Functional connectivity, Resting-state functional MRI, On and off states in PD, Mini-mental state examination, Motor and non-motor symptoms

Parkinson's disease (PD) is one of the most common and progressive neurodegenerative diseases, characterized by motor and non-motor symptoms. Cognitive impairment, a key non-motor manifestation of PD, reportedly accompanies disease progression and considerably impacts the quality of life of patients with PD[1]. In line with PD pathology, α-synuclein aggregates lead to the loss of dopaminergic, serotonergic, and other neurons. Numerous in vitro and in vivo studies have reported on dopamine-induced neurotoxicity[2]. Chronic use of levodopa results in dopamine-induced neurotoxicity, which causes various adverse reactions, including the wearing-off and on-off phenomena and dyskinesia[2]. The abnormal deposition of α-synuclein in the brain is considered the major pathogenic factor responsible for several non-motor symptoms of PD, including cognitive impairment[3,4]. Memory and attention disorders affect motor language and sentence comprehension, which are important for verbal communication[5,6]. Cognitive dysfunction in PD can be classified as dopaminergic or cholinergic. Dopaminergic dysfunction, which is causally linked to neuronal loss in the midbrain and mesolimbic system, leads to attention and executive dysfunction. In contrast, cholinergic dysfunction affecting the occipital and temporal lobes leads to memory and visuospatial impairments. One study suggested that memory impairments are mediated through the valence dimension, while attention disorders are mediated through arousal. Both may result from the effects of the disease progression as well as the therapeutic drug[7]. Cognitive impairment, particularly attentional dysfunction, can occur in the early stages of PD, even before the onset of pathological changes in the cerebral cortex[8,9]. However, the mechanisms underlying cognitive impairment in patients with PD are poorly understood.

Functional connectivity (FC) in brain networks indirectly indicates synaptic reciprocity via neurotransmitters[10]. Resting-state functional magnetic resonance imaging (rsfMRI) has been used to

[1]Department of Neurology, Nara Medical University, Kashihara, Japan. [2]Department of Rehabilitation Medicine, Nara Prefecture General Medical Center, Nara, Japan. ✉email: manoneuro@naramed-u.ac.jp

examine inter-regional correlations of brain activity and applied to analyze FC within the brain in various neurodegenerative diseases[11]. FC as a potential biomarker has been analyzed using various methods to evaluate functional integration by measuring the inter-regional temporal synchronization of neural activity[12,13]. A deeper understanding of the functional connectome can help bridge the gap between pathological changes in the brain and clinical presentation in patients with PD. Previous rsfMRI studies have revealed that aberrant FC in cortico-striatal and cortico-cortical circuits is strongly associated with motor and non-motor symptoms in PD[14]. Recently, abnormal FC in brain networks has been associated with the cognitive dysfunction in patients with PD[3]. It has been reported that FC in the brain changes between on and off states and that these changes may relate to various motor and non-motor symptoms[15–17]. FC analysis has provided new insights into the association between changes in functional brain networks between on and off states and fluctuations in cognitive dysfunction at different stages of PD[16,18].

On-off fluctuations can cause variability in motor and non-motor symptoms, affecting the overall quality of life and daily functioning of patients with PD[19]. They have a significant impact on patients' daily lives and can contribute to cognitive impairment in PD[20]. We hypothesized that fluctuations in FC between on and off states in patients with PD are involved in cognitive impairment. We aimed to investigate FC in brain networks using rsfMRI in patients with PD during the on and off states to explore the association between cognitive impairment and on-off FC alterations in brain networks. Most previous studies utilizing rsfMRI have defined the on and off states practically. For example, patients with PD who received levodopa therapy before MRI sessions were classified as being in the on state, while those who were withdrawn from anti-Parkinsonian medications before MRI sessions were classified as being in the off state[21,22]. However, these protocols did not reflect the natural fluctuations of on and off states experienced by patients with PD in daily life. Therefore, our study aimed to evaluate the changes in neural synchronization between clinically defined on and off states based on a PD symptom diary. In addition, intrahemispheric FC changes between on and off states might be potential indicators of PD. We explored the association between these FC changes caused by intrinsic dopamine depletion and the severity of cognitive impairment.

Methods

Patients

Twenty-nine patients with sporadic PD who visited Nara Medical University Hospital (Nara, Japan) between June 2020 and December 2021 were enrolled. Twenty-six right-handed patients diagnosed by two or more neurologists met the inclusion criteria.

The major inclusion criteria were:

(1) Confirmed PD and meeting the UK PD Society Brain Bank criteria [23].
(2) Age 20–90 years.
(3) Presenting with the wearing-off phenomenon.
(4) Absence of significant lesions on MRI.

The exclusion criteria were:

(1) Operations for deep brain stimulation and cardiac pacemaker placement.
(2) Severe cognitive dysfunction (Mini-Mental State Examination [MMSE] score < 10)
(3) Severe mental disorders.
(4) Claustrophobia or involuntary movements that could not remain still during MRI acquisition.
(5) Clinically unstable medical conditions, including serious cardiovascular and respiratory diseases.

All patients were clinically assessed by a single neurologist (KK) to increase evaluation reliability. This study was approved by the Nara Medical University Clinical Research Ethics Board (protocol number: 2670). Written informed consent was obtained from all patients. All study procedures were performed in accordance with the ethical standards of the Institutional Research Committee and adhered to the principles of the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Clinical assessments and study design

Before the MRI examinations, the patients were monitored for 1 week to assess their daily motor fluctuations and medication effects, ensuring accurate classification of on and off states. We evaluated the on and off states using a PD symptom diary. Alterations or adjustments to the prescribed medications were not allowed during the study. The on state was defined as the phase characterized by the effectiveness of dopamine replacement therapy, ensuring controlled symptoms and representing the period when patients exhibited optimal motor symptomatology as assessed by the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS–UPDRS) Part III[24]. The off state was defined as the phase characterized by the diminishing effects of treatment and the re-emergence of symptoms, which corresponded to when patients exhibited the most severe motor symptoms, as assessed by the MDS–UPDRS Part III. MRI examinations were conducted during the on and off states across two testing days, with patients concurrently undergoing assessment via the MDS–UPDRS Part III. Cognitive and neurological assessments were performed on separate days using the MMSE, Frontal Assessment Battery, and MDS–UPDRS (Parts I, II, and IV)[25]. We determined the time for cognitive assessment by identifying times when subjects were neither in their best on nor off state based on their PD symptom diary. The MMSE scores were divided into five subscales: "orientation," "memory," "language," "attention," and "visuospatial ability." The subscales were computed as follows: Orientation was the sum of the orientation to time and place items. Memory was the sum of the registration and recall items. Language was

the sum of the items assessing naming, repetition, comprehension, reading, and writing. Attention was the item assessing serial sevens. Visuospatial ability was assessed by copying intersecting pentagons[26]. We used the subscales of attention and memory to analyze the correlations with FC. The levodopa-equivalent daily dose (LEDD) was calculated as previously described[27]. The clinical features of the patients are summarized in Table 1.

MRI acquisition

MRI examinations were conducted on two separate testing days: one on an on day and the other on an off day. Before the MRI examinations, a clinical assessment using the MDS–UPDRS Part III was conducted. Functional and structural MRI data were acquired using a 3-Tesla MRI scanner (MAGNETOM Skyra, Siemens Healthcare) with a 20- or 32-channel head coil at Nara Medical University Hospital. Four patients underwent an MRI with a 20-channel head coil because of postural instability. The functional images were obtained through a gradient-echo echo-planar pulse sequence, which is sensitive to blood oxygen level-dependent (BOLD) contrasts, with the following parameters: repetition time (TR) = 1190 ms, echo time (TE) = 31 ms, matrix size = 64×64 mm^2, flip angle (FA) = 90°, field of view (FOV) = 212×212 mm^2, slice thickness = 3.2 mm, and voxel size = $3.3 \times 3.3 \times 3.2$ mm^3, for a total of 40 slices. Every patient underwent two runs, each consisting of 245 volumes. The T1-weighted structural images were obtained using the following parameters: TR = 1900 ms, TE = 2.75 ms, inversion time = 900 ms, matrix size = 256×256 mm^2, FA = 9°, FOV = 256×256 mm^2, slice thickness = 1 mm, and voxel size = $1.0 \times 1.0 \times 1.0$ mm^3, for a total of 192 slices. The patients were instructed to focus on a fixation cross and clear their minds from other thoughts during the acquisition phase[28].

Functional MRI data preprocessing

The MRI data were preprocessed using MATLAB (version R2020a, MathWorks, Natick, MA, USA), Statistical Parametric Mapping software (version 12), and the CONN toolbox (version 17)[29]. Functional and structural data were preprocessed according to the default pipeline provided by the CONN toolbox. The first ten scans of the functional images were excluded to address equilibration effects. Subsequently, the functional images underwent realignment, unwarping, slice-timing correction (ascending order), segmentation into gray matter

	PD ($n = 26$)		p-value
Age	72.77 ± 7.94		
Sex	12 male/14 female		
Disease duration, years	10.46 ± 6.36		
LEDD, mg	719.41 ± 291.23		
H–Y stages			
H–Y II	4 (15.4%)		
H–Y III	10 (38.5%)		
H–Y IV	10 (38.5%)		
H–Y V	2 (7.7%)		
MDS–UPDRS			
Total	On	Off	< 0.05
	66.04 ± 31.89	79.96 ± 32.25	
Part I	14.08 ± 7.56		
Part II	17.15 ± 10.20		
Part III	On	Off	< 0.05
	26.88 ± 15.51	41.19 ± 17.49	
Part IV	7.54 ± 3.93		
MMSE score			
Total	24.88 ± 3.69		
Orientation	8.08 ± 1.74		
Memory	5.46 ± 0.8		
Language	7.53 ± 0.58		
Attention	3.0 ± 1.74		
Visuospatial ability	0.77 ± 0.43		
FAB score	12.46 ± 2.77		

Table 1. Demographic and clinical characteristics of the patients. Disease duration was calculated as the number of years since PD diagnosis. The H–Y stage was used to assess the severity of motor symptoms. The MDS–UPDRS Part III was administered during the on and off states at the time of MRI examinations. The total dose of the medication was converted to LEDD (mg). Data are presented as means ± SDs. PD, Parkinson's disease; LEDD, levodopa-equivalent daily dose; H–Y, Hoehn and Yahr; MDS–UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; FAB, frontal assessment battery; SD, standard deviation.

(GM), white matter (WM), and cerebrospinal fluid (CSF), spatial normalization to the Montreal Neurological Institute (MNI) space (Montreal, Canada) with a functional target resolution of 2 mm, screening for outliers using artifact detection tools (ART)-based scrubbing with intermediate settings (97th percentile in normative data), and smoothing using an 8 mm full-width at half-maximum Gaussian kernel. Default denoising procedures were applied to the functional images, encompassing band-pass filtering (0.008–0.09 Hz), linear detrending, and removal of motion-related components using the component-based noise correction technique. We detected outlier time points in the motion parameters and global signal intensity using ART, an integral component of the CONN toolbox, to eliminate the effects of head movements and artifacts during the experiment. The ART approach is based on frame displacement greater than 0.9 mm and a global signal z-score greater than 5. Structural images were segmented into GM, WM, and CSF, followed by normalization to the MNI space with a structural target resolution of 2 mm.

FC analysis

Resting-state FC analysis was performed using a seed-based approach within the CONN toolbox framework. Regions of interest (ROIs) were selected from the FMRIB Software Library Harvard-Oxford cortical and subcortical structural atlases[29,30]. Based on previous literature, we selected the following 19 ROIs associated with cognitive impairment: frontal pole (FP), superior frontal gyrus (SFG), precentral gyrus (PreCG), postcentral gyrus (PostCG), temporal pole (TP), occipital pole (OP), thalamus (Tha), caudate (Cd), globus pallidus (GP), and brainstem (BS) (Table S1)[3,15,31–33]. We also selected two brain networks, namely the default mode network (DMN) and frontoparietal network (FPN), as additional ROIs. The DMN includes regions of the medial prefrontal cortex, precuneus cortex (PCC), and bilateral lateral parietal cortex (LPC). The FPN includes regions of the bilateral lateral prefrontal cortex (LPFC) and posterior parietal cortex (PPC) (Table S2)[11,15]. We selected representative regions from each brain lobe, avoiding closely positioned areas to minimize interaction and interference. In addition, we targeted regions linked to the basal ganglia network, which notably impacted PD. Each ROI was used as a seed region for further analyses. During the first-level analysis, seed-based FC analysis was performed using the weighted general linear modeling and bivariate correlation options in the CONN toolbox. The mean BOLD time series from each ROI was estimated by averaging the time-series data across all voxels within each ROI. Correlation coefficients between pairs of BOLD time series derived from the selected ROIs were computed using bivariate analysis. The resulting coefficient values were subjected to Fisher's transformation. Each transformed coefficient represented the FC value between the two brain regions. We calculated the intrahemispheric FC values by examining FC between regions within the same hemisphere. Specifically, we measured the FC between pairs of ROIs in the right hemisphere and in the left hemisphere. These intrahemispheric FC values were used for further analysis. Correlations between the MMSE scores and FC values were assessed using Pearson's correlation coefficient.

Statistical analyses

All statistical analyses were performed using MATLAB version R2020a. Pearson's correlation coefficient was used to evaluate the associations between the clinical assessment scores and FC values. Multiple regression analysis was performed using the MMSE total, attention, and memory scores as the dependent variables, while age, disease duration, LEDD, Hoehn and Yahr (H–Y) stage, UPDRS Part III, and FC between ON and OFF with significant changes or trends were used as independent variables. The normality of the data distribution was evaluated using the Shapiro–Wilk test. Statistical significance was defined as $p < 0.05$, whereas a trend toward significance was observed for p-values between 0.05 and 0.15. A correlation coefficient (r) > 0.35 was interpreted as demonstrating a strong correlation, whereas values between 0.35 and 0.30 indicated a weak correlation[34,35].

Results

Demographic and clinical characteristics

This study included 26 right-handed patients with sporadic PD (age, 72.77 ± 7.94 years; sex, 12 male/14 female; disease duration, 10.46 ± 6.36 years). No changes to patients' medication regimens were made during the study period. All patients demonstrated medication adherence through self-reporting. The mean H–Y stage of the patients was 3.38 ± 0.85, the mean LEDD was 719.41 ± 291.23 mg, and the mean MDS–UPDRS total scores in the on and off periods were 66.04 ± 31.89 and 79.96 ± 32.25, respectively. During the on state, the UPDRS Part III scores were 33.50 ± 19.23 for the 20-coil group (4 patients) and 25.68 ± 14.95 for the 32-coil group (22 patients, $p = 0.36$); during the off state, the scores were 45.0 ± 19.88 for the 20-coil group and 40.50 ± 17.44 for the 32-coil group ($p = 0.65$). The mean MMSE score was 24.88 ± 3.69, with a range of 17 to 30, and was divided into five subscales: orientation (8.08 ± 1.74), memory (5.46 ± 0.8), language (7.53 ± 0.58), attention (3.0 ± 1.74), and visuospatial ability (0.77 ± 0.43). The demographic characteristics and clinical features of the patients are summarized in Table 1.

Correlation between FC changes during the on and off states and cognitive function

To investigate how FC changes during the on and off states were associated with cognitive function, the correlation between intrahemispheric changes in FC from the on-to-off state and MMSE scores was analyzed. The memory and attention subscales were used in the correlation analysis of these subscales. The MMSE total score was positively correlated with changes in FC between the bilateral FP and Tha (right: $r = 0.35$, $p = 0.080$; left: $r = 0.34$, $p = 0.089$), and the bilateral GP, and Cd (right: $r = 0.39$, $p = 0.052$; left: $r = 0.64$, $p < 0.05$) (Fig. 1). The MMSE total score was negatively correlated with changes in FC between the bilateral FP and SFG (right: $r = -0.43$, $p < 0.05$; left: $r = -0.40$, $p < 0.05$) (Fig. 1). The MMSE subscale scores for memory were positively correlated with changes in FC between the BS and left SFG ($r = 0.30$, $p = 0.13$), PreCG ($r = 0.32$, $p = 0.11$), PostCG

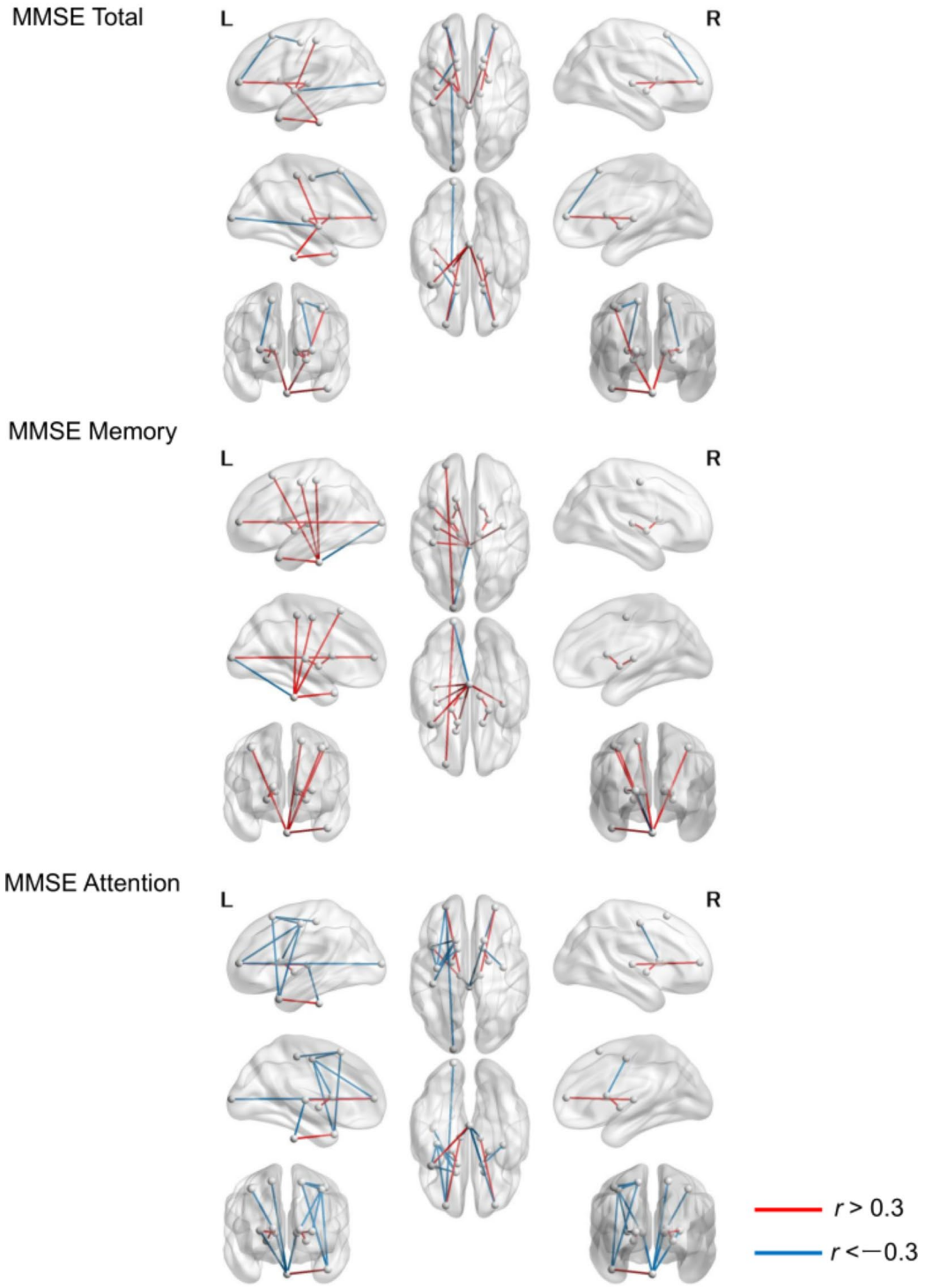

Fig. 1. Network analysis of correlation coefficients between MMSE scores and intrahemispheric FC changes during on and off states. In the eight-brain model, the first row, from left to right, shows the lateral view of the left hemisphere, the top view, and the lateral view of the right hemisphere. The second row, from left to right, shows the medial view of the left hemisphere, the bottom view, and the medial view of the right hemisphere. The third row displays the frontal view and the back view. The red lines indicate positive correlations ($r > 0.3$), while the blue lines indicate negative correlations ($r < -0.3$). MMSE, Mini-Mental State Examination; FC, functional connectivity; right; L, left. Images were created using the BrainNet Viewer toolbox[36].

($r=0.30$, $p=0.13$), and TP ($r=0.49$, $p<0.05$), as well as the bilateral GP and Cd (right: $r=0.36$, $p=0.073$; left: $r=0.66$, $p<0.05$), Tha (right: $r=0.37$, $p=0.059$; left: $r=0.66$, $p<0.05$) (Fig. 1). The MMSE subscale scores for attention were positively correlated with the changes in FC between the bilateral FP and Tha (right: $r=0.32$, $p=0.11$; left: $r=0.35$, $p=0.076$), and the bilateral GP and Cd (right: $r=0.33$, $p=0.10$; left: $r=0.47$, $p<0.05$) (Fig. 1). The MMSE subscale scores for attention were negatively correlated with bilateral changes in FC between Cd and PreCG (right: $r=-0.38$, $p=0.058$; left: $r=-0.42$, $p<0.05$) and changes in FC between the left SFG and PreCG ($r=-0.45$, $p<0.05$), PostCG ($r=-0.32$, $p=0.11$), and TP ($r=-0.36$, $p=0.068$) (Fig. 1)[36]. In the multiple regression analysis, we analyzed the correlation matrix and found no variables with $p<0.05$, and all variance inflation factors were less than 10.0, indicating no issues with multicollinearity. MMSE total was influenced by the left Cd-GP (Standardized coefficient (β)$=0.677$, $p<0.001$). Attention was influenced by the left PreCG-Cd ($\beta=-0.5287$, $p<0.001$) and H–Y Stage ($\beta=-0.350$, $p<0.05$), while memory was influenced by the left Cd-GP ($\beta=0.512$, $p<0.05$) and left GP-Tha ($\beta=0.379$, $p<0.05$).

Correlation between FC changes in brain networks and cognitive function

The correlation between intrahemispheric changes in FC in the brain network from the on-to-off state and MMSE scores was analyzed to investigate how changes in FC during the on and off states were associated with cognitive function. The DMN and FPN were used for the seed-based FC analyses. In the DMN, the MMSE total score was positively correlated with changes in FC between the left LPC and PCC ($r=0.31$, $p=0.12$). The MMSE subscale scores for memory were positively correlated with changes in FC between the left LPC and PCC ($r=0.43$, $p<0.05$). No correlation with changes in FC between the right LPC and PCC was observed (Fig. 2). The MMSE subscale scores for attention showed no correlation with the changes in FC between the bilateral LPC and PCC (Fig. 2). In the FPN, the MMSE total score was negatively correlated with changes in FC between the

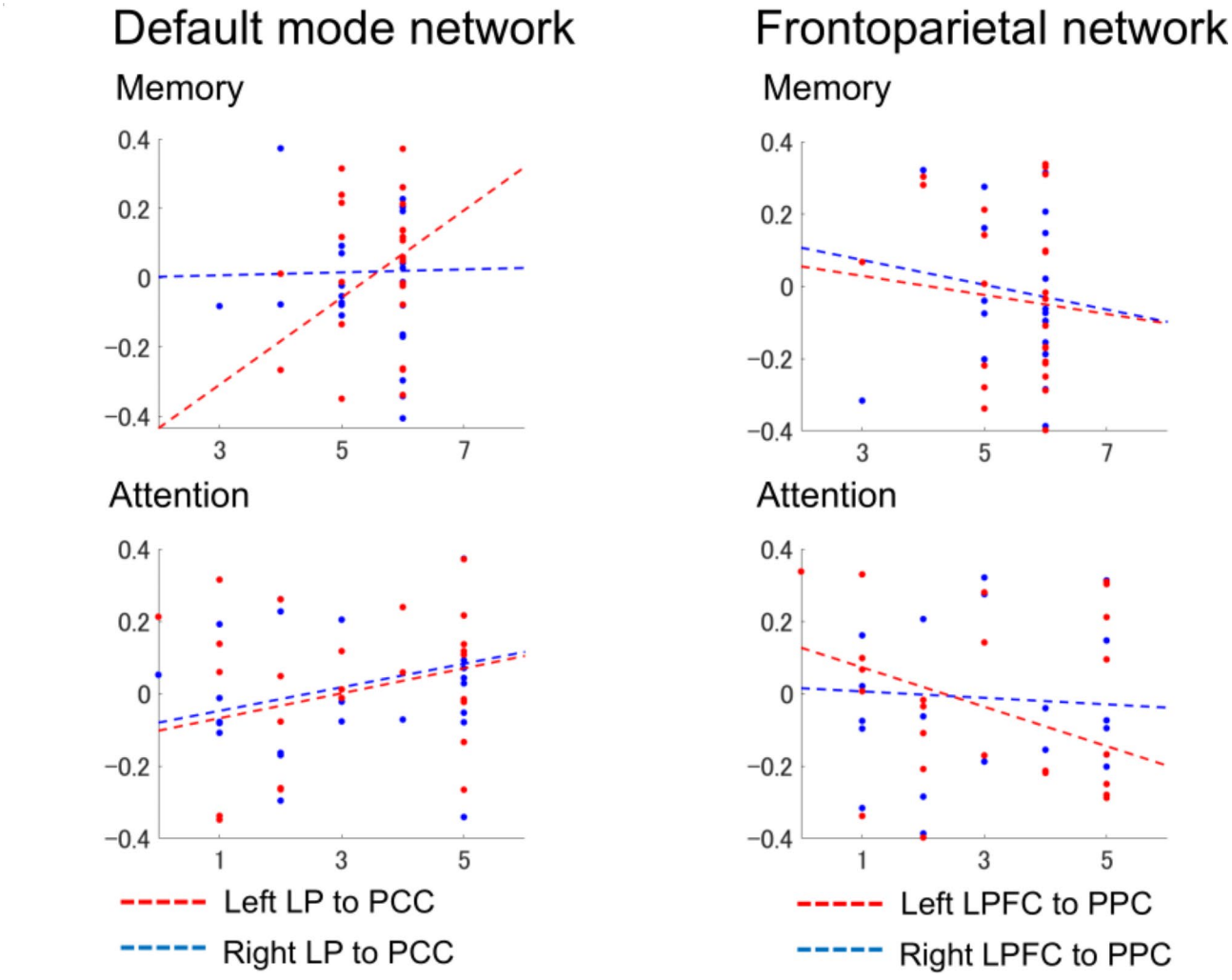

Fig. 2. Pearson's correlation coefficients and graphs showing the correlation of MMSE scores with intrahemispheric FC in brain networks during on and off states. The default mode network and the frontoparietal network were analyzed. The dotted lines indicate the approximate line calculated using the least squares method. MMSE, Mini-Mental State Examination; FC, functional connectivity; LPC, lateral parietal cortex; PCC, precuneus cortex; LPFC, lateral prefrontal cortex; PPC, posterior parietal cortex.

left LPFC and PPC ($r = -0.47$, $p < 0.05$) (Fig. 2). The MMSE subscale scores for memory showed no correlation with changes in FC between the bilateral LPFC and PPC (Fig. 2). The MMSE subscale scores for attention were negatively correlated with changes in FC between the left LPFC and PPC ($r = -0.30$, $p = 0.13$). No correlation with changes in FC between the right LPFC and PPC was observed (Fig. 2).

Discussion

This study assessed the association between FC alterations in the on and off states and the severity of cognitive impairment in patients with PD. Our results showed that intrahemispheric FC changes in the on and off states were positively correlated with cognitive impairment of memory and negatively correlated with that of attention. These findings suggest that the changes in neuronal synchronization in the brain network should be further studied to understand their potential in identifying patients with PD at risk of developing cognitive impairment.

As PD pathology progresses, α-synuclein aggregates lead to the loss of dopaminergic, serotonergic, and other neurons, potentially promoting changes in brain regions by altering their connectivity[3]. Aberrant deposition of α-synuclein in cortical lesions has been implicated in brain dysfunction and cognitive impairment[1]. As the disease progresses, patients undergo treatment adjustments and experience various motor complications. In PD, on-off fluctuations not only affect motor symptoms but also the frequency and severity of non-motor symptoms[37]. It has been proposed that fluctuations in non-motor symptoms are associated with the stimulation of dopaminergic pathways and modulation of other neurotransmitter systems[38]. FC in brain networks changes between on and off states, suggesting that these changes contribute to cognitive impairment in PD.

In this study, the correlation between changes in brain connectivity during the on and off states and cognitive function differed for each cognitive function item. Items related to memory impairment were positively correlated with changes in FC during the on and off states between the BS and specific regions in the left cerebral hemisphere, such as the PreCG and TP. Items related to attention deficits were positively correlated with changes in FC during the on and off states between the bilateral Tha and frontal lobes and negatively correlated with changes in FC within the left cerebral hemisphere, such as between the SFG, PreCG, and TP. These findings suggest that FC changes between on and off states are differentially associated with various cognitive impairments in PD.

A weak correlation was observed between changes in FC between the BS and left cerebral cortex during the on and off states and memory function. Memory function is related to the connections between the BS and cerebral cortex, and anti-Parkinsonian drugs can affect memory by altering these connections[39,40]. This relationship suggests that a direct dopaminergic pathway from the BS to the cerebral cortex via the nucleus accumbens is involved in memory impairment. The connections from the BS to the cerebral cortex have been shown to influence other brain structures involved in memory, such as the hippocampus and amygdala[41]. Alterations in connectivity to these structures may also contribute to memory impairments. This alteration in connectivity indicates that the greater the variation in brain connectivity between on and off, the better the memory function is retained. Previous reports have also shown a relationship between memory and the left cerebral hemisphere[42], a finding which our results support.

We further observed a strong correlation between changes in FC between the Tha and frontal lobes during the on and off states and attentional function. This result suggests that anti-Parkinsonian drugs may contribute to attention deficits owing to changes in the connectivity between the Tha and cerebral cortex. This correlation underscores the importance of considering the impact of pharmacological interventions on the neural circuits involved in attention regulation. It also highlights the potential role of the Tha as a key hub in coordinating attention-related processes between different brain regions[31] which suggests that the output to the cerebral cortex via the basal ganglia loop is considerably involved. This involvement of the basal ganglia loop indicates that the greater the variation in brain connectivity between the on and off states, the worse the cognitive function becomes. It has been reported that abnormal brain FC is associated with attention deficits in PD[43] and the attention disorder is thought to be due to fluctuations in abnormal brain FC in the cerebral cortex[44].

This study indicated a differential impact of on-off changes in FC on memory and attention performance in patients with PD. It revealed that memory scores were not correlated with changes in FC during on-off within the left cerebral hemisphere. Memory performance is affected by neurotransmitters from the BS, which may reflect pathological changes related to substantia nigra degeneration in PD[3]. In contrast, attentional scores were negatively correlated with changes in FC during on-off within the left cerebral hemisphere. This negative correlation suggests that fluctuations in brain FC are associated with lower attentional performance and reflect changes in FC within the hemispheres due to changes in neurotransmitters caused by oral drugs. It is known that attention deficits in PD appear early, and that memory impairments appear later[3]. These two cognitive function items showed different relationships with brain FC and may be accompanied by different functional abnormalities depending on the progression of the disease.

Our results should be interpreted with caution because this study has some limitations. First, this study only assessed cognitive function midway between the on and off states, limiting our understanding of FC changes in relation to cognitive fluctuations in PD. The current study could only partially capture the imaging connectivity changes and their relationship with cognitive changes in PD. This limitation restricts our ability to fully understand the dynamic interactions between FC and cognitive performance across both states. Future studies should aim to conduct cognitive assessments during both the on and off states to provide a more detailed understanding of how FC changes correspond to fluctuations in cognitive function. Second, we observed variability among participants in the MMSE scores, potentially reflecting differences in the severity of cognitive impairment. This study did not perform a detailed analysis of these subgroups due to the limited sample size. Additionally, using the MMSE as a screening tool has limitations because it may not capture all aspects of cognitive impairment. Future research with larger cohorts should explore the relationship between FC changes and varying levels of cognitive function using more comprehensive cognitive assessments, including on-and-off

fluctuations to compare them directly with FC changes. Third, we performed a seed-based rsfMRI analysis using a small number of ROIs because it allowed for a focused investigation into specific brain networks, minimizing computational complexity and enhancing the interpretability of the results. Detailed analyses of additional ROIs and whole-brain FC are required to elucidate the mechanisms underlying cognitive impairment. Fourth, we did not categorize the different types of anti-Parkinsonian drugs in our analysis. Future studies should consider analyzing the effects of specific medications to better understand their impact on FC and cognitive impairment in PD. Fifth, several factors may lead to the reorganization of functional neural networks, including increasing disease severity, age, sex, medical history, and years of education[14]. Further studies are required to evaluate potential variations in treatment and monitor disease progression in participants with a uniform severity of cognitive impairment. Sixth, this was a pilot study with a limited sample size. Therefore, we only included patients with PD and did not include a control group comprising healthy individuals. Moreover, because all patients with PD were analyzed together without stratification based on cognitive status, it remains unclear whether the observed connectivity changes are related to cognitively normal PD or mild cognitive impairment/dementia. Furthermore, no correction for multiple comparisons was applied. Several of these limitations arose from the small sample size, which prevented more detailed analyses. A comprehensive clinical study with a larger sample size, applying stratification and appropriate corrections, is warranted to validate our findings.

In conclusion, we performed an rsfMRI analysis in patients with PD to explore the relationship between changes in FC during on and off states and cognitive impairment. The results enhance our understanding of the mechanisms underlying abnormal FC underpinning cognitive impairment in patients with PD. Incorporating multimodal imaging techniques, such as combining rsfMRI with structural MRI or positron emission tomography, could offer a more comprehensive understanding of the neurobiological basis of cognitive impairment in PD[45]. Furthermore, exploring potential therapeutic approaches to regulate FC patterns in distinct brain networks could lead to innovative treatments designed to preserve cognitive function and improve the quality of life in patients with PD.

Data availability

The datasets generated in this study are available upon reasonable request from the corresponding author.

Received: 30 April 2024; Accepted: 4 November 2024
Published online: 09 November 2024

References

1. Aarsland, D. et al. Parkinson disease-associated cognitive impairment. *Nat. Rev. Dis. Primers*. **7**, 47. https://doi.org/10.1038/s41572-021-00280-3 (2021).
2. Asanuma, M., Miyazaki, I. & Ogawa, N. Dopamine- or L-dopa-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson's disease. *Neurotox. Res.* **5**, 165–176. https://doi.org/10.1007/BF03033137 (2003).
3. Gratwicke, J., Jahanshahi, M. & Foltynie, T. Parkinson's disease dementia: a neural networks perspective. *Brain*. **138**, 1454–1476. https://doi.org/10.1093/brain/awv104 (2015).
4. Braak, H. et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging*. **24**, 197–211. https://doi.org/10.1016/s0197-4580(02)00065-9 (2003).
5. Grossman, M., Carvell, S., Stern, M. B., Gollomp, S. & Hurtig, H. I. Sentence comprehension in Parkinson's disease: the role of attention and memory. *Brain Lang.* **42**, 347–384. https://doi.org/10.1016/0093-934x(92)90074-o (1992).
6. Liu, Y. et al. Attention/memory complaint is correlated with motor speech disorder in Parkinson's disease. *BMC Neurol.* **19**, 309. https://doi.org/10.1186/s12883-019-1535-8 (2019).
7. Hälbig, T. D. et al. Differential role of dopamine in emotional attention and memory: Evidence from Parkinson's disease. *Mov. Disord.* **26**, 1677–1683. https://doi.org/10.1002/mds.23728 (2011).
8. Williams-Gray, C. H. et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. **132**, 2958–2969. https://doi.org/10.1093/brain/awp245 (2009).
9. Kobayakawa, M., Koyama, S., Mimura, M. & Kawamura, M. Decision making in Parkinson's disease: analysis of behavioral and physiological patterns in the Iowa gambling task. *Mov. Disord.* **23**, 547–552. https://doi.org/10.1002/mds.21865 (2008).
10. Ruggiero, R. N. et al. Neuromodulation of hippocampal-prefrontal cortical synaptic plasticity and functional connectivity: Implications for neuropsychiatric disorders. *Front. Cell. Neurosci.* **15**, 732360. https://doi.org/10.3389/fncel.2021.732360 (2021).
11. Hohenfeld, C., Werner, C. J. & Reetz, K. Resting-state connectivity in neurodegenerative disorders: Is there potential for an imaging biomarker? *NeuroImage Clin.* **18**, 849–870. https://doi.org/10.1016/j.nicl.2018.03.013 (2018).
12. Kinugawa, K. et al. Bradykinesia and rigidity modulated by functional connectivity between the primary motor cortex and globus pallidus in Parkinson's disease. *J. Neural Transm (Vienna)*. **130**, 1537–1545. https://doi.org/10.1007/s00702-023-02688-5 (2023).
13. Mano, T., Kinugawa, K., Ozaki, M., Kataoka, H. & Sugie, K. Neural synchronization analysis of electroencephalography coherence in patients with Parkinson's disease-related mild cognitive impairment. *Clin. Park Relat. Disord.* **6**, 100140. https://doi.org/10.1016/j.prdoa.2022.100140 (2022).
14. Gao, L. L. & Wu, T. The study of brain functional connectivity in Parkinson's disease. *Transl Neurodegener*. **5**, 18. https://doi.org/10.1186/s40035-016-0066-0 (2016).
15. Filippi, M., Sarasso, E. & Agosta, F. Resting-state functional MRI in parkinsonian syndromes. *Mov. Disord Clin. Pract.* **6**, 104–117. https://doi.org/10.1002/mdc3.12730 (2019).
16. Engels, G., Vlaar, A., McCoy, B., Scherder, E. & Douw, L. Dynamic functional connectivity and symptoms of Parkinson's disease: resting-state fMRI study. *Front. Aging Neurosci.* **10**, 388. https://doi.org/10.3389/fnagi.2018.00388 (2018).
17. Cerasa, A., Novellino, F. & Quattrone, A. Connectivity changes in Parkinson's disease. *Curr. Neurol. Neurosci. Rep.* **16**, 91. https://doi.org/10.1007/s11910-016-0687-9 (2016).
18. Amboni, M. et al. Resting-state functional connectivity associated with mild cognitive impairment in Parkinson's disease. *J. Neurol.* **262**, 425–434. https://doi.org/10.1007/s00415-014-7591-5 (2015).
19. Sprenger, F. & Poewe, W. Management of motor and non-motor symptoms in Parkinson's disease. *CNS Drugs*. **27**, 259–272. https://doi.org/10.1007/s40263-013-0053-2 (2013).
20. Bayulkem, K. & Lopez, G. Nonmotor fluctuations in Parkinson's disease: Clinical spectrum and classification. *J. Neurol. Sci.* **289**, 89–92. https://doi.org/10.1016/j.jns.2009.08.022 (2010).
21. Vancea, R. et al. Cognitive performance in mid-stage Parkinson's disease: Functional connectivity under chronic antiparkinson treatment. *Brain Imaging Behav.* **13**, 200–209. https://doi.org/10.1007/s11682-017-9765-0 (2019).

22. Kwak, Y. et al. Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. *Front. Syst. Neurosci.* **4**, 143. https://doi.org/10.3389/fnsys.2010.00143 (2010).
23. Hughes, A. J., Daniel, S. E., Kilford, L. & Lees, A. J. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry*. **55**, 181–184. https://doi.org/10.1136/jnnp.55.3.181 (1992).
24. Goetz, C. G. et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's disease rating scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov. Disord*. **23**, 2129–2170. https://doi.org/10.1002/mds.22340 (2008).
25. Takemoto, M. et al. Different clinical and neuroimaging characteristics in early stage Parkinson's disease with dementia and dementia with Lewy bodies. *J. Alzheimers Dis.* **52**, 205–211. https://doi.org/10.3233/JAD-150952 (2016).
26. Cameron, J., Worrall-Carter, L., Page, K., Stewart, S. & Ski, C. F. Screening for mild cognitive impairment in patients with heart failure: Montreal cognitive assessment versus mini mental state exam. *Eur. J. Cardiovasc. Nurs.* **12**, 252–260. https://doi.org/10.1177/1474515111435606 (2013).
27. Tomlinson, C. L. et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov. Disord*. **25**, 2649–2653. https://doi.org/10.1002/mds.23429 (2010).
28. Barkhof, F., Haller, S. & Rombouts, S. A. Resting-state functional MR imaging: A new window to the brain. *Radiology*. **272**, 29–49. https://doi.org/10.1148/radiol.14132388 (2014).
29. Whitfield-Gabrieli, S. & Nieto-Castanon, A. A. Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* **2**, 125–141. https://doi.org/10.1089/brain.2012.0073 (2012).
30. Desikan, R. S. et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. **31**, 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021 (2006).
31. Saalmann, Y. B. & Kastner, S. Cognitive and perceptual functions of the visual thalamus. *Neuron*. **71**, 209–223. https://doi.org/10.1016/j.neuron.2011.06.027 (2011).
32. Rucco, R. et al. Brain networks and cognitive impairment in Parkinson's disease. *Brain Connect.* **12**, 465–475. https://doi.org/10.1089/brain.2020.0985 (2022).
33. Zhu, Y. et al. Cortical atrophy is associated with cognitive impairment in Parkinson's disease: A combined analysis of cortical thickness and functional connectivity. *Brain Imaging Behav.* **16**, 2586–2600. https://doi.org/10.1007/s11682-022-00714-w (2022).
34. Mano, T. et al. Tongue pressure as a novel biomarker of spinal and bulbar muscular atrophy. *Neurology*. **82**, 255–262. https://doi.org/10.1212/WNL.0000000000000041 (2014).
35. Catalano, P. M. et al. Fetuses of obese mothers develop insulin resistance in utero. *Diabetes Care*. **32**, 1076–1080. https://doi.org/10.2337/dc08-2077 (2009).
36. Xia, M., Wang, J. & He, Y. BrainNet Viewer: a network visualization tool for human brain connectomics. *PLoS One*. **8**, e68910. https://doi.org/10.1371/journal.pone.0068910 (2013).
37. Storch, A. et al. Nonmotor fluctuations in Parkinson disease: Severity and correlation with motor complications. *Neurology*. **80**, 800–809. https://doi.org/10.1212/WNL.0b013e318285c0ed (2013).
38. Chaudhuri, K. R. & Schapira, A. H. Non-motor symptoms of Parkinson's disease: Dopaminergic pathophysiology and treatment. *Lancet Neurol.* **8**, 464–474. https://doi.org/10.1016/S1474-4422(09)70068-7 (2009).
39. Chowdhury, A. et al. A locus coeruleus-dorsal CA1 dopaminergic circuit modulates memory linking. *Neuron*. **110**, 3374–3388e8. https://doi.org/10.1016/j.neuron.2022.08.001 (2022).
40. Duszkiewicz, A. J., McNamara, C. G., Takeuchi, T. & Genzel, L. Novelty and dopaminergic modulation of memory persistence: A tale of two systems. *Trends Neurosci.* **42**, 102–114. https://doi.org/10.1016/j.tins.2018.10.002 (2019).
41. Yetnikoff, L., Lavezzi, H. N., Reichard, R. A. & Zahm, D. S. An update on the connections of the ventral mesencephalic dopaminergic complex. *Neuroscience*. **282**, 23–48. https://doi.org/10.1016/j.neuroscience.2014.04.010 (2014).
42. Pourzinal, D. et al. Hippocampal resting-state connectivity is associated with posterior-cortical cognitive impairment in Parkinson's disease. *Brain Behav.* **14**, e3454. https://doi.org/10.1002/brb3.3454 (2024).
43. Bezdicek, O. et al. Mild cognitive impairment disrupts attention network connectivity in Parkinson's disease: A combined multimodal MRI and meta-analytical study. *Neuropsychologia*. **112**, 105–115. https://doi.org/10.1016/j.neuropsychologia.2018.03.011 (2018).
44. Kucyi, A., Hove, M. J., Esterman, M., Hutchison, R. M. & Valera, E. M. Dynamic brain network correlates of spontaneous fluctuations in attention. *Cereb. Cortex*. **27**, 1831–1840. https://doi.org/10.1093/cercor/bhw029 (2017).
45. Tahmasian, M. et al. Based on the network degeneration hypothesis: Separating individual patients with different neurodegenerative syndromes in a preliminary hybrid PET/MR study. *J. Nucl. Med.* **57**, 410–415. https://doi.org/10.2967/jnumed.115.165464 (2016).

Acknowledgements

We thank the staff of the Department of Neurology at Nara Medical University Hospital for their contribution.

Author contributions

K.K. and T.M. contributed to the study conception and design. K.K. and T.M. collected the clinical data. K.K. and T.M. wrote the manuscript. K.S. supervised the study. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-78642-6.

Correspondence and requests for materials should be addressed to T.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.