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Visuoperceptual disturbances in Parkinson's disease

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ABSTRACT

Introduction: Parkinson's disease (PD) shows a variety of visual deficits including visuoperceptual disturbances, however, the neural basis remains unclear. We aimed to clarify clinical and neural features of visuoperceptual disturbances in PD.
Methods: The visuospatial/perceptual abilities of ninety-six participants (48 patients with PD and 48 healthy controls) were evaluated using the subtest part 1 and 5–8 of the Visual Object and Space Perception battery (VOSP), cube/pentagon copying and clock drawing tasks. Resting-state fMRI images were acquired and analyzed the differences between PD with incomplete letters below the cut-off and above for intranetwork (primary/medial/higher visual networks) and interregional functional connectivity changes, and spectral dynamic causal modeling was performed to examine the causality.
Results: In the PD group, position discrimination and incomplete letter scores were significantly decreased among VOSP subtests, the latter having the largest effect size. The incomplete letter scores correlated with the position discrimination while not with the dot counting, number location and cube analysis, cube/pentagon copying or clock drawing. The group with the incomplete letter scores below the cut-off had regions with decreased functional connectivity surrounding the calcarine sulcus in the primary visual network. These regions had decreased interregional functional connectivity with bilateral lingual gyri and cunei but increased with the thalamus. In this group, effective connectivity from the lingual gyrus to the calcarine sulcus was significantly decreased.
Conclusion: The incomplete letters may be sensitive to detect visuoperceptual disturbances in PD. Decreased connectivity in the ventral visual feedback pathway may contribute to these deficits.

1. Introduction

Patients with Parkinson's disease (PD) exhibit heterogeneous motor and nonmotor symptoms. Visuoperceptual disturbances in PD include contrast sensitivity, color discrimination, overlapping object identification, face recognition and facial emotion recognition [1]. Various aspects of the visual system are also affected, such as inner retinal layer thinning, retinal dopaminergic deficiency and progressive cortical thinning in the posterior cortex [1,2]. Posterior cortical deficits are risk factors for developing dementia [3,4] The Visual Object and Space Perception Battery (VOSP) comprises tests for the evaluation of visuoperceptual functions [5]. The VOSP consists of eight subcomponent tests for evaluating object and space perceptual disturbances based on the two-stream hypothesis, encompassing the ventral and dorsal stream pathways [6]. The ventral stream involves the flow of visual information from the occipital lobe of the primary visual cortex to the medial temporal lobe and has a role in object recognition, while the dorsal stream involves the flow of information from the occipital to parietal lobe and is related to space recognition and construction.

In this study, we aimed to clarify clinical features and neural basis of visuoperceptual disturbances in nondemented Parkinson's disease. We conducted cross-sectional study to evaluate visuoperceptual abilities using VOSP to investigate the features of visuoperceptual disturbances in PD. We also examined intra-resting state network (RSN) and interregional functional connectivity (FC) alterations related to the visuoperceptual disturbances of identification of incomplete letters, which showed the highest effect size and larger number of patients below the cut-off in our study, and spectral dynamic causal modeling (spDCM) analysis to determine the causality of aberrant FC regions.

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Table 1
Demographics and cognitive scores of PD and HC.

	PD N = 48	HC N = 48	Effect size (Cohen's d)	p value
Age	69.5 (8.8)	69.3 (8.6)	0.024	0.697
Gender M/F, n	20/28	20/28	0.000	1.000[a]
Education, y	13.1 (2.8)	13.4 (2.0)	0.120	0.405
MMSE (30)	28.5 (1.3)	29.2 (1.0)	0.607	0.003*
Cube copying (20)	17.1 (2.4)	17.9 (2.7)	0.285	0.046*
Pentagon copying (10)	9.9 (0.3)	9.9 (0.4)	0.063	0.982
Clock drawing (10)	9.3 (1.1)	9.3 (1.0)	0.000	0.759
VOSP				
Incomplete letters (20)	18.4 (1.9)	19.6 (0.5)	0.867	<0.001*
Dot counting (10)	9.8 (0.4)	9.8 (0.4)	0.053	0.971
Position discrimination (20)	19.4 (1.1)	20.0 (0.1)	0.738	<0.001*
Number location (10)	9.1 (1.2)	9.1 (1.1)	0.018	0.858
Cube analysis (10)	9.3 (0.9)	9.5 (0.7)	0.188	0.574
Duration, y	6.0 (3.9)	–	–	–
MDS-UPDRS part 1	9.2 (5.7)	–	–	–
MDS-UPDRS part 2	10.1 (7.2)	–	–	–
MDS-UPDRS part 3	33.7 (14.3)	–	–	–
MDS-UPDRS part 4	2.5 (3.8)	–	–	–
Hoehn and Yahr scale	2.1 (0.6)		–	–
Levodopa Equivalent Dose	501 (332)		–	–
RBDSQ-J (13)	4.8 (3.0)		–	–

Data are expressed as mean (SD); RBDSQ-J, the Japanese version of RBD screening questionnaire; VOSP, Visual Object and Space Perception battery.
[a] Chi-square test.
* Statistically significant ($p < 0.05$).

2. Methods

2.1. Participants

To assess clinical and network features of visuoperceptual disturbances, we recruited 65 patients diagnosed with PD for this study at the Department of Neurology, Nagoya University, Japan. We excluded 17 patients using the following exclusion criteria: (1) Mini-Mental State Examination (MMSE) scores <26 or the presence of dementia according to the Movement Disorders Society (MDS) criteria [7], (2) incomplete MRI scans, (3) the existence of anatomical abnormality, (4) under fifty years old and (5) excessive head motion during RS-fMRI scans with a mean framewise-displacement value above 0.5 mm [8] and (6) insufficient visual acuity. All neurological evaluations and MRI scans were performed during ON state. Classification of clinical phenotype was followed by Stebbins et al. [9]. To obtain normative data for the VOSP, we applied the VOSP to 151 healthy controls (HCs) recruited from our ongoing healthy aging cohort study. 48 age- and gender-matched HCs were incorporated in the analysis (Table 1). We evaluated the Japanese version of the MDS Unified PD Rating Scale (MDS-UPDRS) [10] and RBD screening questionnaire [11].Written informed consent was obtained from all participants. The study conformed to the Ethical Guidelines for Medical and Health Research Involving Human Subjects endorsed by the Japanese government and was approved by the Ethics Committee of Nagoya University Graduate School of Medicine.

For MRI analysis, we divided patients into two groups based on an incomplete letter score cut-off described below. One group comprised of 18 patients with incomplete letter scores below the cut-off, and we named this group PD with visuoperceptual disturbance positive (PD-VDP) for convenience. The other group was composed of 30 patients with scores above the cut-off, and we named this group PD with visuoperceptual disturbance negative (PD-VDN).

2.2. Visuoperceptual tests

After taking a history of ophthalmic disorders and checking near vision, we performed the screening test (cut-off 15/20) in the VOSP. Once we judged that patients had sufficient visual acuity, we proceeded to the tests in the VOSP. The VOSP consists of two domains of 4 object (test 1–4) and space perception (test 5–8) batteries. Test 1 is incomplete letters, and tests 5–8 are *dot counting*, *position discrimination*, *number location* and *cube analysis* [5]. We did not apply *silhouettes test*, *object decision* and *progressive silhouettes* (test 2–4), which were judged as inappropriate because they required unfamiliar semantic knowledge of objects for Japanese cultural populations. We also conducted the cube copying task that was scored using a 20 point-grading system [12] and clock drawing using a 10 point-grading system [13]. The pentagon copying task, which was incorporated into the MMSE, was rescored from 0–1 point to 0–10 [14]. We set the cut-offs at 5 percentile scores of the normative data, below this value are considered not normal (Supplementary Table S-1).

2.3. MRI acquisition and preprocessing

MRI scans were performed using a Siemens Magnetom Verio (Siemens, Erlangen, Germany) 3.0-T scanner with a 32-channel head coil at the Brain and Mind Research Center, Nagoya University. High-resolution T1-Weighted Images (T1-WI) were acquired using the following parameters: repetition time (TR) 2.5 s, echo time (TE) 2.48 ms, 192 sagittal slices with a distance factor of 50% and 1-mm thickness, field of view (FOV) 256 mm, 256 × 256 matrix size, and an in-plane voxel resolution of 1 × 1 mm^2. Resting-state functional images were obtained with gradient echo (GE) echo-planar imaging sequence using the following parameters: TR 2.5 s, TE 30 ms, 39 transversal slices with a 0.5-mm inter-slice interval and 3-mm thickness, FOV = 192 mm, 64 × 64 matrix dimension, flip angle 80° and 198 total volumes. The participants were instructed to stay awake and close their eyes during the 8-min scan.

The pipelines used for the analysis were described in detail in our previous reports [15]. Anatomical and functional images were preprocessed using Statistical Parametric Mapping 12 software (SPM12; Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Briefly, T1-WI images were segmented, normalized, and smoothed using an 8-mm full-width-at-half-maximum (FWHM) Gaussian filter. For functional images, the first 5 volumes were discarded, and the remaining volumes were slice-time corrected, realigned, coregistered to the bias-corrected T1-WI, normalized, resampled and spatially smoothed using an 8-mm FWHM Gaussian filter. Additionally, we regressed out 24 motion-related regressors. Signals within the CSF and WM and the global signal were also removed. Finally, the preprocessed data were bandpass filtered within 0.01–0.1 Hz.

2.4. Group independent component analysis (ICA) and seed-based analysis

The method of group ICA was described in detail in our previous reports [15]. Group ICA was performed using FSL [16]. All participants' images were concatenated and decomposed into 20 independent components. We selected three vision-related RSNs (primary/medial/higher visual networks) located mainly in the occipital lobe and excluded the other RSNs or noise components [17]. For dual-regression analysis, we used a nonparametric approach with 5000 permutations [18]. Voxels located outside the respective RSNs were masked out. A threshold-free cluster enhancement (TFCE) technique was applied in the resulting statistical maps. Reported statistical maps were corrected for multiple comparisons with family-wise error (FWE) correction at $p < 0.05$. Age and gender were included as covariates of no interest. We also included voxelwise gray matter values as covariate to minimize the effect of regional atrophies [19].

To perform seed-based connectivity analysis, we created seed regions from regions with significantly decreased FC in the PD-VDP group compared with those in the PD-VDN group. The estimated correlation coefficients from the seed were converted into z-scores using the Fisher transform. Two-sample *t*-test was performed to examine intergroup differences, and age, gender and voxel-wise gray matter values were included as covariates of no interest. To conduct the analysis with voxel-wise gray matter correction, we used the VoxelStats toolbox

[20]. Statistical significance was set at $p < 0.05$ corrected for multiple comparisons using a cluster-level FWE correction with a cluster-forming threshold set at $p = 0.001$. The resulting clusters were visualized using BrainNet Viewer [21]. Peak MNI coordinates and anatomical location were estimated using the xjview toolbox (http://www.alivelearn.net/xjview8).

2.5. Spectral dynamic causal modeling (spDCM)

To investigate causal architecture, we conducted spDCM analysis using DCM12 as implemented in SPM12 [22]. Candidate nodes were selected from aberrant FC regions identified using ICA and seed-based analysis in the PD-VDP group compared with those in the PD-VDN group. Specifically, we created spherical volumes-of-interest (VOIs) with a 4-mm radius from the four peak MNI coordinates located in the right calcarine cortex [center (x, y, z) = (8, −74, 12)] representing the seed region, the right lingual gyrus (24, −50, −4), the right cuneus (16, −88, 28) and the thalamus (−2, −18, 2), representing regions exhibiting significant interregional FC change with the right calcarine seed region in the seed-based analysis. We represented the ipsilateral side of cuneal and lingual gyral nodes, which showed the bilateral FC changes. The time course of each VOI was represented by the time series of the principal eigenvariate of all voxels within the VOI as identified using SPM12. To obtain the best model for this 4-node network, we computed all possible models representing the 4096 patterns (2^{12}, 4 × 4 connections less 4 self-connections and each connection taking 2 possible values) of possible endogenous connections without exogenous inputs. For each participant, we used DCM12 from SPM to estimate the different model parameters for all models [22]. To select the optimal model structure, we performed random effects Bayesian model selection using the estimated models from all participants [23]. Finally, we compared the estimated coupling parameters of endogenous connections of the winning optimal model among the three groups of participants.

2.6. Statistical analyses

Participant demographics and cognitive scores were compared using the Mann-Whitney *U* test for two group comparisons, and the Kruskal–Wallis test followed by the Steel–Dwass test for three. Cohen's d was calculated to estimate effect size. Gender and clinical phenotype differences were tested using the Chi-square test and the differences between the number of patients below the cut-off were performed using the McNemar's test with Yates correction. Comparisons among mean coupling parameters of endogenous connections were adjusted with age and gender using general linear model and p values were corrected for multiple comparisons using Bonferroni correction. These analyses were conducted using R version 3.5.2 (http://www.r-project.org/).

3. Results

3.1. Clinical evaluation

The PD group had lower cognitive battery scores in MMSE and cube copying but not in pentagon copying. With regard to VOSP scores, the PD group had lower scores in the incomplete letters and position discrimination but no differences in dot counting, number location or cube analysis tests, and the incomplete letters had the highest value of the effect size (Table 1). Among the VOSP scores, 18 out of 48 patients (37.5%) had the scores below the cut-off in incomplete letter while 1 in dot counting, 2 in number location, 7 in position discrimination and 6 in cube analysis, and that of incomplete letters was statistically larger than that of position discrimination ($p = 0.0098$). Focused on the incomplete letters, the incomplete letter scores correlated with position discrimination (rho = 0.39, $p = 0.006$) but not with other cognitive batteries including visuoconstruction tasks of the cube copying ($p = 0.140$), pentagon copying ($p = 0.459$) or clock drawing tests ($p = 0.700$) (supplementary Table S-2).

Table 2
Differences between the PD-VDP group and the PD-VDN group.

	PD-VDP N = 18	PD-VDN N = 30	Effect size (Cohen's d)	p value
Age, y	72.7 (6.5)	67.5 (9.5)	0.609	0.057
Gender (M/F)	7/11	13/17	–	1.000[a]
Education, y	12.7 (2.8)	13.3 (2.9)	0.223	0.510
MMSE (30)	28.2 (1.3)	28.7 (1.3)	0.346	0.195
Cube copying (20)	16.6 (3.1)	17.4 (1.9)	0.338	0.483
Pentagon copying (10)	9.9 (0.3)	9.9 (0.3)	0.158	0.609
Clock drawing (10)	9.2 (1.2)	9.3 (1.1)	0.112	0.815
VOSP				
Incomplete letters (20)	16.4 (1.7)	19.6 (0.5)	2.85	< 0.001*
Dot counting (10)	9.8 (0.5)	9.8 (0.4)	0.000	0.676
Position discrimination (20)	18.9 (1.4)	19.7 (0.7)	0.746	0.022*
Number location (10)	8.7 (1.6)	9.4 (0.8)	0.618	0.185
Cube analysis (10)	8.9 (1.1)	9.6 (0.6)	0.867	0.015*
Duration, y	5.6 (3.9)	6.2 (4.0)	0.149	0.593
MDS-UPDRS part 1	11.1 (7.3)	8.0 (4.1)	0.566	0.109
MDS-UPDRS part 2	11.1 (9.5)	9.5 (5.5)	0.220	0.966
MDS-UPDRS part 3	36.8 (14.6)	31.8 (14.0)	0.351	0.359
MDS-UPDRS part 4	3.2 (4.4)	2.1 (3.5)	0.278	0.664
part 1.2 score ≥ 2, n	2	3	0.169	1.000[b]
Hoehn and Yahr scale	2.3 (0.8)	2.0 (0.5)	0.518	0.161
Motor phenotype (T/I/P), n	5/0/13	9/4/17	–	0.314[b]
Levodopa Equivalent Dose	514.3 (412.7)	493.2 (279.5)	0.063	0.516
RBDSQ-J (13)	5.4 (3.1)	4.4 (2.9)	0.333	0.213

Data are expressed as Mean (SD); T/I/P, Tremor dominant/Intermittent/Postural instability and gait difficulty; VOSP, Visual Object and Space Perception battery.
[a] Chi-square test.
[b] Fisher's exact test.
* Statistically significant.

The divided PD group differences between the PD-VDP group (n = 18, 37.5%) and the PD-VDN group (n = 30, 62.5%) are shown in Table 2 and Supplementary Table S-3. The PD-VDP group showed lower scores in position discrimination ($p = 0.022$) and cube analysis ($p = 0.015$) than did the PD-VDN group. There were no significant differences between the PD-VDP and PD-VDN groups in gender, disease duration, each part of the MDS-UPDRS, the number of patients with a score greater than or equal to 2 in part I question 2 that represents manifesting structured hallucination, Hoehn and Yahr scale, motor phenotype, RBDSQ-J or levodopa equivalent dose.

3.2. Network changes in the PD-VDP group

The PD-VDP group showed regions with significantly decreased FC (FWE $p < 0.05$) in the primary visual network compared with the PD-VDN and HC groups (Fig. 1A, B). Regions with decreased FC in the PD-VDP group were larger compared with those in the HC group than compared with those in the PD-VDN group. No regions with significantly decreased FC existed in the medial visual and higher visual networks. In the PD-VDP group, seed-based analysis showed regions with decreased FC in the occipital bilateral lingual gyri and cunei from the right seed within the right lingual gyrus and increased FC regions in the thalamus compared with the PD-VDN group (Fig. 1C). There were no regions with significantly altered FC from the left seed.

In the spDCM analysis, the full-connected model was the winning model based on the exceedance probability calculated with random effect Bayesian model selection. The effective connectivity (EC) from the right lingual gyrus to calcarine sulcus was significantly lower in PD-VDP than that in PD-VDN and HC (Fig. 2, Supplementary Table S-4). EC from the calcarine sulcus to lingual gyrus was also lower in the PD-VDP group, however, this difference did not survive after correction for multiple comparisons.

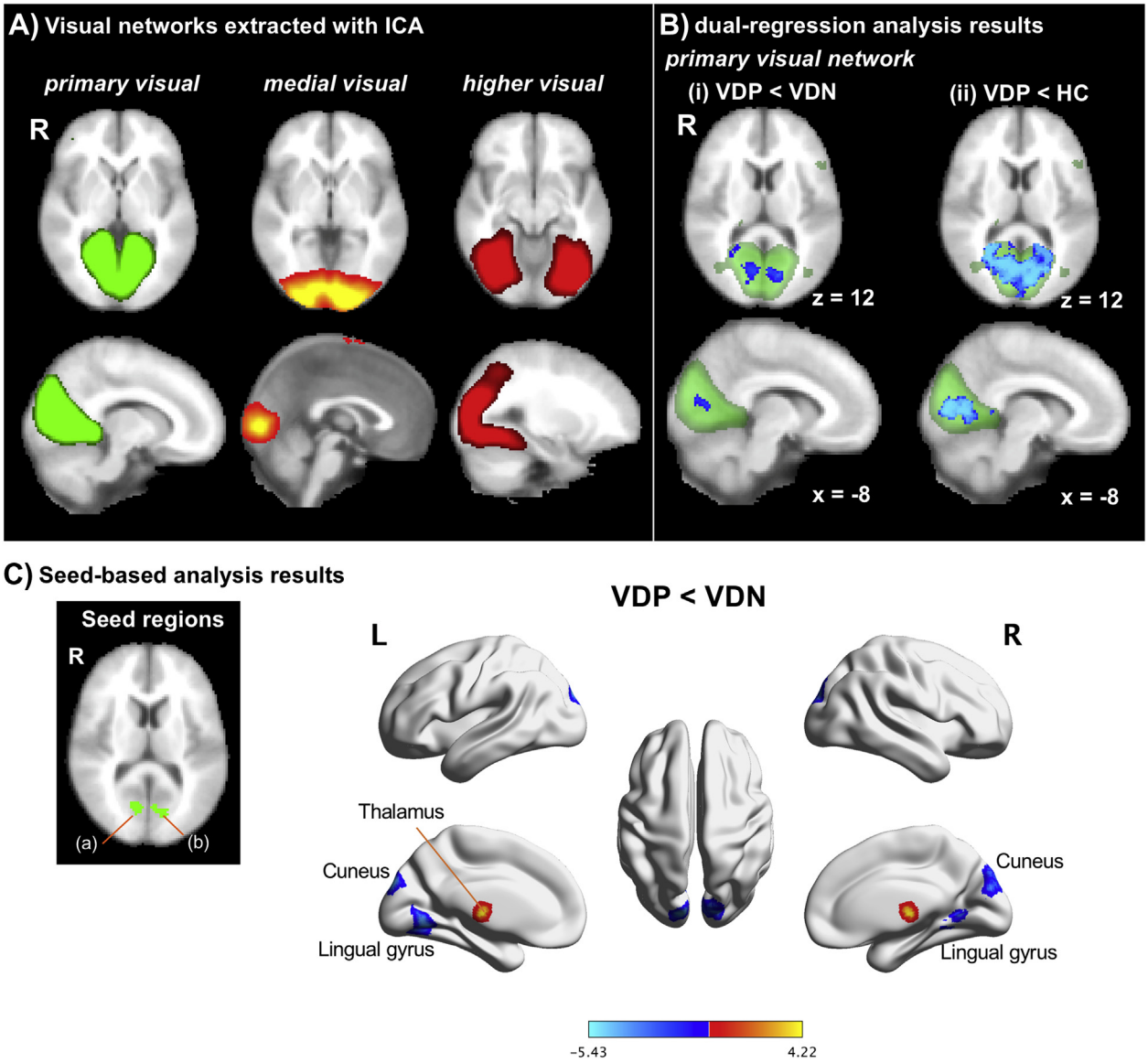

Fig. 1. Functional connectivity changes in the PD-VDP group. A. Extracted resting-state networks related to the visual functions. Green, red-yellow and red areas indicate the primary visual, medial visual and higher visual networks, respectively. B. Dual-regression analysis results. The regions with decreased functional connectivity. Blue indicates the regions with decreased functional connectivity in the PD-VDP group, and green indicates the primary visual network. (i) Compared with the PD-VDN group. (ii) Compared with the HC group. C. Seed-based analysis results. Seed regions were created from the peak regions with decreased functional connectivity in the primary visual network. (a) Right seed. (b) Left seed. Blue indicates the regions with decreased interregional functional connectivity from the right seed shown in (a), and red-yellow indicates the regions with increased inter-regional functional connectivity from the right seed in the PD-VDP group compared with the PD-VDN group.

4. Discussion

We found that nondemented PD patients showed reductions in the VOSP subtests of incomplete letters and position discrimination and approximately one third of patients exhibited impaired identification of incomplete letters.

PD shows visual deficits in a number of visual processes. Earlier stages of visual deficits include visual acuity and contrast and color sensitivity, and these can be partly due to retinal dopaminergic deficiency [1]. Incomplete letter tasks, which require the examinee to interpolate the missing pieces in their mind, were constructed to evaluate the ventral stream pathway from primary visual (V1) to the temporal cortices (V2, V4) of visual process for object perception. Incomplete letters were recommended for evaluating visuoperceptual abilities to diagnose patients with PD dementia (PDD) [7]. Nevertheless, previous reports regarding the use of incomplete letter scores in PD are very limited. Biundo et al. reported that patients with PDD showed lower incomplete letter scores than did patients with normal cognition or mild cognitive impairment (PD-MCI) [24], however, mean ages at examination were significantly different. In the other subtests, position discrimination scores were also significantly lower, but a smaller number of only seven patients were below the cut-off. Although the cube analysis scores did not significantly correlate with the incomplete letters, the PD-VDP group, which the patients had incomplete letter scores below the cut-off, had lower scores in the cube analysis, and group difference of the number location test also had medium effect size. A previous study in healthy participants showed weak correlations between incomplete letters and the other space perception subtests except dot counting [6], although object and space perceptions are assumed to be distinct domains. In addition, incomplete letter scores were not associated with visuoconstruction of cube copying, pentagon copying, or clock drawing scores. Our results

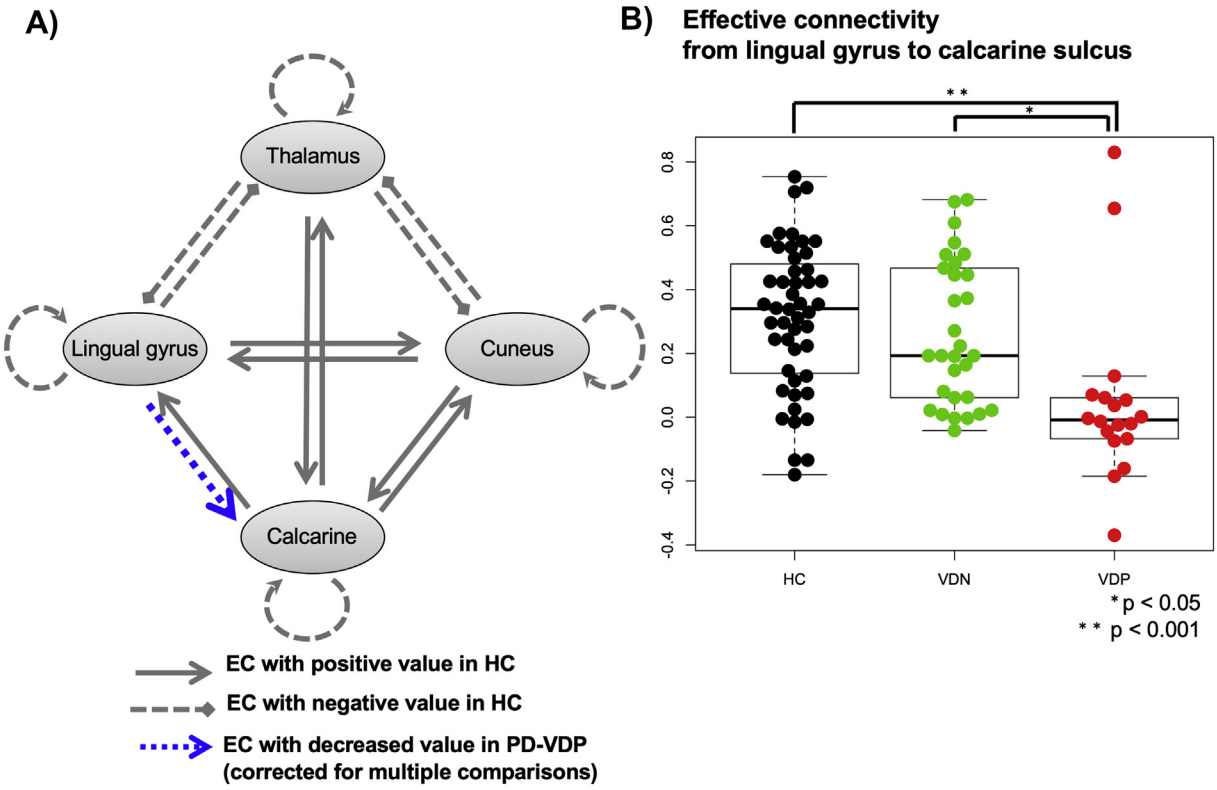

Fig. 2. Altered effective connectivity in the PD-VDP group. A. This schema represents effective connectivity alterations in the PD-VDP group. B. Scatter plot of effective connectivity from the right lingual gyrus to the calcarine sulcus. Vertical axis: individual mean coupling parameters. Statistical analyses were performed after adjusting for age and gender (see Supplementary materials Table S-4). Black = HC, green = PD-VDN, red = PD-VDP.

suggest that incomplete letters may be sensitive in PD and related to the space perception abilities but evaluating different visual abilities of visuoconstruction.

Patients with decreased incomplete letter scores were older, albeit no statistical significance. Disturbances in incomplete letter tests may occur in age-related PD subtypes. Visuoperceptual disturbances were related several clinical phenotypes such as PD with (RBD), postural instability and gait disorder (PIGD) phenotype as well as genetic mutations in the LRRK2 and GBA [1]. We did not find the relationship with RBDSQ-J scores or motor phenotypes, but further studies are needed to identify associations with clinical phenotypes.

With regard to the network alterations, PD patients with deficits in identifying incomplete letters had decreased FC in the primary visual network. The primary visual network is located in the occipital lobe including primary visual cortex and relates to visual and vision-associated functions [25]. The beginning of the visual cortical pathways of the primary visual cortex (V1), which receives subcortical input from the lateral geniculate nucleus and be most sensitive to low-level features such as the orientation of lines and edges [26]. In addition, seed-based analysis showed that the right seed region surrounding the V1 area of the calcarine sulcus had decreased interregional FC with bilateral lingual gyri and cunei, implying that the seed region was functionally isolated from adjacent structures, but the left seed did not. This laterality may suggest that disturbances in incomplete letters is more right posterior hemisphere driven [27] and visuoperceptual task-based fMRI study also showed right-laterality predominance [28].

Among these aberrant regions, spDCM analysis showed that EC reductions from the regions around the medial occipital part of the lingual gyrus (BA 19, close to BA37 of the occipitotemporal area) to the calcarine sulcus (BA 17) were the most significant.

The visual process has feedforward and feedback connections [29]. The feedforward pathway starts at V1 in the primary visual cortex, receiving visual information from the lateral geniculate nucleus that flows to the inferior temporal lobe through V2, V4 and medial temporal area. Moreover, a feedback pathway has been observed in the reciprocal pathway of the feedforward pathway as well as between cortical areas mediated by the pulvinar. Disturbances in this pathway could account for the impaired identification of fragmented letters because this task was generated based on the hypothesis that object perception is related to the ventral pathway. On the other hand, PD shows a number of oculomotor deficits and they can be associated with perception [30]. Increased basal ganglia output can cause the abnormal intermediate layer of the superior colliculus inhibition, affect the action and perception coupling, and worsen the misperception [30]. These may relate to the visuoperceptual impairments and further studies are needed to clarify their relationship. However, our findings provide new insights into the neural basis of visuoperceptual dysfunction in PD.

There are limitations in this study. The VOSP battery has a ceiling effect and scoring ranges vary among the subtests. These characteristics may affect neuropsychological results. Second, we performed both scanning and cognitive evaluation during the ON state, therefore, our findings must be carefully interpreted when compared with other studies performed under different conditions (e.g., scanning during the OFF state). Third, atypical Parkinsonian syndromes were not included in this study. This limits the specificity of the deficits. Last, we did not fully investigate the clinical relevance of PD subtypes such as MCI, RBD confirmed by video polysomnography, disease stages, motor phenotype and genetic mutations in this study and the number of patients after classified the PD groups was relatively small. Larger studies are needed to establish clinical significance.

5. Conclusions

PD had lower scores in incomplete letters and position discrimination, and larger number of patients showed impaired identification of

incomplete letters. Decreased connectivity of the ventral feedback visual pathway may be related to this impairment.

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Authors' roles

KK, RO and HW contributed to the conception and design of the study. KK, RO, KH, AO, MM, TK and TY contributed to the acquisition of the data. KK and EB contributed the analysis of the data. KK, RO, EB, HW, MK and GS contributed to the interpretation of the data. KK contributed to the draft of the article. KK, RO, EB, KH, AO, MM, TK, TY, HW, MK and GS revised the manuscript critically for important intellectual content and approved the final version of the manuscript.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2020.100036.

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