

**ORIGINAL ARTICLE**

Associations Between the Vestibulo-Ocular Reflex and Cognitive Function in de novo Parkinson's Disease

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ABSTRACT

Objective Vestibulo-ocular reflex (VOR) impairment has been reported in Parkinson's disease (PD). However, its clinical implications, particularly with respect to cognition, remain unclear. We investigated canal-specific VOR changes and their associations with cognitive function, motor symptoms, gaits, and dopamine transporter (DAT) uptake in de novo PD patients.

Methods We prospectively enrolled 127 patients with de novo PD who underwent video head-impulse tests (video-HITs), comprehensive neuropsychological assessments, gait analysis, and ¹⁸F-N-(3-fluoropropyl)-2 β -carbon ethoxy-3 β -(4-iodophenyl) nortropane positron emission tomography. Associations between VOR gains and the clinical characteristics of PD were evaluated using general linear models adjusted for age, sex, and education level. Cognitive analyses were performed after the patients were stratified into PD with normal cognition (PD-NC) and PD with mild cognitive impairment (PD-MCI) groups. Partial correlation analyses were performed to assess the relationships between VOR gains and regional DAT uptake.

Results Decreased VOR gain in at least one canal was observed in 22 patients (17.32%). Horizontal canal (HC) gain was positively associated with the Korean version of Montreal Cognitive Assessment score ($p=0.040$), and anterior canal (AC) gain was negatively associated with the base of support ($p=0.018$). The patterns of association between VOR gains and neuropsychological measures differed between the PD-NC and PD-MCI groups. In addition, VOR-cognition relationships were canal-specific: HC gain was positively related to visuospatial function, whereas AC and posterior canal gains were negatively related to language and frontal-executive functions. DAT uptake in the locus coeruleus was positively correlated with HC gain ($p=0.020$).

Conclusion VOR integrity is associated with cognitive and gait function in patients with PD. Video-HITs may serve as potential biomarkers for disease monitoring in PD patients.

Keywords Parkinson's disease; Vestibulo-ocular reflex; Cognitive function.

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized by cardinal parkinsonism, including bradykinesia, rigidity, and resting tremors. In addition to these motor symptoms, non-motor symptoms are common in PD patients and significantly affect their quality of life. Among these non-motor symptoms, dizziness, although relatively underexplored, is commonly reported in approximately 48%–68% of patients with PD.^{1,2} Although dizziness in patients with PD has traditionally been attributed to orthostatic hypotension and autonomic dysfunction, recent studies have reported that impairments in vestibulo-ocular (VOR) and vestibulo-spinal reflexes may contribute to dizziness in PD patients, suggesting that vestibular mechanisms other than autonomic dysfunction may also contribute to dizziness in these patients.²⁻⁷ Moreover, studies have revealed the possible contribution of vestibular dysfunction to gait, freezing, and posture control in PD patients.⁸⁻¹⁰ However, the impact of the vestibular system on other motor and non-motor features has not been well investigated.

The vestibular system provides information about self-motion and spatial orientation, coordinating postural and ocular motor reflexes to maintain balance and visual stability during head movement.¹¹ Moreover, a growing body of evidence suggests that the vestibular system contributes to cognitive processes, including visuospatial, memory, and frontal-executive functions.¹²⁻¹⁵ These cognitive functions may be linked to the central vestibular network, which extends from the brainstem, thalamus, cerebellum, and insular-opercular cortex to the “vestibular” cortex.^{16,17} Prior studies have consistently demonstrated that the VOR is linked to visuospatial function in patients with vestibulopathy as well as in healthy participants.¹⁸ However, this relationship has rarely been demonstrated in PD patients. Similarly, the relationships between the VOR and other cognitive functions remain unclear.

Therefore, in this study, we aimed to evaluate VOR function and its relationship with clinical features, including cognitive functions and gait parameters, in PD patients. We also evaluated the radiologic–electrophysiological correlation by examining the relationship between VOR function and dopamine transporter (DAT) uptake.

MATERIALS & METHODS

Participants

We prospectively recruited 127 consecutive patients with de novo PD between February 2022 and March 2024 at Korea University Medical Center. PD was diagnosed based on the di-

agnostic criteria of the United Kingdom Parkinson's Disease Brain Bank.¹⁹ All patients underwent neurological examinations and semistructured clinical interviews, conducted by a movement disorder specialist to assess the presence of rapid eye movement sleep behavior disorder (RBD). These assessments were conducted as part of routine phenotyping in de novo parkinsonism, prior to initiating dopaminergic treatment. The Beck Depression Index was used to assess depression. Parkinsonism severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III²⁰ and the Hoehn and Yahr (H&Y) stage.²¹ Finally, general cognition and dementia severity were evaluated using the Korean versions of the Mini-Mental State Examination (K-MMSE),²² the Korean version of Montreal Cognitive Assessment (K-MoCA),²³ and the Clinical Dementia Rating (CDR).²⁴ Patients underwent magnetic resonance imaging, including sequences for high-resolution T1-weighted images and ¹⁸F-N-(3-fluoropropyl)-2 β -carbon ethoxy-3 β -(4-iodophenyl) nortropane (¹⁸F-FP-CIT) positron emission scans. Video head-impulse tests (video-HITs) were performed as part of the initial assessment of every patient with parkinsonism, prior to the administration of PD-specific medications. In addition, gait analysis and a comprehensive neuropsychological study were conducted. This study was approved by the Institutional Review Board of Korea University Medical Center (2023AN0442). Informed consent was obtained from all participants. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Video-HITs

Head and eye movements were recorded using video-based equipment (video-HITs; SLVNG, SLMED), as described previously.^{25,26} Any medications that may affect the results of the head impulse tests were discontinued at least 48 hours before the test.

Passive, unpredictable, high-acceleration, small-amplitude head rotations were delivered in the plane of the horizontal canals (HCs). After the HCs were evaluated, head impulses targeting the vertical canals were administered with the patient's head turned 30–40° to the left or right of the fixation point, aligned with the plane of the right anterior-left posterior and left anterior-right posterior canals (PCs). Eye and head movement data were synchronously sampled at a rate of 120 Hz. At least ten valid head impulses were recorded in each direction, excluding trials contaminated by blinks and outliers.

VOR gain was calculated by comparing the ratio of the area under the eye velocity curve to that of the head velocity curve. VOR gain for each canal was measured for individual impulse trials as the ratio of the mean eye velocity to mean head veloci-

ty during a 40-ms time window centered at the peak head acceleration. For statistical analyses, we calculated the mean VOR gains for the HC, anterior canal (AC), and posterior canal (PC) on both sides.

The results of the video-HITs were considered abnormal if VOR gain fell outside the normal range established from 19 healthy age- and sex-matched participants (mean age $\pm$ standard deviation [SD]=62 $\pm$ 6 years, 8 men). Reference ranges were defined as mean $\pm$ 2SD. Normal values of 0.86–1.20, 0.75–1.23, and 0.73–1.32 were observed for the HC, AC, and PC, respectively.⁴ An increase in VOR gain was not considered pathological (i.e., abnormal) unless it was accompanied by reversed catch-up corrective saccades, as overestimation can occur due to neck rigidity during the delivery of head impulses.²⁷

Image acquisition

Patients underwent positron emission tomography/computed tomography (PET/CT) imaging after they were intravenously administered 185 MBq (5 mCi) of ¹⁸F-FP-CIT. Two hours after injection, PET/CT was performed using a dedicated PET/CT scanner (Discovery MI, GE Medical Systems). Low-dose CT scans (120 kVp, 250 mA) were performed first for attenuation correction and anatomic localization. PET images were reconstructed on a 512 $\times$ 512 matrix using the Q. Clear reconstruction algorithm with a β value of 350.

Image preprocessing and analysis

All the PET images were spatially normalized to an in-house ¹⁸F-FP-CIT template by using statistical parametric mapping software (SPM12, University College of London). The voxel size of the spatially normalized PET images was 2.0 $\times$ 2.0 $\times$ 2.0 mm³. DAT binding was analyzed semiquantitatively by measuring the voxel counts and calculating the specific-to non-specific binding ratio of striatal lesions, using the occipital cortex as the non-specific reference region. Automated Anatomical Labeling 3 was used to define volumes of interest for the occipital cortex, striatum, and brainstem regions, including the ventral segmental area, substantia nigra pars compacta and reticulata, red nucleus, locus coeruleus, and raphe nucleus.

Motion analysis

Temporal and spatial gait characteristics were measured using a gait analyzer (GaitRite, 12 ft AP1105; CIR systems). Ten gait cycles were measured, and the average values were calculated. Among the various parameters, we analyzed the cadence (steps/min), velocity (cm/s), cycle time (s), swing time (s), single support time (s), double support time (s), stride length (cm), and base of support (cm).

Neuropsychological tests

All participants underwent the Seoul Neuropsychological Screening Battery.²⁸ The following tests were conducted for domain-specific assessments. The digit span test and Trail Making Test A (TMT-A) to assess attention domain; the Korean version of the Boston Naming Test (K-BNT) and the semantic Controlled Oral Word Association Test (COWAT) for the language domain; the Rey–Osterrieth Complex Figure Test (RCFT) and clock drawing test (CDT) for the visuospatial domain; the immediate recall, 20-min delayed recall, and recognition items of the RCFT and Seoul Verbal Learning Test for the memory domain; and the phonemic COWAT, Stroop color reading and Trail Making Test B for the frontal–executive domain. Standardized z scores were calculated for all scorable tests based on age- and education-matched norms, except for the CDT. CDT scores were analyzed as raw scores based on three components (contour, numbers, and time setting; total=3 points). Each cognitive domain was assessed using at least two individual tests. Impairment in neuropsychological tests was determined on the basis of performance of at least one SD below population-based norms.

Statistical analyses

Statistical analyses of demographic and clinical data were performed using the Statistical Package for the Social Sciences version 26.0 (IBM Corp.).

General linear models (GLMs) were used to investigate the association between VOR gains and the clinical characteristics of PD, including motor function, gait parameters, and cognitive function test scores, after controlling for age, sex, and education level. Ordinal logistic regression analyses were performed for the CDT scores and H&Y stages, as their limited score ranges may violate the normality assumption, using the same covariates including age, sex, and education level. In addition, logistic regression analysis was used to identify factors associated with the presence or absence of RBD.

To consider the influence of baseline cognitive status, GLM analyses of the relationship between VOR gains and cognitive function test scores were performed after stratifying the patients into PD with normal cognition (PD-NC, $n=53$) and PD with mild cognitive impairment (PD-MCI, $n=74$) groups, using age, sex, and education level as covariates.

We performed partial correlation analyses to examine the association between VOR gain in each canal and regional DAT uptake, controlling for age, sex, and educational level. As this study was exploratory, formal correction for multiple comparisons was not applied.

Data availability

The data and code used in this study are available from the

corresponding authors upon request.

RESULTS

Demographics and clinical characteristics

A total of 127 patients with PD were included in the analysis.

Table 1. Demographics and clinical characteristics ($n=127$)

Number of participants	Value
Age (yr)	66.84±9.76
Sex, Male	65 (51.18)
Education (yr)	10.53±4.83
UPDRS Part III	24.61±11.80
H&Y stage	2 (2–2.5)
Mean both HC video-HIT gain	1.05±0.13
Decreased HC video-HIT gain	14 (11.02)
Overestimated HC video-HIT gain	20 (15.75)
Mean both AC video-HIT gain	1.09±0.16
Decreased AC video-HIT gain	4 (3.15)
Overestimated AC video-HIT gain	42 (33.07)
Mean both PC video-HIT gain	1.02±0.16
Decreased PC video-HIT gain	12 (9.45)
Overestimated PC video-HIT gain	5 (3.94)
K-MMSE	27.57±2.58
K-MoCA	24.24±4.32
CDR	
0	60 (47.24)
0.5	67 (52.76)
BDI	11.60±8.69
RBD	48 (37.80)

Data are expressed in mean±standard deviation, median (interquartile range), or number (%).

UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr; HC, horizontal canal; video-HIT, video head-impulse test; AC, anterior canal; PC, posterior canal; K-MMSE, Korean versions of the Mini-Mental Status Examination; K-MoCA, Korean version of Montreal Cognitive Assessment; CDR, Clinical Dementia Rating scale; BDI, Beck Depression Inventory; RBD, rapid eye movement sleep behavior disorder.

The demographics and clinical characteristics of the patients are summarized in Table 1. The mean patient age was 66.84±9.76 years, and 65 patients were (51.18%) male. The mean UPDRS part III score was 24.61±11.80, and the median H&Y stage was 2 (interquartile range 2–2.5). VOR gains decreased in at least one canal in 22 patients (17.32%), including 14 patients (11.02%) in the HC, 4 (3.15%) in the AC, and 12 (9.45%) in the PC. Overestimated VOR gains were observed in at least one canal in 53 patients (41.73%), with 20 patients (15.75%) in the HC, 42 patients (33.07%) in the AC, and 5 patients (3.94%) in the PC. The mean K-MMSE score was 27.57±2.58, and 60 and 67 of the 127 patients had CDR scores of 0 and 0.5, respectively (Table 1). Detailed neuropsychological test scores are summarized in Supplementary Table 1.

Associations between the VOR and clinical characteristics

HC gain was positively associated with the K-MoCA score ($B=5.47$, standard error [SE]=2.63; $p=0.040$). No significant associations were found for AC or PC gain. Additionally, none of the VOR gains were associated with parkinsonian motor severity, as measured using the UPDRS part III or H&Y stage (Table 2).

Associations between the VOR and gait parameters

Increased AC gain was related to a narrower base of support ($B=-3.56$, $SE=1.48$; $p=0.018$) (Table 3). However, no significant associations were found for HC or PC gain.

Associations between the VOR and cognitive function in patients with PD-NC

As 4 of the 53 PD-NC patients had a CDT score of 2 and 49 had a score of 3, the severe skewness precluded stable ordinal regression modeling of CDT within the PD-NC group. AC gain was negatively associated with the TMT-A score ($B=-3.38$, $SE=1.61$; $p=0.041$) and semantic COWAT score ($B=-1.93$, $SE=0.83$;

Table 2. Independent effects of video-HIT gain on clinical characteristics

	HC			AC			PC		
	B (SE)	OR (95% CI)	p value	B (SE)	OR (95% CI)	p value	B (SE)	OR (95% CI)	p value
UPDRS Part III	-12.03 (6.20)		0.085	-4.52 (5.64)		0.424	-2.05 (5.66)		0.718
H&Y stage		0.19 (0.01–2.76)	0.225		0.35 (0.04–2.97)	0.332		0.15 (0.02–1.30)	0.086
K-MMSE	2.44 (1.51)		0.108	-0.91 (1.24)		0.464	0.13 (1.24)		0.914
K-MoCA	5.47 (2.63)		0.040	-0.84 (2.37)		0.723	3.52 (2.26)		0.123
RBD		0.05 (0.002–1.18)	0.063		0.55 (0.05–6.25)	0.627		0.74 (0.06–8.50)	0.807
BDI	0.51 (7.00)		0.943	4.78 (5.66)		0.400	3.87 (5.85)		0.510

Data were results of ANCOVA, ordinal logistic regression, or logistic regression for clinical characteristics using vHIT gain as a predictor. The covariates included age, sex, and educational level. ANCOVA outputs are presented as B (SE), and ordinal logistic regression and logistic regression results are presented as OR (95% CI).

video-HIT, video head-impulse test; HC, horizontal canal; AC, anterior canal; PC, posterior canal; SE, standard error; OR, odds ratio; CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr; K-MMSE, Korean versions of the Mini-Mental Status Examination; K-MoCA, Korean version of Montreal Cognitive Assessment; RBD, rapid eye movement sleep behavior disorder; BDI, Beck Depression Inventory; ANCOVA, analysis of covariance.

$p=0.024$). PC gain showed no association with any cognitive function test score (Table 4).

Associations between the VOR and cognitive function in patients with PD-MCI

HC gain was positively associated with better visuospatial

function, as indicated by a higher CDT score (odds ratio=3.220; 95% confidence interval=1.89–5.5 $\times$ 10⁶; $p=0.033$). AC gain was negatively correlated with the semantic COWAT test score ($B=-1.33$, $SE=0.48$; $p=0.007$), phonemic COWAT test score ($B=-1.77$, $SE=0.65$; $p=0.008$), and Stroop color reading test score ($B=-2.09$, $SE=0.60$; $p<0.001$). PC gain was negatively associated

Table 3. Independent effects of video-HIT gain on gait parameters

	HC		AC		PC	
	B (SE)	p value	B (SE)	p value	B (SE)	p value
Cadence	5.10 (11.45)	0.657	15.84 (8.06)	0.053	-1.01 (8.22)	0.902
Velocity	0.01 (19.12)	1.000	20.83 (13.54)	0.128	1.87 (13.69)	0.891
Cycle time	-0.07 (0.15)	0.671	-0.16 (0.11)	0.140	-0.07 (0.11)	0.514
Swing time	0.66 (3.95)	0.868	1.28 (2.85)	0.655	-1.52 (2.85)	0.596
Single support time	2.13 (2.25)	0.346	3.00 (1.60)	0.065	1.55 (1.620)	0.340
Double support time	-3.28 (4.54)	0.472	-5.62 (3.24)	0.086	-2.65 (3.27)	0.420
Stride length	2.64 (18.96)	0.890	20.26 (13.54)	0.138	0.96 (13.69)	0.945
Base of support	1.50 (2.12)	0.480	-3.56 (1.48)	0.018	-2.67 (1.50)	0.078

Data were results of analysis of covariance for gait parameters using the video-HIT gain as a predictor. Covariates included age, sex, and education. video-HIT, video head-impulse test; HC, horizontal canal; AC, anterior canal; PC, posterior canal; SE, standard error.

Table 4. Independent effects of video-HIT gain on cognitive function test scores in PD-NC patients

	HC		AC		PC	
	B (SE)	p value	B (SE)	p value	B (SE)	p value
Attention						
Digit span forward	0.47 (1.05)	0.657	-0.17 (1.01)	0.867	0.16 (0.95)	0.870
Digit span backward	1.49 (1.43)	0.305	-2.12 (1.35)	0.123	-0.48 (1.31)	0.714
Trail Making Test A	2.19 (1.74)	0.213	-3.38 (1.61)	0.041	0.85 (1.59)	0.595
Language						
K-BNT	0.61 (0.99)	0.543	-0.56 (0.94)	0.555	0.93 (0.89)	0.298
COWAT semantic	0.76 (0.91)	0.408	-1.93 (0.83)	0.024	0.91 (0.81)	0.269
Visuospatial						
Rey copy score	1.12 (0.72)	0.124	0.88 (0.69)	0.207	-0.45 (0.66)	0.502
Clock drawing test	Not estimable*		Not estimable*		Not estimable*	
Verbal memory						
SVLT immediate recall	-0.23 (0.89)	0.793	-0.01 (0.85)	0.991	1.26 (0.78)	0.088
SVLT delayed recall	-0.27 (0.76)	0.725	1.59 (0.69)	0.026	1.00 (0.67)	0.146
SVLT recognition	0.98 (0.94)	0.300	0.70 (0.78)	0.441	1.22 (0.84)	0.151
Visual memory						
RCFT immediate recall	1.10 (0.82)	0.186	0.08 (0.80)	0.922	0.62 (0.75)	0.416
RCFT delayed recall	0.45 (0.82)	0.587	0.87 (0.78)	0.268	0.25 (0.75)	0.740
RCFT recognition	0.53 (0.76)	0.495	-0.30 (0.73)	0.688	0.03 (0.69)	0.969
Frontal executive						
COWAT phonemic	1.06 (11.8)	0.929	-18.07 (10.99)	0.107	-2.23 (10.68)	0.835
Stroop color reading	0.08 (0.67)	0.903	0.31 (0.64)	0.628	0.07 (0.60)	0.910
Trail Making Test B	0.82 (1.42)	0.566	-1.17 (1.35)	0.392	-1.24 (1.28)	0.339

Data were results of analysis of covariance or ordinal logistic regression for neuropsychiatric test scores using video-HIT gain as a predictor. Clock drawing test was assessed using ordinal logistic regression. The covariates included age, sex, and educational level.

*estimates were not reliably estimable due to a highly discrete and skewed distribution of clock drawing test scores.

video-HIT, video head-impulse test; PD-NC, Parkinson's disease with normal cognition; HC, horizontal canal; AC, anterior canal; PC, posterior canal; SE, standard error; K-BNT, Korean version of the Boston Naming Test; COWAT, Controlled Oral Word Association Test; SVLT, Seoul Verbal Learning Test; RCFT, Rey-Osterrieth Complex Figure Test.

Table 5. Independent effects of video-HIT gain on cognitive function test scores in PD-MCI patients

	HC		AC		PC	
	B (SE)/OR (95% CI)	p value	B (SE)/OR (95% CI)	p value	B (SE)/OR (95% CI)	p value
Attention						
Digit span forward	-0.64 (0.84)	0.444	-0.26 (0.60)	0.664	-0.73 (0.62)	0.241
Digit span backward	-0.92 (2.49)	0.713	-0.27 (1.82)	0.882	-0.76 (1.85)	0.681
Trail Making Test A	-1.46 (1.72)	0.398	1.26 (1.25)	0.316	0.33 (1.28)	0.797
Language						
K-BNT	-1.21 (1.36)	0.378	0.96 (0.99)	0.338	-2.53 (0.97)	0.011
COWAT semantic	-1.17 (0.69)	0.095	-1.33 (0.48)	0.007	-1.71 (0.48)	<0.001
Visuospatial						
Rey copy score	0.97 (0.94)	0.309	-0.17 (0.68)	0.807	-0.81 (0.69)	0.249
Clock drawing test	3,220 (1.89–5.5×10 ⁶)	0.033	0.74 (0.01–45.9)	0.887	37.6 (0.52–2,745)	0.097
Verbal memory						
SVLT immediate recall	-0.78 (0.93)	0.405	-0.27 (0.68)	0.687	0.13 (0.69)	0.853
SVLT delayed recall	0.14 (1.01)	0.891	0.44 (0.73)	0.548	0.30 (0.75)	0.692
SVLT recognition	-0.96 (0.90)	0.291	-0.36 (0.66)	0.584	-0.25 (0.68)	0.713
Visual memory						
RCFT immediate recall	-0.02 (0.95)	0.980	-1.07 (0.67)	0.117	-0.59 (0.69)	0.402
RCFT delayed recall	-0.96 (0.94)	0.307	-1.14 (0.66)	0.089	-0.99 (0.68)	0.153
RCFT recognition	0.73 (0.82)	0.372	0.51 (0.59)	0.394	-0.42 (0.61)	0.498
Frontal executive						
COWAT phonemic	-0.87 (0.94)	0.355	-1.77 (0.65)	0.008	-1.53 (0.67)	0.026
Stroop color reading	0.27 (0.93)	0.772	-2.09 (0.60)	<0.001	-0.47 (0.69)	0.499
Trail Making Test B	0.86 (1.52)	0.572	-0.79 (1.03)	0.444	-1.33 (1.04)	0.206

Data were results of analysis of covariance or ordinal logistic regression for neuropsychiatric test scores using video-HIT gain as a predictor. Clock drawing test was assessed using ordinal logistic regression, and the results for clock drawing test were displayed as OR (95% CI). The covariates included age, sex, and educational level.

video-HIT, video head-impulse test; PD-MCI, Parkinson's disease with mild cognitive impairment; HC, horizontal canal; AC, anterior canal; PC, posterior canal; SE, standard error; OR, odds ratio; CI, confidence interval; K-BNT, Korean version of the Boston Naming Test; COWAT, Controlled Oral Word Association Test; SVLT, Seoul Verbal Learning Test; RCFT, Rey–Osterrieth Complex Figure Test.

with the K-BNT score ($B=-2.53$, $SE=0.97$; $p=0.011$), semantic COWAT test score ($B=-1.71$, $SE=0.48$; $p<0.001$), and phonemic COWAT test score ($B=-1.53$, $SE=0.67$; $p=0.026$) (Table 5).

Correlations between the VOR and DAT imaging

No significant correlations were found between VOR gains and DAT binding in the striatal regions. However, among the extrastriatal regions, ¹⁸F-FP-CIT binding in the locus coeruleus was positively correlated with HC gain (Table 6).

DISCUSSION

In this study, we evaluated the associations between video-HITs and clinical characteristics, cognitive function test scores, gait parameters, and DAT uptake in patients with de novo PD. Our major findings are as follows. First, VOR–cognition relationships differed according to baseline cognitive status; the patterns of association between VOR gains and neuropsychological

measures were distinct in PD-NC and PD-MCI patients. Second, these VOR–cognition relationships were canal-specific; HC gain was positively related to visuospatial function, whereas AC and PC gains were negatively linked to language and frontal–executive functions. Third, AC gain was negatively associated with the base of support in the motion analysis. Finally, HC gain was positively correlated with increased ¹⁸F-FP-CIT uptake in the locus coeruleus. In conclusion, VOR gains are associated with distinct cognitive and gait functions in PD patients. Taken together, our findings suggest that the results of video-HITs can serve as a potential marker for disease monitoring in PD patients.

We identified a cognitive stage-dependent divergence in the pattern of vestibulo-cognitive associations—an aspect not previously demonstrated in PD. In patients with normal cognition, AC gain is related to attention and language functions. By contrast, in patients with PD-MCI, HC gain was positively associated with visuospatial function, whereas AC and PC gains were negatively associated with language and frontal–executive functions. This stage-dependent shift suggests that the cortical net-

Table 6. Partial correlation test between video-HIT gain and DAT uptake

	HC		AC		PC	
	Rho	p value	Rho	p value	Rho	p value
Caudate	-0.038	0.703	0.135	0.173	-0.067	0.497
Putamen	0.012	0.904	0.136	0.170	-0.027	0.784
Pallidum	0.054	0.589	0.147	0.138	0.007	0.946
Nucleus accumbens	-0.013	0.896	-0.008	0.936	-0.063	0.528
Ventral tegmental area	0.107	0.283	0.025	0.804	-0.058	0.562
Substantia nigra pars compacta	0.074	0.459	0.024	0.812	-0.070	0.481
Substantia nigra pars reticulata	0.098	0.325	0.038	0.706	-0.082	0.409
Red nucleus	0.103	0.299	0.049	0.626	-0.118	0.234
Locus coeruleus	0.229	0.020	0.080	0.424	-0.101	0.305
Raphe nucleus	0.162	0.101	-0.030	0.766	-0.097	0.328

Data were results of a partial correlation test between video-HIT gain and DAT uptake. The covariates included age, sex and educational level. video-HIT, video head-impulse test; DAT, dopamine transporter; HC, horizontal canal; AC, anterior canal; PC, posterior canal.

works integrating vestibular input are not static in PD; rather, as cognitive impairment progresses, vestibular signals appear to be increasingly coupled with frontal and parietal cortical networks.¹⁵ This interpretation is supported by structural and functional imaging studies showing greater frontal and parietal cortical thinning and connectivity disruption in PD-MCI patients than in cognitively normal PD patients.²⁹⁻³² Future longitudinal studies with repeated video-HIT and cognitive assessments will be required to clarify whether vestibular-cortical coupling indeed shifts in parallel with cognitive decline in PD patients.

We found the canal-specific association with cognitive dysfunction in PD patients. While the vestibular system ultimately converges onto shared multisensory cortical areas,^{12,33} each semicircular canal contributes preferentially to different components of head motion, which may differentially engage in cognitive networks: HCs primarily encode yaw-plane rotations^{34,35} and contribute substantially to stabilizing visual input during horizontal motion functions closely linked with self-orientation and visuospatial demands.³⁶ This provides a plausible mechanism for the observed association between HC and visuospatial test scores. In this study, there was a positive correlation between HC gain and K-MoCA scores. K-MoCA is known to be sensitive for detecting MCI.³⁷ This result was observed partly because the test incorporates both executive and visuospatial components.³⁸ Therefore, this association between HCs and the K-MoCA scores may have been driven by visuospatial subitems rather than executive subitems. However, the distribution of CDT scores in the present study was highly skewed in both the PD-NC group (score 0: $n=0$; score 1: $n=0$; score 2: $n=4$; score 3: $n=49$) and the PD-MCI group (score 1: $n=1$; score 2: $n=12$; score 3: $n=61$). The markedly discrete and asymmetric distribution of CDT scores, along with the narrow numerical range of VOR gain, may have inflated the estimated odds ratio between HC gain and CDT performance. Therefore, the ob-

served association between HC gain and CDT performance should be interpreted as indicative of a potential relationship rather than as a precise estimate of the magnitude of the association. Future studies employing more comprehensive visuospatial assessments are warranted to elucidate the relationship between HC gain and visuospatial function.

The vertical canals (AC and PC) encode the pitch and roll components of head motion.^{34,35} Vertical canal gains, particularly increased AC gain, may reflect axial rigidity and the akinetic-rigid motor phenotype,³⁹ which is associated with a higher risk of cognitive decline in PD patients.⁴⁰ The negative associations between PC gain and frontal-executive/language scores suggest that axial rigidity can systematically bias vertical canal HITs, leading to a generalized overestimation of vertical canal gains rather than affecting only a small subset of patients.²⁷ Such an upward shift in the measured VOR gain in vertical canals could therefore artifactually contribute to the observed negative association with cognitive function. Clearer evidence can be drawn from future studies among those with minimal or subtle axial rigidity, who are mostly free of those artefacts.

VOR gain was not associated with DAT uptake in any of the striatal regions. Rather, HC gain was related to FP-CIT uptake in the locus coeruleus, potentially reflecting the activity of molecular noradrenaline transporters.⁴¹ These findings suggest that the modulation of noradrenergic activity in the locus coeruleus may be linked to VOR dysfunction in HCs and cognitive dysfunction in PD patients. In another study, vestibular inputs were related to cognitive functions through the locus coeruleus and the ascending reticular activating system.⁴² In addition, there was a marginal association between HC gain and RBD in our study. Given the central role of the adrenergic system in the pathophysiology of RBD,⁴³ these findings raise additional possibilities for the association between adrenergic circuitry and the vestibular system. These findings underscore the complex

role of the VOR and noradrenergic pathways in cognitive dysfunction in PD and suggest potential therapeutic pathways to enhance neuroprotection and cognitive resilience in PD. Indeed, administration of a selective noradrenaline reuptake inhibitor enhanced activity in the right visual, intraparietal, and superior frontal cortices on functional magnetic resonance images, which are known to engage in sensory processing and visuospatial attention.⁴⁴

Notably, VOR gains across all three canals were not correlated with parkinsonian motor symptoms, as assessed by the UPDRS Part III or H&Y stage. Moreover, the base of support length correlated negatively with AC gain. Given that a narrow base of support is characteristic of parkinsonian gait,⁴⁵ this association may be ascribed to the finding that AC gain reflects neck rigidity rather than accurately assessing VOR integrity in PD patients.²⁷ Rather, it may reflect the differences in head movement required during video-HIT, particularly the limited head velocity generated during AC stimulation due to axial rigidity, which may contribute to the overestimation of VOR gain for the AC.²⁷ Taken together, these findings suggest that AC gain could serve as a potential marker for assessing the severity of axial symptoms in patients with PD. Longitudinal studies are warranted to determine whether such increased (and possibly overestimated) AC gain in PD is associated with the risk of falls, mortality, and dementia conversion, which are conventionally linked to axial rigidity.⁴⁶

This study had several limitations. First, its cross-sectional design limits the ability to infer causal relationships between VOR dysfunction and the clinical or cognitive characteristics of PD. Future longitudinal studies could help clarify whether VOR abnormalities predict disease progression or outcomes such as falls, dementia, or mortality. Second, the data were collected from a single tertiary center, which may limit the generalizability of our findings to broader PD populations with different demographics or clinical profiles. Finally, the associations between VOR gains and regional DAT uptake should be interpreted with caution, as these analyses involved multiple partial correlations without formal correction for multiple comparisons. Given the exploratory nature of this study, we prioritized sensitivity to potential signals over strict control of Type I error. Future studies with larger sample sizes and appropriate multiplicity adjustments will be essential to validate these preliminary observations.

In conclusion, our findings suggest a possible link between the VOR and cognitive and motor functions in patients with de novo PD. We found that the integrity of vestibular afferents was associated with specific cognitive impairments and gait abnormalities in PD patients. These findings highlight the potential of VOR gain as a marker of PD-related cognitive and motor changes.

Moreover, the observed association between HC gain and locus coeruleus uptake suggests a role for noradrenergic pathways in the complex interactions between the vestibular and cognitive systems in PD. This study emphasizes the need for a deeper understanding of the role of the VOR in PD, which could provide new avenues for monitoring and potentially mitigating disease impact.

Supplementary Materials

The Data Supplement is available with this article at <https://doi.org/10.14802/jmd.25230>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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None

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