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ORIGINAL ARTICLE

Diplopia in Parkinson's disease: Indication of a cortical phenotype with cognitive dysfunction?

Wanda Naumann[1] | Jacob Gogarten[1] | Shideh Schönfeld[2] | Fabian Klostermann[1] | Frank Marzinzik[1] | Katharina A. Schindlbeck[1,3]

[1]Department of Neurology, Charité–Universitätsmedizin Berlin, Berlin, Germany

[2]Department of Ophthalmology, Charité–Universitätsmedizin Berlin, Berlin, Germany

[3]Center for Neurosciences, The Feinstein Institute for Medical Research, Manhasset, NY, USA

Correspondence
Katharina A. Schindlbeck, Center for Neurosciences, Feinstein Institute for Medical Research, 350 Community Drive, 11030 Manhasset, NY, USA.
Email: KSchindl@northwell.edu

Abstract

Background: Visual disturbances are increasingly recognized as common non-motor symptoms in Parkinson's disease (PD). In PD patients, intermittent diplopia has been found to be associated with the presence of visual hallucinations and the Parkinson's psychosis spectrum. Here, we investigated whether diplopia in PD is associated with other non-motor traits and cognitive impairment.

Methods: We investigated 50 non-demented PD patients with and without intermittent diplopia and 24 healthy controls for visual disturbances, as well as motor and non-motor symptoms. All participants underwent a neuropsychological test battery; visuospatial abilities were further evaluated with subtests of the Visual Object and Space Perception Battery (VOSP). The two PD patient groups did not differ significantly in age, symptom duration, motor symptom severity, frequency of visual hallucinations, or visual sensory efficiency.

Results: PD patients with diplopia reported more frequent non-motor symptoms including more subjective cognitive problems and apathy without changes in global cognition measures compared to those without diplopia. PD patients with diplopia had greater impairment in several tests of visuospatial function (pentagon copying $p = .002$; number location $p = .001$; cube analysis $p < .02$) and object perception ($p < .001$) compared to PD patients without diplopia and healthy controls. By contrast, no consistent group differences were observed in executive function, memory, or language.

Conclusions: PD patients with diplopia have a greater non-motor symptom burden and deficits in visuospatial function compared to PD patients without diplopia. PD patients with diplopia might be prone to a cortical phenotype with cognitive decline and apathy associated with worse prognosis.

KEYWORDS
cognitive dysfunction, diplopia, hallucinations, Parkinson's disease, visual disturbances

Frank Marzinzik, Katharina A. Schindlbeck, contributed equally.

1 | INTRODUCTION

Increasing focus on the non-motor aspects of Parkinson's disease (PD) has provided valuable insights into the diversity of clinical, pathological, and neurochemical features of the disorder.[1] Motor symptoms constitute the basis for clinical diagnosis of PD and are typically progressing over time. The temporal aspect of non-motor features is more complex given that some of them, including REM sleep behavior disorder, hyposmia, depression, and visual dysfunction, can already develop in the prodromal phase, several years before the onset of motor symptoms.[2,3] Due to the heterogeneity of these symptoms, non-motor subtypes of the disease have been proposed: a brainstem phenotype with sleep and autonomic dysfunction, a limbic phenotype with prominent depression and fatigue symptoms, and a cortical phenotype with cognitive decline and apathy.[4] The cortical subtype is considered to be more malignant with worse prognosis due to the development of PDD and psychosis. Visual hallucinations and mild cognitive impairment (MCI) have been found to predict the later occurrence of dementia in PD (PDD).[5] Visual hallucinations in PD encompass a wide spectrum, including minor illusions, formed hallucinations, delusions without insight, and severe psychosis; these different forms of visual hallucination form the "PD psychosis spectrum" through which a patient may progress over the course of the disease.[5] The presence of visual hallucinations in PD has been identified as a significant predictor of dementia[6] and has been found to be associated with a more rapid cognitive decline over time.[7] Visual hallucinations are associated with different risk factors, such as visual disturbances, longer disease duration, and dopaminergic therapy.[5,8] Selective or isolated diplopia—the duplication of single objects—is considered to be part of this spectrum and may precede progression to formed hallucinations.[5,9] In a previous study, we found that the presence of intermittent diplopia was a predictive factor for visual hallucinations in PD patients.[10] This suggests that some forms of diplopia may precede visual hallucinations, which should be confirmed in longitudinal studies.

Diplopia is a potentially debilitating form of visual disturbance that affects 10–40% of all PD patients.[10–13] In PD, diplopia is usually binocular and associated with peripheral (muscle-related) or central causes.[14] It can be either complete, affecting all objects in an environment, or selective, with only individual objects or persons appearing duplicated. Diplopia in PD patients has been found to be associated with subtle oculomotoric abnormalities, changes in dopaminergic treatment, and visual hallucinations.[9,10,15]

To date, it is not known whether diplopia is associated with a particular subtype of PD. We hypothesized that diplopia is associated with a cortical phenotype of PD with cognitive decline, which is considered to be more malignant. This is the first study investigating PD patients with diplopia using motor and non-motor assessments, including detailed neuropsychological testing. We investigated non-demented PD patients with and without diplopia, which were matched for motor severity, disease duration, visual hallucinations, and a healthy control group. We were particularly interested in whether these groups differ in their overall cognitive function and whether they exhibit impairment in specific domains related to visuoperceptive and visuospatial function.

2 | METHODS

2.1 | Study design and sample

PD patients were recruited prospectively in our outpatient unit specialized in movement disorders in the Neurology Department of the Charité Universitätsmedizin Berlin.

Inclusion criteria were as follows: (A) diagnosis of PD by a movement disorder expert according to the UK PD Society Brain Bank criteria, (B) absence of severe cognitive impairment (Mini-Mental State Examination MMSE ≤24) or a diagnosis of dementia based on neuropsychological evaluation, and 3) absence of severe or unstable depression assessed by the Beck's Depression Inventory.[16] PD patients with binocular diplopia were included in this cross-sectional study. A group of PD patients without diplopia matched for age, level of education, impairment of motor functions, and visual hallucinations was recruited in parallel. Additionally, a healthy control (HC) group free of neurologic and psychiatric illnesses was recruited via publicly posted flyers and relatives of PD patients. All participants were native German speakers and had had regular ophthalmologic checkups, except for two participants, where this information was missing. All participants gave written informed consent to the study protocol, approved by the ethics committee of the Charité. All healthy controls were assessed with the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I and Part III in order to detect symptoms that could reveal a movement disorder.[17]

2.2 | Clinical assessments in the PD cohorts

Motor and non-motor symptoms were evaluated with the MDS-UPDRS I and MDS-UPDRS III while the patients were on their dopaminergic medication. Non-motor symptoms were assessed with the Non-Motor Symptoms Questionnaire (NMSQuest),[18] the Fatigue Severity Scale (FSS),[19] and the Epworth Sleepiness Scale (ESS).[20] The levodopa equivalent daily dose (LEDD)[21] was calculated for each patient.

A structured interview on visual disturbances and history of ophthalmologic comorbidities was performed with all participants[10] [see Suppl. Material in *Schindlbeck et al*, *PARD 2017* to access the full interview]. In brief, this interview investigates the symptoms of diplopia and visual hallucinations, including frequency, severity, form, and accompanying factors.[10] Diplopia was evaluated including frequency (rare, frequent, often, very often) and severity (mild, moderate, severe, very severe) according to the metric properties of the NMSQuest and Scale for Parkinson's disease. Furthermore, the duration (intermittent versus permanent), character (selective/isolated versus complete), impairment in everyday life, and trigger factors were assessed via interview. Visual hallucinations were assessed with regard to duration (transient,

permanent, history of visual hallucinations), severity, and frequency according to the Non-Motor Symptoms Scale for Parkinson's disease. Other visual problems including spatial perception, problems with contrast sensitivity, presence of blurred vision, and history of ophthalmological comorbidities (cataract, maculopathy, retinal detachment, loss of visual acuity, glaucoma, history of surgery, or tumor) were assessed via interview.

2.3 | Neuropsychological testing

Global cognitive function was assessed with the Mini-Mental State Examination (MMSE) and the total score of the Consortium to Establish a Registry for Alzheimer's Disease Plus test (CERAD+),[22] a neuropsychological test battery used in different neurodegenerative diseases.[23] The CERAD + battery included the Boston Naming Test (BNT); word list learning, recall, and recognition; figure copying and delayed recall of figures; reciting S-words and animals; the Trail Making Tests A and B, and the MMSE. The clock-drawing test was rated with a grading system from 1 (perfect) to 6 (no reasonable representation of a clock).[24]

Visuospatial abilities were further evaluated with the Visual Object and Space Perception Battery (VOSP).[25] Before assessing the VOSP test, a preliminary test of visual sensory efficiency (shape detection) is performed to determine whether the patient has sufficient visual and sensorial capacity to complete the VOSP subtests. Object perception was assessed with the "object decision" test, in which subjects had to identify the silhouette of a real object out of four silhouettes, with three being silhouettes of fictional, nonexistent objects. Three further tests of spatial perception were performed: "dot counting," "number location" (determining which number's location within a square corresponds to the location of a dot in another square), and "cube analysis" (counting the number of cubes in a complex formation). Another visuospatial test, the subitem of the MMSE "pentagon copying," was separately graded 0 to 3 points (correct representation of two pentagons, overlapping, and overlapping part being a rectangle). Neuropsychological test scores were transformed into z-scores; the healthy control subjects with normal cognition served as the reference group in calculating z-scores.

In addition to the evaluation of each cognitive test separately, we grouped subtests of the CERAD + into five major cognitive domains (executive function: phonematic fluency, TMT-B, memory: word list learning, figure delayed recall, attention: TMT-A, language: BNT, and visuospatial function: figure copying, pentagon copying). A domain was considered impaired if one domain-specific test result was 1.5 standard deviations (SDs) below the norm value.

2.4 | Statistical analysis

The Statistical Package for Social Sciences (SPSS Version 26) was used for data management and processing. The Kolmogorov–Smirnov test was used to examine the distribution of the data. Since most parameters assessing sociodemographic and cognitive characteristics were not normally distributed, nonparametric methods were used. The demographic characteristics and clinical symptoms were compared between PD patients with diplopia, PD patients without diplopia, and healthy controls using the Kruskal–Wallis test or Mann–Whitney *U* test. The chi-squared test was used to compare nominal parameters between the different groups; p-values were adjusted using Bonferroni's correction according to the number of comparisons. The results were considered significant at $p < .05$ (2-tailed).

3 | RESULTS

We enrolled 24 PD patients with binocular diplopia (PD diplopia), 26 PD patients without diplopia (PD controls), and 24 HC subjects.

TABLE 1 Sociodemographic and clinical characteristics

	Healthy controls (*n* = 24)	PD controls (*n* = 26)	PD diplopia (*n* = 24)	*p*-value
Age (years)	69.7 ± 9.1	70.4 ± 8.8	74.3 ± 8.0	.138[a]
Sex (male: female)	7:17	14:12	18:6	.006[b]
Education (years)	13.0 ± 3.6	12.2 ± 3.1	11.8 ± 3.4	.354[a]
Disease duration (years)		7.4 ± 6.5	8.5 ± 6.2	.572[c]
MDS-UPDRS III		31.1 ± 10.2	35.8 ± 11.8	.268[c]
LEDD (mg)		658 ± 550	793 ± 523	.214[c]

Note: Means and standard deviations (SD) are shown if not otherwise indicated. There was a higher ratio of men to women in the PD diplopia group compared with HC ($p = .003$), while there were no significant other group differences (HC vs. PD controls: $p = .093$; PD controls vs. PD diplopia: $p = .149$).

[*p*-value:

[a]Kruskal–Wallis test.

[b]chi-squared test (Bonferroni-corrected *p*-value $p < .016$).

[c]Mann–Whitney *U* test; Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS III, max. 72 points), levodopa equivalent daily dose (LEDD)].

The three groups did not differ significantly in age or education, and the two PD groups were matched for symptom duration, motor symptom ratings, and visual hallucinations (Table 1). There was also no significant difference in motor subtypes of PD across the two groups (p = .71, chi-square test). Performance on the visual sensory efficiency test (shape detection, VOSP) did not differ across the three groups, assuring that the patients have sufficient visual and sensorial capacity to complete the other subtests (mean ± SD of HC: 19.9 ± 0.34; PD controls: 19.6 ± 0.71; PD diplopia: 19.55 ± 0.67; p = 0.183).

3.1 | Clinical group characteristics

In the PD diplopia group, intermittent binocular diplopia was reported to occur several times a week (33.3%) or daily (58.3%) with mostly moderate intensity affecting near and/or far vision. The average duration of diplopia was 15.4 ± 12.3 months. All patients had intermittent diplopia. Of those, 60% of patients described complete diplopia and 40% selective diplopia (duplication of single objects). Visual hallucinations (p < .001), blurred vision (p < .001), and contrast sensitivity (p < .01) were more frequently reported among PD patients compared with HC, but did not differ between PD patients with and without diplopia (p > .05), except blurred vision, which was more frequent among PD with diplopia (p = .04). There were no significant differences regarding spatial perception, color vision, and ophthalmologic comorbidities across the three groups.

3.2 | Non-motor symptoms

Overall, non-motor symptoms were more frequently reported by PD patients with diplopia compared to those without diplopia (p = .02; NMSQuest; see Table 2). PD patients with diplopia reported significantly more cognitive problems than PD patients without diplopia and HC in the MDS-UPDRS Part I interview (p < .001) (Figure 1). With respect to the MDS-UPDRS categories, they mostly reported slight cognitive deficits, whereas the majority of HC and PD patients without diplopia had no cognitive deficits. PD patients with diplopia reported more frequently about attention and memory problems (p < .001), apathy (p < .05), perceptual problems (p < .001), and gastrointestinal symptoms (p < .05). No differences were noticed with

TABLE 2 Group characteristics of non-motor symptoms

Healthy controls (n = 24)	PD controls (n = 26)	PD diplopia (n = 24)	p-value	Post hoc tests	
MDS-UPDRS Part I					
Cognitive impairment	0.46 ± 0.59	0.35 ± 0.56	1.29 ± 0.86	<.001	HC–PDc p = 1.0
					HC–PDdip p = .002
					PDc–PDdip p < .001
Hallucinations and psychosis	0 ± 0.0	0.46 ± 0.71	0.71 ± 0.75	<.001	HC–PDc p = .025
					HC–PDdip p < .001
					PDc–PDdip p = .436
Apathy	0.08 ± 0.28	0.15 ± 0.46	0.63 ± 0.97	.014	HC–PDc p = 1.00
					HC–PDdip p = .023
					PDc–PDdip p < .05
NMSQuest Dimensions					
Sum score	42.8 ± 20.9	64.2 ± 31.9	0.021		
Perceptual problems	0.6 ± 1.4	9.6 ± 7.5	<0.001		
Attention/memory	1.2 ± 2.3	4.6 ± 4.3	0.001		
Gastrointestinal	6.4 ± 8.0	10.0 ± 7.1	0.036		
Cardiovascular	2.0 ± 2.7	3.2 ± 3.7	0.247		
Sleep/fatigue	9.2 ± 8.1	10.9 ± 10.7	0.704		
Mood/cognition	2.5 ± 4.9	3.1 ± 4.0	0.256		
Urinary	9.9 ± 6.0	10.3 ± 8.4	0.961		
Sexual function	2.2 ± 4.0	3.0 ± 4.6	0.529		
Miscellany	8.9 ± 6.5	9.5 ± 7.9	0.945		

Note: Non-motor symptoms in healthy controls (HCs) and PD patients without (PD controls) and with diplopia (PD diplopia) are shown as means and standard deviations. The Kruskal–Wallis test was used for group comparisons in MDS-UPDRS Part I, post hoc tests are shown for significant group differences only, and Mann–Whitney U test was used for NMS dimensions.

Abbreviations: MDS-UPDRS Part I, I.1 cognitive impairment, I.2 hallucination and psychosis, I.3 depressed mood, reported symptoms by patients with a maximum of 4 points each.

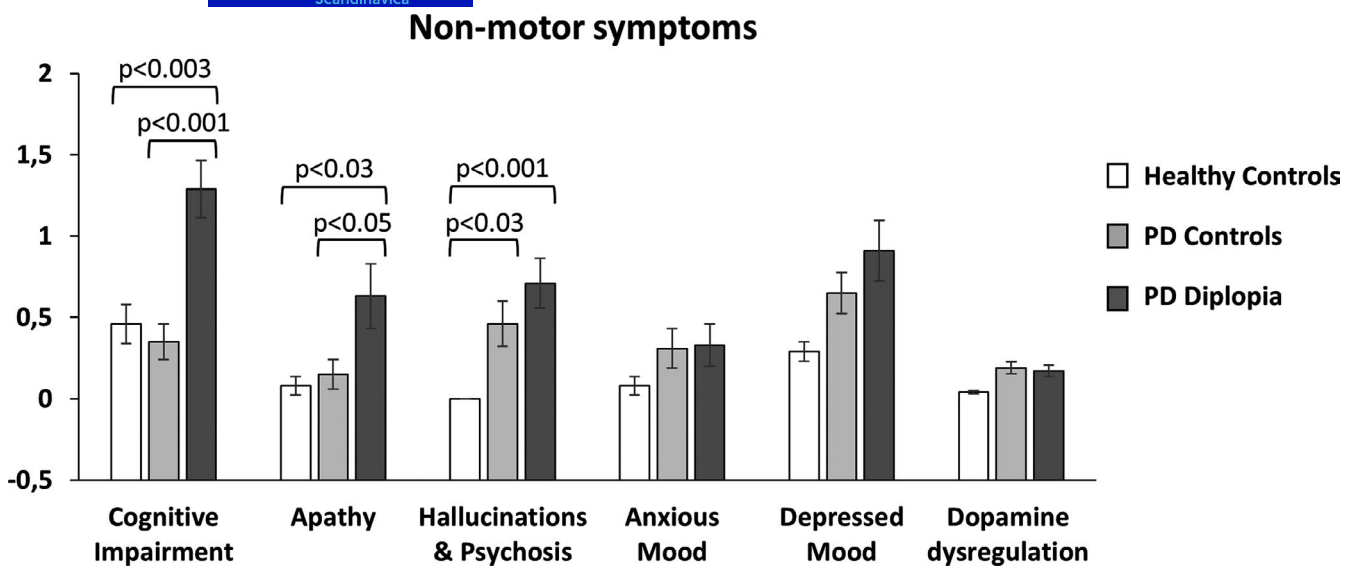

FIGURE 1 Non-motor symptoms across groups. Non-motor symptoms assessed by the MDS-UPDRS Part I in healthy controls (HC), and PD patients without (PD controls) and with diplopia (PD diplopia) are shown as means and standard errors. PD patients with diplopia had significantly more cognitive problems and apathy compared to PD patients without diplopia. The Kruskal–Wallis test was used for group comparisons in MDS-UPDRS Part I, and post hoc tests are shown for significant group differences only

regard to cardiovascular, mood, sleep-related, urinary-related, and sexual-related symptoms (Table 2).

Hallucinations ($p < .03$), symptoms of fatigue ($p < .005$), daytime sleepiness ($p < .03$), and depression (BDI, $p < 0.01$) are more frequently reported among PD patients compared with HC subjects, but did not differ among the PD patients with and without diplopia (Table S1). No group differences were seen in the occurrence of symptoms of depression ($p > 0.45$), anxiety ($p > .24$), and dopamine dysregulation ($p > .41$) assessed by the MDS-UPDRS Part I (Table S1).

3.3 | Cognitive function

There were no differences in the global cognitive function measured with the MMSE ($p = .55$) and the CERAD total score ($p = .11$) across the three groups. All cognitive test results across the three groups are presented in Table 3. PD patients with diplopia had lower scores on the TMT-A (measuring attention) compared with HC participants ($p = .002$), but not compared to their counterparts without diplopia ($p > .12$). No group differences were found in language and memory function. With regard to executive function, PD patients with diplopia performed significantly worse on the TMT-B and phonematic fluency test compared to PD patients without diplopia ($p < .05$). Other measures of executive function, including semantic fluency ($p = .33$) and the clock-drawing test ($p = .30$), did not differ across the three groups. Visuospatial function was assessed using several independent tests (Figure 2): PD patients with diplopia had significantly lower scores on the pentagon copying test ($p < .02$), the object decision test ($p < .02$), the number location test ($p < .04$), and the cube analysis test ($p < .02$) compared to PD patients without diplopia. A trend was observed in the figure copying test ($p = .07$) (Table 3).

We further combined subtests of the CERAD + to evaluate the impairment across the five major cognitive domains (executive function, memory, attention, language, and visuospatial function) in each group (Figure 2). PD patients with diplopia had significantly higher visuospatial impairment compared to both PD patients without diplopia ($p = .009$) and HC subjects ($p < .001$). They were also more impaired in the attention domain compared with HC ($p < .03$), but not compared with the PD control group.

4 | DISCUSSION

Intermittent diplopia is a common but often under-recognized, treatable non-motor symptom in PD patients.[12,26] We investigated non-demented PD patients with and without diplopia that were matched for motor severity, disease duration, and the presence of visual hallucinations, along with a group of healthy controls. Overall, PD patients with diplopia experienced more non-motor symptoms including cognitive problems, perceptual problems, and apathy compared to those without diplopia. PD patients with diplopia reported more subjective cognitive problems in an interview compared to those without, but the two groups did not differ in measures of global cognition. More detailed neuropsychological testing uncovered that PD patients with diplopia had more visuospatial and visuoperceptive impairment. They performed significantly worse on four out of six visuocognitive tests, and the figure copying test showed a trend ($p = 0.07$) toward worse performance. Only one test (dot counting) revealed worse results in the diplopia group compared with HC, but did not differ across PD patients with and without diplopia, potentially because it was not sensitive enough. The combined analysis of the five major cognitive domains further confirmed that visuospatial

TABLE 3 Group characteristics of cognitive impairment

Cognitive domain	Test	HC (n = 24)	PD control (n = 26)	PD diplopia (n = 24)	p-value	Post hoc tests	
GCF	CERAD	0.0 ± 1.0	−0.21 ± 1.03	−0.67 ± 1.24	0.105		
	MMSE	0.0 ± 1.0	−0.31 ± 1.06	−0.38 ± 1.37	0.554		
Attention	TMT-A	0.0 ± 1.0	−0.35 ± 1.27	−1.96 ± 3.50	0.002	HC–PDc	p = .408
						HC–PDdip	p = .002
						PDc–PDdip	p = .125
Language	BNT	0.0 ± 1.0	−0.28 ± 1.27	−0.59 ± 1.24	0.152		
Memory—verbal/visual	Word list learning	0.0 ± 1.0	−0.01 ± 1.03	−0.26 ± 1.00	0.609		
	Word list recall	00.0 ± 1.	−0.29 ± 1.03	−0.39 ± 1.03	0.371		
	Word list recognition	0.0 ± 1.0	−0.52 ± 3.42	−1.00 ± 3.32	0.684		
	Figure delayed recall	0.0 ± 1.0	−0.44 ± 1.21	−0.81 ± 1.45	0.094		
Executive function	Semantic fluency	0.0 ± 1.0	−0.01 ± 0.99	−0.32 ± 1.30	0.331		
	Phonemic fluency	0.0 ± 1.0	0.29 ± 1.18	−0.58 ± 1.03	0.032	HC–PDc	p = 1.0
						HC–PDdip	p = .237
						PDc–PDdip	p = .030
	TMT-B	0.0 ± 1.0	0.77 ± 2.11	−2.33 ± 3.16	<0.001	HC–PDc	p = .430
						HC–PDdip	p < .001
						PDc–PDdip	p = .044
	Clock-drawing test	0.0 ± 1.0	−0.92 ± 1.96	−1.50 ± 1.48	0.007	HC–PDc	p = .318
						HC–PDdip	p = .005
						PDc–PDdip	p = .297
Visuospatial function	Figure copying	0.0 ± 1.0	−1.17 ± 2.81	−2.63 ± 3.12	0.002	HC–PDc	p = .562
						HC–PDdip	p = .001
						PDc–PDdip	p = .074
	Pentagon Copying	0.0 ± 1.0	−0.52 ± 2.08	−2.36 ± 3.34	0.002	HC–PDc	p = 1.0
						PDc–PDdip	p = .002
						HC–PDdip	p = .016
	Object decision VOSP 3	0.0 ± 1.0	−0.80 ± 1.67	−2.49 ± 1.99	<0.001	HC–PDc	p = .237
						HC–PDdip	p < .001
						HC–PDdip	p = .015
	Dot counting VOSP 5	0.0 ± 1.0	−0.79 ± 2.82	−2.19 ± 4.62	0.040	HC–PDc	p = 1.0
						PDc–PDdip	p = .039
						PDc–PDdip	p = .267
	Number location VOSP 7	0.0 ± 1.0	−0.41 ± 1.14	−2.43 ± 2.99	0.001	HC–PDc	p = .778
						HC–PDdip	p = .001
						PDc–PDdip	p = .035
	Cube analysis VOSP 8	0.0 ± 1.0	0.46 ± 0.57	−0.94 ± 2.06	0.020	HC–PDc	p = .485
						HC–PDdip	p = .500
						PDc–PDdip	p = .015

Note: performance across the different cognitive categories is shown as means and standard deviations of the z-scores (see Methods) in healthy controls (HC), and PD patients without (PD controls) and with diplopia (PD diplopia). The Kruskal–Wallis test was used for group comparisons, and post hoc tests are shown for significant group differences.

Abbreviations: Mini-Mental State Examination (MMSE), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Boston Naming Test (BNT), Trail Making Test (TMT), Visual Object and Space Perception Battery (VOSP)].

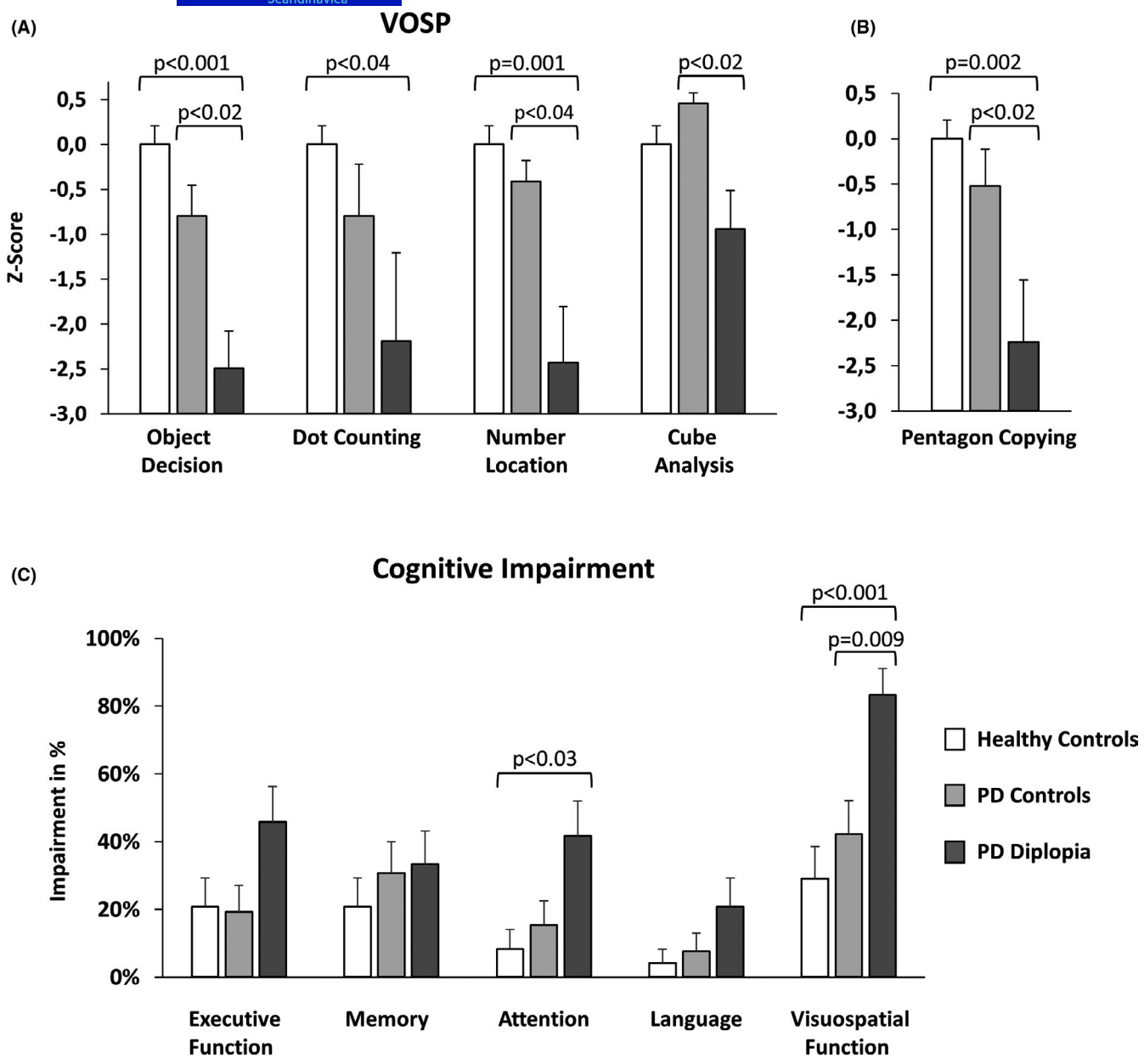

FIGURE 2 Cognitive function across groups. (A) Parkinson's disease (PD) patients with diplopia performed worse on tests for object decision ($p < .001$), dot counting ($p = .04$), and number location ($p = .001$) relative to HC. They also performed worse in object decision ($p < .02$), number location ($p < .04$), and cube analysis ($p < .02$) relative to PD patients without diplopia. (B) PD patients with diplopia performed worse on the pentagon copying test relative to HC subjects ($p = .002$) and PD patients without diplopia ($p < .02$). (C) Impairment in the five cognitive subcategories is shown in percent for healthy control (HC) subjects, PD patients without diplopia (PD controls), and PD patients with diplopia (PD diplopia). The groups differed significantly in visuospatial function impairment ($p < .001$): PD patients with diplopia had greater impairment in visuospatial function compared with HC ($p < .001$) as well as compared to PD patients without diplopia ($p = .009$). PD patients with diplopia had significantly more impairment in attention compared with HC ($p < .03$). [Bar graphs show means and standard errors; the Kruskal–Wallis test was used for group comparisons, and post hoc tests are shown for significant group differences only]

function was the only domain that was impaired in PD patients with diplopia compared to those without diplopia and healthy controls. Mixed test results were found regarding executive dysfunction. Overall, PD patients with diplopia performed worse in two out of four tests compared to their counterparts without diplopia. PD patients with diplopia performed worse on the clock-drawing test compared with HC but not with the PD control group. Overall, this might indicate early and subtle changes in this cognitive domain in PD patients with diplopia that could result in significant impairment over time. No consistent differences in PD patients with and without diplopia were found across other cognitive domains including attention, memory, or language.

A screening test (see methods) ensuring that the participants' visual and sensory capacity during the tests was not diminished by diplopia did not reveal group differences. Furthermore, a potential bias by the reduced visual capacity in the PD group with

diplopia would have resulted in worse test performance across all cognitive tests that involve a visual component (ie clock-drawing test, TMT-A, visual memory test). However, we cannot exclude the possibility that diplopia might have influenced visual cognition resulting in worse visuospatial function in the group with diplopia. We compared groups of PD patients that did not differ in visual hallucinations to avoid a bias regarding cognitive dysfunction in favor of the group with higher frequency of visual hallucinations. While the PD groups were matched for age, education, and motor disease severity, there were significantly more men in the PD group with diplopia compared to the healthy control group, resulting in a potential bias when assessing cognitive tests including language or visuospatial tasks, that are known to be influenced by sex.[27] However, men do typically perform better in visuospatial tests than women.[28] Despite the greater percentage of male participants in the PD diplopia group, we found greater visuospatial impairment in the PD diplopia group compared with the HC group and the PD group without diplopia.

Visuospatial deficits can typically result in difficulties in the everyday lives of patients, including feeling unsafe when driving, having trouble navigating new routes, and forgetting where they parked their car or placed their keys.[11,29] PD patients are especially dependent on their visual environment, as they often compensate for their motor deficits by guiding their movements visually.[10,26] For example, visual cues including lines on the floor and width of doorways can help to overcome freezing. Thus, impairments in visuospatial function such as estimating distances are associated with increased freezing of gait and difficulties in car driving.[11,30,31] Overall, visuospatial and visuoperceptive deficits are associated with impairments in activities of daily life and reduced quality of life.[12] The visuospatial deficits experienced by the PD patients with diplopia in this study may have contributed to more frequently self-reported cognitive problems. Even in the absence of any evidence of cognitive impairment on cognitive testing, PD patients with subjective cognitive decline are more likely to be diagnosed with cognitive impairment at follow-up.[32]

Intermittent diplopia in PD is related to heterogeneous mechanisms including ophthalmic and oculomotor pathology, motor fluctuations, and mechanisms associated with intermediate- and higher-level processing of the visual system. Most forms are treatable with ophthalmological interventions, optimization of dopaminergic therapy, or anticholinergic therapy. Early and correct diagnosis and treatment of this symptom may also prevent more severe symptoms. Selective diplopia is considered to be part of a continuum of symptoms including visual illusions, hallucinations, and delusions that are related to the PD psychosis spectrum, which can progress over the course of the disease.[5] Although diplopia and visual hallucinations are phenomenologically different, the cognitive correlates of those symptoms seem to overlap and particularly involve visual-related cognition. Formed visual hallucinations in PD patients are typically associated with deficits in visuospatial function, object perception, and executive dysfunction.[5] Recent studies of PD patients with minor visual hallucinations, however, did not find differences in cognitive function compared to patients without minor hallucinations,[33] though they do exhibit gray matter volume loss in the dorsal visual stream area compared with healthy controls.[34]

Our findings are clinically relevant since visual hallucinations represent the main modifiable predictor for the development of dementia in PD.[35] Indeed, appropriate and timely treatment of visual hallucinations has been shown to delay further exacerbation of hallucinations in PD.[36] Dementia, psychosis, and apathy are associated with reduced functionality, more frequent nursing home placement, higher mortality, and therapeutic complications.[35,37] Therefore, the early detection of dementia and psychosis symptoms is critical in the clinical management of PD. Intermittent diplopia can occur early in the course of the disease and has been found to be a predictive factor for visual hallucinations in PD patients.[10] The cross-sectional nature of our dataset and the relatively small sample size represent a limitation regarding the generalizability of our findings. Therefore, the predictive value of intermittent diplopia for psychosis and dementia should be investigated in longitudinal studies.

5 | CONCLUSIONS

In clinical practice, neurologists should be vigilant about diplopia in PD patients, since it can be successfully treated with ophthalmological interventions or through optimization of dopaminergic therapy.[15,26] They should actively inquire about diplopia as it can be easily overlooked because many patients do not recognize this symptom as part of their PD diagnosis. The presence of diplopia in PD patients should raise the physician's level of awareness regarding other visual deficits including visual hallucinations, cognitive problems, and apathy. Our findings indicate that PD patients with intermittent diplopia might belong to a cortical phenotype with prominent cognitive decline and apathy and thus associated with a worse prognosis and the need for closer clinical supervision. According to the dual syndrome hypothesis,[38] early deficits in visuospatial function are indicative of posterior cortical and temporal lobe dysfunction, a subtype prone to rapid decline to dementia in which cholinergic treatment may offer some clinical benefit. Whether timely and successful treatment of diplopia in PD patients could potentially prevent the development of more severe visual deficits over the course of the disease needs to be investigated in future studies.

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CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

K.A.S., W.N., F.K. and F.M. contributed to the conception and design of the study. K.A.S., W.N., S.S., and F.M. acquired the clinical data; K.A.S., J.G. and W.N. performed the data and statistical analysis; K.A.S., W.N., and F.M. prepared the figures; K.A.S. and W.N. drafted the article. All authors revised the article.

ETHICS APPROVAL

All participants gave written informed consent to the study protocol, approved by the ethics committee of the Charité.

DATA AVAILABILITY STATEMENT

Deidentified data will be made available to interested investigators for the purpose of replicating results.

ORCID

Katharina A. Schindlbeck https://orcid.org/0000-0002-5643-556X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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