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ORIGINAL COMMUNICATION

Diplopia in Parkinson's disease: visual illusion or oculomotor impairment?

Femke Visser[1] · Annemarie M. M. Vlaar[1] · Carlijn D. J. M. Borm[2] · Valentin Apostolov[3] · Y. X. Lee[4] · Irene C. Notting[5] · Henry C. Weinstein[1,6] · Henk W. Berendse[6]

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Abstract

Introduction Approximately 20% of patients with Parkinson's disease (PD) experience diplopia; however, the cause of the diplopia is unclear. We aimed to explore the association of diplopia, and its subtypes, with oculomotor abnormalities, impaired vision, and visual hallucinations, in patients with PD.

Methods This exploratory study included 41 PD patients, recruited from two general hospitals, of whom 25 had diplopia and 16 did not have diplopia, as well as 23 healthy controls (HCs). We defined subtypes of diplopia as selective diplopia, i.e., diplopia of single objects, and complete diplopia, i.e., diplopia of the entire visual field. All participants underwent a full orthoptic and ophthalmologic examination.

Results PD patients with diplopia had a high prevalence of oculomotor abnormalities (84%), impaired vision (44%), and visual hallucinations (44%), compared to PD patients without diplopia (33%, 6%, and none, respectively, $p < 0.01$), and compared to HCs (23%, 9%, and none, respectively, $p < 0.01$). Oculomotor abnormalities were equally prevalent in both subtypes of diplopia (selective and complete), whereas impaired vision was predominantly found in patients with selective diplopia. Moreover, only patients with selective diplopia had visual hallucinations.

Conclusions In PD patients, diplopia may be indicative of oculomotor or visual impairments. Hence, it is worthwhile to refer PD patients with diplopia to an orthoptist and an ophthalmologist for evaluation and, possibly, treatment of diplopia. Furthermore, in the case of selective diplopia, the neurologist should consider the presence of visual hallucinations, which may require the adjustment of the patient's medication.

Keywords Diplopia · Ocular motility · Ocular disorders · Hallucinations · Parkinson's disease

✉ Femke Visser
visser.femke@gmail.com

Annemarie M. M. Vlaar
a.vlaar@olvg.nl

Carlijn D. J. M. Borm
carlijn.borm@radboudumc.nl

Valentin Apostolov
v.apostolov@olvg.nl

Y. X. Lee
yingxinglee@gmail.com

Irene C. Notting
i.c.notting@lumc.nl

Henry C. Weinstein
h.weinstein@olvg.nl

Henk W. Berendse
h.berendse@amsterdamumc.nl

[1] Department of Neurology, Onze Lieve Vrouwe Gasthuis (OLVG), Location OLVG West, Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands

[2] Department of Neurology, Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Parkinson Centre (ParC), Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands

[3] Department of Ophthalmology, Onze Lieve Vrouwe Gasthuis (OLVG), Location OLVG West, Jan Tooropstraat 164, 1061 AE Amsterdam, The Netherlands

[4] Department of Neurology, Maasstad Hospital, Maasstadweg 21, 3079 DZ Rotterdam, The Netherlands

[5] Department of Ophthalmology, Leids University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

[6] Department of Neurology, Amsterdam UMC, Location VU University Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Introduction

Approximately 20% of patients with Parkinson's disease (PD) experience diplopia, and this figure is even higher in PD dementia [1-3]. Since diplopia has a negative impact on the quality of life in PD patients [4], it is important to recognize and treat this symptom. The first step to treatment is to understand the underlying cause [5]. Unfortunately, studies investigating PD patients with diplopia are scarce [4]. In a clinical study involving PD patients with and without diplopia, an association of diplopia with oculomotor abnormalities (convergence insufficiency and strabismus) was reported, as well as an association with visual hallucinations [4]. In a small-sized pioneering study in PD, visual hallucinations were linked to a specific subtype of binocular diplopia: selective diplopia, i.e., diplopia of single objects, while complete diplopia, i.e., diplopia of the entire visual field, was hypothesised to result from oculomotor disorders [6]. Although the presence of visual hallucinations has also been linked to impaired vision [7], it is unclear whether impaired vision is associated with diplopia.

We aimed to show an association of diplopia with oculomotor abnormalities, impaired vision and visual hallucinations, in PD patients. Secondarily, we tried to establish a relationship of oculomotor abnormalities, impaired vision, and visual hallucinations with specific subtypes of diplopia, i.e., selective versus complete diplopia.

Methods

Study design

This pilot study employed an observational cross-sectional design which followed the Declaration of Helsinki Principles. The study protocol was approved by the Medical Ethics Committee of Amsterdam UMC, location VU University Medical Centre in Amsterdam, the Netherlands, and all participants gave written informed consent. The study took place in the OLVG West (Amsterdam) between July 1, 2017 and November 21, 2017.

Participants

The study population consisted of a group of PD patients having daily or weekly complaints of diplopia, a group of PD patients without diplopia, and a group of age- and sex-matched healthy controls (HC) without diplopia. PD patients were recruited from two general hospitals (OLVG and Zaans Medical Centre) in the Netherlands, and HCs were recruited among the partners and acquaintances of PD patients. Inclusion of PD patients required a diagnosis of PD fulfilling the UK Parkinson's Disease Society Brain Bank criteria [8], a Hoehn and Yahr stage 2–5, a disease duration of at least 3 years and an age above 50 years. Exclusion criteria for all participants were the presence of a neurodegenerative disorder (other than PD in PD patients), amblyopia, traumatic or congenital strabismus, and visual acuity of the best eye below 0.1. To avoid deterioration in motor function, all patients were examined while they were on medication.

Neurologic and ophthalmologic examinations

A neurologist specialised in movement disorders examined all participants to establish a diagnosis of PD in PD patients and to exclude the presence of a neurodegenerative disorder in HCs. In the PD patients, disease severity was assessed using the motor section of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS part III) [9], whereas disease stage was rated using the modified Hoehn and Yahr scale. Data on medication use were collected, and the total daily dose of dopaminergic medication was calculated as a levodopa equivalent dose (LED) [10]. The Montreal Cognitive Assessment (MoCA) was used to evaluate cognitive function [11]. In addition, the neurologist interviewed all participants using the standardized questions on symptoms of diplopia and visual hallucinations within the last month. In patients with diplopia, additional information was collected on diplopia characteristics. Selective diplopia was defined as diplopia of an actual single person or object, and complete diplopia was defined as diplopia of the entire visual field [6]; distance diplopia was defined as diplopia of objects at a distance of more than 1 m, whereas nearby diplopia was defined as diplopia of objects at less than 1 m distance.

In all participants, the neurological evaluation was followed by a thorough orthoptic examination to identify (extra-ocular) eye movement abnormalities, i.e., oculomotor abnormalities. Relevant for this study were oculomotor abnormalities which may cause a misalignment of both eyes and, therefore, diplopia. Oculomotor abnormalities comprised heterotropia (strabismus), convergence insufficiency, reduced fusion range, impaired stereopsis, and abnormalities of conjugate eye movements. Heterophoria or heterotropia, i.e., a latent or manifest deviation of one eye, respectively, was examined with a cover test. In this test, the orthoptist first covered one of the subjects' eyes, while observing the uncovered eye, which makes a corrective movement if it is the non-dominant eye in heterotropia [12]. Subsequently, alternate covering was used to further determine heterotropia and to identify heterophoria (see Ansons and Davis for a detailed description of this and following orthoptic tests [12]). To indicate the angle of deviation, a prism was placed in front of the squinting eye

(or in case of latent strabismus in front of either eye) and adjusted in strength until alternate covering did not longer cause corrective eye movements. This prism cover test was followed by a convergence test. Convergence insufficiency, defined as a near point of convergence (NPC) more than 10 cm from the nasal bridge, causes misalignment of the visual axes when the object of fixation is very close to the eyes, and may cause diplopia during reading or other activities requiring convergence of the eyes. Following the convergence test, the orthoptist performed a horizontal binocular fusion test at a distance of one-third of a meter. While the subject fixates on an object, a prism increasing in strength is placed in front of the eye until diplopia occurs, indicating the maximal angle of possible fusion. The smaller the fusion range, the sooner diplopia occurs, and we pragmatically defined a reduced fusion range as a fusion range of less than the 25th percentile of the fusion range in the entire study population [which was 16 prism dioptres (Δ)]. Additional testing of binocular function comprised a Stereo Fly test with stereoscopic images for testing stereo-acuity, i.e., depth perception, and impaired stereopsis was defined as a score above 800 arc seconds. At last, the orthoptist observed the eye movements, including saccades and smooth pursuit eye movements (without eye tracking devices).

The orthoptic assessment was followed by a thorough ophthalmologic examination to identify ocular disorders which may cause impaired vision. Relevant ocular visual impairments comprised best-corrected visual acuity of the best eye ≤ 0.6, moderate-to-severe cataract, and moderate-to-severe macular changes (e.g., macular degeneration, macular pucker, etc.). Best-corrected visual acuity was measured by an ophthalmologic technician (using a Snellen chart with decimal notation, 1.0 equivalent to normal acuity), who subsequently performed tonometry to measure intraocular pressure (IOP) [12]. After mydriasis was achieved by tropicamide 1% eye drops, if necessarily complemented by phenylephrine 5% eye drops, an ophthalmologist evaluated obtained diagnostic optical coherence tomography (OCT) scans (Heidelberg Engineering, Dossenheim, Germany; software version 6.0c) of the optic nerve and of the macula, and performed slit lamp examination and funduscopy. The OCT scans were used for diagnostic purposes, and analysis of OCT data was deemed outside the scope of this study (yet OCT data from this study will be analysed in future research). In light of the exploratory character and small sample size of this study, we aimed to determine only the presence or absence of oculomotor abnormalities and impaired vision, which were defined as present when we identified at least one oculomotor abnormality or at least one ocular visual impairment, respectively.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 23. To investigate the association of oculomotor abnormalities, impaired vision, and visual hallucinations with participant groups and subtypes of diplopia, the Fisher–Freeman–Halton test or, where appropriate, the Fisher's exact test was used. To assess the correlation of convergence insufficiency, fusion range, and visual acuity of the best eye with disease severity (MDS-UPDRS motor score), we used the Spearman rank correlation. A p value of $p < 0.05$ was considered statistically significant. In view of the exploratory nature of this study, we decided not to correct for multiple testing [13].

Results

Participant characteristics and main orthoptic and ophthalmologic data are presented in Table 1.

Participants

We included 25 PD patients with diplopia, 16 PD patients without diplopia, and 23 HCs. Compared to the HC group, both patient groups had a low MoCA score, while the three groups were well balanced in age, sex, and comorbidity. Of the eight included participants with diabetes mellitus, none had a diabetic retinopathy or a diabetic cranial nerve palsy.

Disease duration was similar in the diplopia group and the PD group without diplopia. However, the diplopia group had a higher modified Hoehn and Yahr stage, a higher MDS-UPDRS motor score, and a higher LED than the PD group without diplopia (see Table 1). One patient with diplopia and one patient without diplopia used cholinesterase inhibitors and/or neuroleptics.

Diplopia

PD patients with diplopia all had intermittent, binocular diplopia, which occurred daily in 40% and weekly in 60% of patients. Three PD patients with diplopia could not define the type of their diplopia, and of the 22 remaining patients, 41% had selective diplopia (diplopia of single objects), 41% complete diplopia (diplopia of the entire visual field), and 18% had both short episodes of selective diplopia and short episodes of complete diplopia. None of the patients spontaneously mentioned their type of diplopia. During the interview, patients with selective diplopia typically described seeing a person or object briefly double, during a few seconds at most, and often during twilight periods. In contrast, patients with compete diplopia typically had diplopia of the entire visual field during reading or writing,

Table 1 Clinical characteristics, orthoptic data, and ophthalmologic data of the patient groups and the healthy control group

	Main study groups			Diplopia subtypes		
	PD+ $n=25$	PD− $n=16$	HC $n=23$	Selective $n=9$*	Complete $n=9$*	Both $n=4$*
Age (years), mean (SD)	72 (9)	73 (8)	70 (8)	80 (5)	64 (6)	77 (7)
Male, *n*	18	10	12	5	6	4
Comorbidity, *n*	10	7	8	3	2	2
Hypertension, *n*	5	4	4	2	2	0
Diabetes mellitus, *n*	3	3	2	1	0	1
Cardiac disease, *n*	5	2	3	2	0	1
MoCA, median (IQR)	23 (4)	23 (4)	28 (2)	19 (9)	24 (5)	26 (6)
MDS-UPDRS III, mean (SD)	24 (9)	19 (10)	NA	31 (8)	20 (6)	20 (9)
Modified H&Y, median (IQR)	3 (1)	2 (0)	NA	3 (2)	2 (1)	3 (2)
Disease duration[a], median (IQR)	6 (5)	6 (5)	NA	6 (3)	7 (7)	4 (13)
Daily LED, median (IQR)	825 (851)	563 (678)	NA	594 (703)	1075 (781)	531 (864)
On dopamine agonists, *n*	9	6	0	1	6	1
On psychotogenic medication[b], *n*	5	2	0	2	2	1
NPC (cm), median (IQR)	13 (11)	7 (10)	6 (11)	13 (17)	12 (14)	18 (23)
Convergence insufficiency, n	15	2	5	5	5	3
Fusion range (Δ), median (IQR)	16 (12)	23 (15)	22 (10)	11 (14)	16 (8)	18 (26)
Fusion range < 16 Δ, *n*	12	2	0	6	4	1
Heterotropia, *n*	8	1	0	5	1	1
Eye movement impairment, *n*	5	1	0	2	2	1
Impaired stereopsis, *n*	3	0	0	3	0	0
VA (best eye), median (IQR)	1.0 (0.4)	1.0 (0.4)	1.1 (0.2)	0.9 (0.4)	1.0 (0.1)	0.7 (0.5)
VA (best eye) ≤ 0.6, *n*	5	0	0	2	0	2
Relevant macular changes, *n*	6	1	1	4	1	1
Relevant cataract, *n*	3	1	1	1	0	1
IOP ODS, median (IQR)	12 (3)	12 (4)	15 (4)	11 (2)	12 (3)	19 (13)
Visual hallucinations, *n*	11	0	0	7	0	2

PD+ patients with Parkinson's disease with diplopia, *PD-* patients with Parkinson's disease without diplopia, *HC* healthy controls, *Selective* PD patients with selective diplopia, i.e., diplopia of single objects, *Complete* PD patients with complete diplopia, i.e., diplopia of the entire visual field, *Both* PD patients with both short episodes of selective diplopia and short episodes of complete diplopia, *n* number, *SD* standard deviation, *IQR* interquartile range, *MoCA* Montreal Cognitive Assessment, *IQR* interquartile range, *MDS-UPDRS III* Movement disorder society-unified Parkinson's Disease Rating Scale part III: motor section, *Modified H&Y* Modified Hoehn and Yahr stage, *LED* Levodopa equivalent dose, *NPC* near point of convergence, Δ prism dioptres, *VA* visual acuity, *IOP* intraocular pressure, *ODS* oculus dexter et sinister, *NA* not applicable

*Three patients were unable to identify their type of diplopia and were not included in data on diplopia subtypes

[a]Disease duration in years

[b]Psychotogenic medication included medication with hallucinogenic side effects and comprised amantadine, anticholinergics, and opioids

which disappeared if they closed one eye or interrupted their activity. Diplopia was horizontal in 52%, vertical in 4%, both horizontal and vertical in 9%, oblique in 9%, and could not be defined in 26% of PD patients with diplopia.

Oculomotor abnormalities

Oculomotor abnormalities were found in 84% of PD patients with diplopia, in 33% of PD patients without diplopia, and in 23% of HCs. The most prevalent finding in the diplopia group was convergence insufficiency, followed by a reduced fusion range, heterotropia (one exotropia and the remainder decompensated exophoria), impaired conjugate eye movements (consisting of a small abduction impairment of both eyes in all but one patient, who had a small impairment of the superior oblique muscle in one eye), and impaired stereopsis, see Table 1. Oculomotor abnormalities were significantly more frequent in the diplopia group than in the PD group without diplopia and the HC group ($p < 0.01$).

Impaired vision

Impaired vision was found in 44% of PD patients with diplopia, in 6% of PD patients without diplopia and in 9% of HCs. A visual acuity of the best eye ≤ 0.6, moderate-to-severe macular changes (e.g. macular degeneration, macular

drusen, and macular pucker), and moderate-to-severe cataract were all more frequent in the diplopia group than in the PD group without diplopia and the HC group (see Table 1). Analysis showed a significantly higher prevalence of impaired vision in the diplopia group than in the PD group without diplopia and the HC group ($p < 0.01$).

Visual hallucinations

Forty-four percent of the PD patients with diplopia had complex visual hallucinations, 12% monthly, 12% weekly, and 20% daily. Visual illusions occurred only in patients who also had complex visual hallucinations with retained insight. Complex visual hallucinations comprised insects, smaller animals, gnomes, and persons, and occurred more frequently during twilight periods than during the day. None of the patients had visual hallucinations with loss of insight or delusions. In 13% of PD patients with diplopia, the visual hallucinations occurred simultaneously with diplopia, although diplopia without visual hallucinations and vice versa also occurred. In contrast with the diplopia group, none of the PD patients without diplopia and none of the HCs had visual hallucinations ($p < 0.01$).

Selective versus complete diplopia

The main patient characteristics and main ophthalmologic and orthoptic data classified according to subtype of diplopia in PD patients are shown in Table 1. Compared to the PD patients with complete diplopia, PD patients with selective diplopia were older, had a lower MoCA score and a higher MDS-UPDRS motor score, with yet a lower LED. Most patients with selective diplopia had distance diplopia, while most patients with complete diplopia had nearby diplopia (see Fig. 1a).

Oculomotor abnormalities were prevalent in both subtypes of diplopia ($p = 0.8$, see Fig. 1b). However, the prevalence of impaired vision was higher in the selective

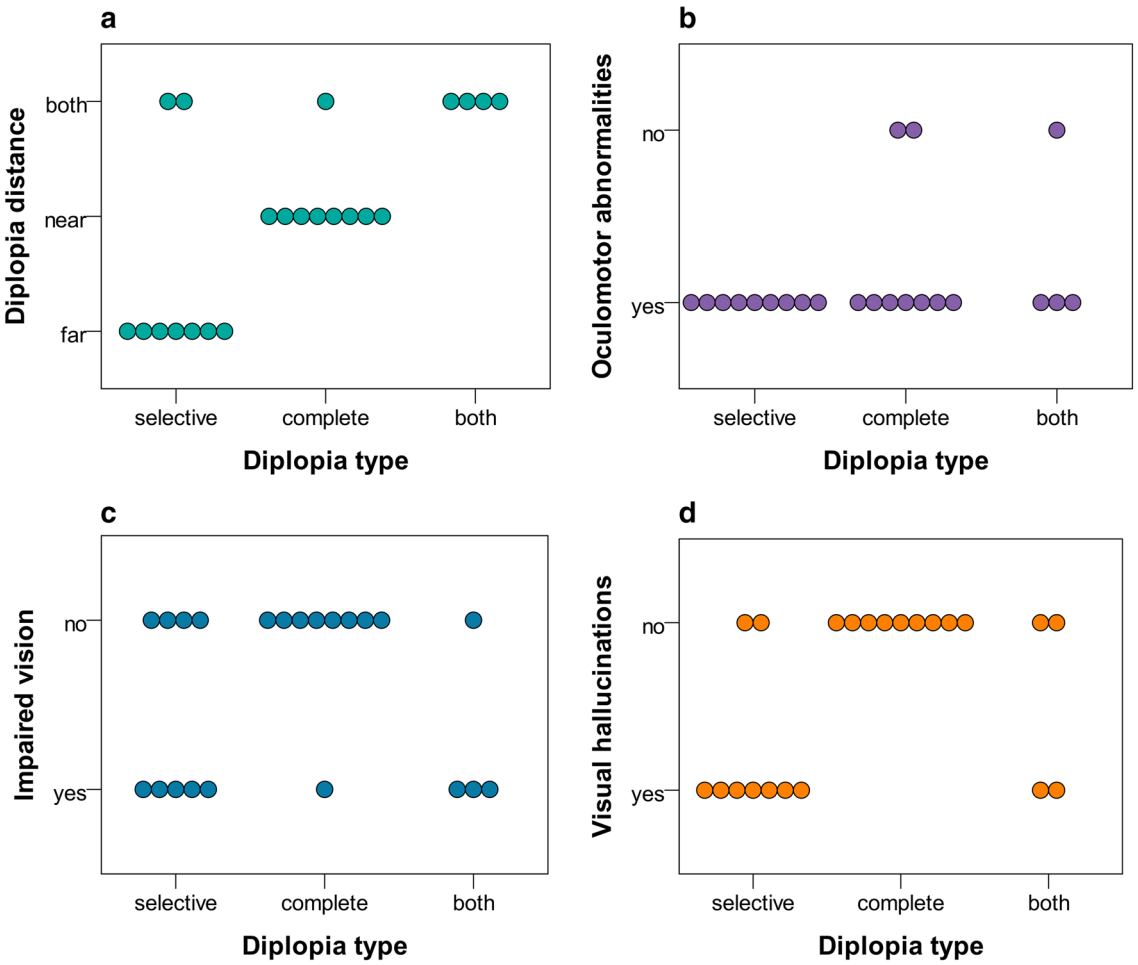

Fig. 1. Ocular impairments and visual hallucinations in diplopia subtypes. The coloured dots in the figure represent the patients, showing the number of patients in each category. Three patients with diplopia were unable to identify their type of diplopia and were not included in this figure

diplopia group (and the group with both selective diplopia and complete diplopia) than in the complete diplopia group ($p < 0.05$, see Fig. 1c). Furthermore, visual hallucinations only occurred in patients with selective diplopia (or with both selective and complete diplopia), and analysis showed a significant association of visual hallucinations with selective diplopia ($p < 0.01$, see Fig. 1d).

Correlations with disease severity

In the PD patients, near point of convergence was correlated with disease severity, although only a trend and not significant (rho 0.3, $p = 0.05$), whereas fusion range and visual acuity of the best eye were inversely correlated with disease severity (rho −0.5, $p < 0.01$ and rho −0.4, $p < 0.01$, respectively).

Discussion

The purpose of this study was to explore the underlying mechanisms of diplopia in PD patients and, hereby, to identify targets for the treatment of diplopia. The results of this study show an association of diplopia with oculomotor abnormalities, impaired vision, and visual hallucinations in PD. Whereas oculomotor abnormalities were prevalent in both subtypes of diplopia (selective and complete), impaired vision occurred predominantly in patients with selective diplopia, and only patients with selective diplopia had visual hallucinations.

The high prevalence of oculomotor abnormalities which we found in PD patients with diplopia is in line with the results of a previous study [4], and, although the association of diplopia with impaired vision has not been reported before (to the best of our knowledge), diplopia and impaired vision were each individually associated with a diagnosis of PD in previous research [14]. Furthermore, this study supports evidence from previous observations linking diplopia to visual hallucinations, as in our study, visual hallucinations only occurred in PD patients with diplopia, more specifically, selective diplopia [1, 4, 6]. Nebe and Ebersbach studied patients with selective diplopia and found a high prevalence of oculomotor abnormalities as well as visual hallucinations, in line with our present results [6]. In addition, we found that, in the PD patients, convergence insufficiency, fusion range, and visual acuity of the best eye were all correlated with disease severity, which is consistent with the literature, and supports the theory that ocular disorders are part of the disease process in PD [3, 14].

The oculomotor abnormalities which we observed in PD patients with diplopia most frequently comprised fusional disorders: convergence insufficiency, a reduced fusion range, and decompensated exophoria, which can all cause intermittent binocular diplopia. These impaired vergence movements may result from basal ganglia dysfunction, since basal ganglia dysfunction may cause excessive inhibition of the superior colliculus [15]. The superior colliculus contributes to saccades, smooth eye movements, and vergence movements [16, 17], and excessive inhibition of the superior colliculus by the basal ganglia in PD may result in reduced amplitudes of eye movements [15]. In line with this theory, improving basal ganglia function with dopaminergic replacement therapy has improved convergence movements in PD patients [18].

Impaired vision is not a likely cause of binocular diplopia, yet we did find an association of impaired vision with diplopia, more specifically, with selective diplopia. Possibly, a visual impairment, e.g., a central visual field defect or monocular diplopia, can be interpreted (or recalled) by PD patients as binocular diplopia. Impaired vision included reduced visual acuity, macular changes and cataract, which all have been associated with PD, however, of which the pathological mechanism is unclear [14, 19, 20]. Possible contributing factors are a retinal dopamine deficiency and abnormal phosphorylated alpha-synuclein in the inner retinal layers and ocular lens in PD [20-25].

We also found an association of diplopia with visual hallucinations, which occurred only in PD patients with selective diplopia. Diplopia of a single object is not likely the result of oculomotor abnormalities, and may rather represent a type of visual illusion, as previously suggested by Nebe and Ebersbach [6]. A recent review on the psychosis spectrum in PD hypothesises that minor hallucinations, including selective (isolated) diplopia, may result from dysfunction of attentional networks when ambiguous visual input occurs, in combination with remembered images intruding into consciousness [7, 26]. This theory may be supported by the higher prevalence of impaired vision in the patients with selective diplopia in the present study and by the previous studies in PD showing an association between ocular disorders, including RNFL thinning, and the occurrence of visual hallucinations [27, 28]. The minor hallucinations are suggested to reflect brainstem pathology (and its impact on visual processing pathways) and to form the beginning of the psychosis spectrum [26]. Minor hallucinations may progress over time, reflecting the Braak progression of Lewy body pathology, to visual hallucinations with retained insight, indicating involvement of the basal forebrain (and its impact on cortical cholinergic projections including those to the ventral occipitotemporal cortex). Further disease progression may eventually lead to multimodality hallucinations with loss of insight and delusions when the disease process involves widespread cortical brain areas (see Ffytche et al. for review) [26]. The higher prevalence of complex visual hallucinations in the patients with selective diplopia may support this theory, suggesting that selective diplopia is a

visual illusion and may reflect the mild end of the psychosis spectrum in PD.

In contrast with selective diplopia, complete diplopia seems to be unrelated to visual hallucinations based on the results of this study, and may have a different underlying mechanism. Complete diplopia, which occurred mostly at nearby vision (e.g., during reading or writing), may result directly from oculomotor abnormalities in PD patients, e.g., convergence insufficiency or decompensated exophoria.

Since more than 80% of PD patients with diplopia had oculomotor abnormalities and almost half had impaired vision, PD patients with diplopia should be referred to an orthoptist and an ophthalmologist for evaluation and, if possible, treatment of diplopia. Although mainly investigated in subjects without PD, treatment of fusional disorders (e.g., convergence insufficiency, decompensated heterophoria, etc.), certain macular disorders and cataract, is effective and can improve quality of life [29-34].

As visual hallucinations were associated with selective diplopia, selective diplopia should alert treating physicians to the presence of visual hallucinations, which may influence treatment choices [5, 7]. Although levodopa treatment might theoretically worsen selective diplopia and provoke hallucinations [6, 7], PD patients with complete diplopia may benefit from optimization of levodopa treatment, as this may improve ocular motor function [5, 18]. It is, therefore, important to accurately define the type of diplopia.

There are limitations to the present study. First and foremost, the presence and characteristics of diplopia and visual hallucinations were based on subjects' recall. Especially patients with cognitive deficits may have forgotten diplopia symptoms or visual hallucinations, which may have caused an underestimation of the prevalence of these symptoms. This potential recall bias may also have contributed to the distribution of symptoms, where patients without diplopia had no visual hallucinations, while patients recalling diplopia also frequently recalled having visual hallucinations. Alternatively, this distribution of symptoms could be coincidental due to the small sample size of this study. However, the association of diplopia with visual hallucinations in PD may also be caused by shared pathophysiological mechanisms underlying both symptoms.

Second, all PD patients were on treatment, which may have influenced our findings. While levodopa treatment is presumed to improve motor symptoms in Parkinson's disease [35], and may improve convergence movements [18], visual hallucinations may worsen with this treatment [7]. In addition, dopamine agonists, amantadine, anticholinergics, and opioids may also contribute to the presence of visual hallucinations [7]. Although patients with selective diplopia did not use more of these medications than patients with complete diplopia (see Table 1), we cannot exclude the possibility that these medications were tapered because of the occurrence of visual hallucinations, which had not (yet) resolved. Furthermore, PD patients with selective diplopia were older than patients with complete diplopia (mean age 80 years and 64 years, respectively), and were, therefore, more at risk for visual hallucinations than patients with complete diplopia [7].

Another limitation of this study is that blinding of investigators was not possible, as patients were questioned on their visual symptoms during neurological, orthoptic, and ophthalmologic investigations, which might have caused a confirmation bias. We tried to reduce this risk by strictly defining the study parameters and outcome measures before the start of this study.

Finally, in light of the small sample size in this study, we did not correct for confounders (e.g., age, disease severity, cognition, and LED). With this exploratory study, we merely aimed to verify the association of diplopia in PD with orthoptic and ophthalmologic abnormalities and with visual hallucinations, and to relate these findings to the type of diplopia. Future longitudinal studies are required to establish causal relationships between these study parameters.

In conclusion, in PD patients, diplopia may be indicative of oculomotor or visual impairments. Hence, it is worthwhile to refer PD patients with diplopia to an orthoptist and an ophthalmologist for evaluation and, possibly, treatment of diplopia. Furthermore, in the case of selective diplopia, the neurologist should consider the presence of visual hallucinations, which may require the adjustment of the patient's medication.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval This pilot study followed the 1964 Declaration of Helsinki Principles. The study protocol was approved by the Medical Ethics Committee of Amsterdam UMC, location VU University Medical Centre in Amsterdam, the Netherlands, and all participants gave written informed consent prior to their inclusion in the study.

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