Journal of the Optical Society of America A
OPTICS, IMAGE SCIENCE, AND VISION

Visual losses in early-onset and late-onset Parkinson's disease

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Received 6 November 2019; revised 13 March 2020; accepted 14 March 2020; posted 16 March 2020 (Doc. ID 382042); published 17 April 2020

Patients with Parkinson's disease (PD) manifest visual losses. However, it is not known whether these losses are equivalent in both early-onset (EOPD) and late-onset (LOPD) patients. We evaluated contrast sensitivity and color vision in EOPD and LOPD patients and in age-matched controls. Losses occurred in both patient groups but were more pronounced in EOPD, consistent with the notion that non-motor symptoms are affected by age of symptom onset. More studies of visual function in EOPD and LOPD patients are needed to understand how aging is related to the pathophysiology of non-motor PD symptomatology. This would permit earlier diagnosis and, perhaps, better management of the disease.

https://doi.org/10.1364/JOSAA.382042

1. INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by motor and non-motor symptoms. The non-motor manifestations include several visual impairments that lead to difficulties in daily activities, including reading and driving, as well as falls and injuries, causing an early loss of independence [1]. Thus, a better understanding of the visual problems associated with PD can augment scientific efforts in the search for maximizing the quality of life for these patients [1,2].

Better understanding of visual impairment associated with PD could also aid in the development of earlier diagnostic procedures, which can be difficult due to the subtlety of clinical manifestations [3,4]. Visual symptoms are more frequent in advanced stages of the disease, but may be present at the earliest stages of the disease [5]. These early signs of visual impairment are mostly found in the form of subclinical manifestations, e.g., loss in contrast sensitivity (CS) [5], changes in dopaminergic retinal neurons, and thinning of inner retina [6], which could potentially be detected by more sensitive psychophysical and electrophysiological methods. However, standardization and longitudinal studies are still necessary for any of these methods to be applied as a biomarker for PD [4].

Loss in CS is one of the most common visual impairments in the early stages of PD [5], whereas loss in color vision (CV) is more controversial [7,8]. However, both types of visual loss generally increase with disease progression, challenging many essential daily tasks such as reading and driving at later stages of the disease [1]. Beyond primary sensory deficits, such as CS and CV losses, the disease can even lead to debilitating hallucinations [9].

Visual losses may also be associated with motor symptoms and associated brain mechanisms. For example, losses in the dorsal pathway which emanate from the primary visual cortex may impact the accuracy and dynamics of ocular movements, which in turn may impair gait, movement perception, and combined with attention deficits, may result in an increased number of dangerous falls [10]. Dorsal-stream impairment can also lead to errors in judgment of position and distance [11], which, in turn, increase the likelihood of accidents in daily life activities.

PD may manifest itself by a combination of different symptoms. Some of the patients predominantly exhibit tremor,

others rigid-akinetic symptoms or postural and impaired gait disorders (PIGDs), and others a mixed motor symptomatology. PD patients with onset beginning at older ages (LOPD) predominantly manifest early PIGD as well as early cognitive-behavioral symptoms, while PD patients with onset at younger ages (EOPD) usually manifest rigid-akinetic symptoms or early motor fluctuations as well as late cognitive-behavioral symptoms. Also, genetic mutations are believed to occur more often among the EOPD patients. Regarding medications, lifetime usage is usually longer for the EOPD patients, suggesting a slower progress of PD for these patients [12,13].

Comparative analysis of visual performance among the various subtypes of PD patients could help to better characterize the spectrum of clinical manifestations in diagnosis and in differentiation between stages of the disease. To our knowledge, to date, no vision studies have been realized to compare the visual performance of EOPD and LOPD patients. Therefore, the primary objective of this study was to evaluate the visual performance of EOPD (onset before 45 years of age) and LOPD (onset after 45 years of age) by means of psychophysical evaluation of achromatic spatiotemporal CS and CV.

2. METHODS

A. Participants

This study was done in accordance with the Declaration of Helsinki (2013), and the ethics committees of the University of São Paulo (USP) and the Albert Einstein Israelite Hospital (HIAE) approved it. All participants have provided informed consent prior to being included in the study.

PD patients were referred from the Movement Disorders Outpatient Clinic of the Neurology and Neurosurgery Department, Federal University of São Paulo, and the Neurological Outpatient Clinic at the Clinicas Hospital, University of São Paulo. Detailed demographic information and detailed medical histories were collected (Table 1). In order to ensure cooperation in the test, we only included patients who scored less than 4 on item 18 (speech) in section 3 (motor assessment) of the Unified Parkinson's Disease Scale (UPDRS), i.e., patients scoring 4 on this item have incomprehensible speech and the data obtained would not be completely reliable.

All participants received an ophthalmological examination. Visual acuity was measured using the ETDRS, logMAR (Early

Table 1. Demographic Data of All 28 PD Patients[a]

								Family		Edu.		Previous History				Other Diseases		
ID	PD	sex	age	dur	onset	eye	VA	Y/N	obs	L	obs	diseases	rur.	yrs	oc. exp.	pres.	obs	hal.
1	EOPD	M	57	25	32	R	0.0	Y	M	2	I	—	N	—	—	N	—	N
2	EOPD	M	52	9	43	R	0.0	Y	M/B	1	I	—	N	—	agrotoxic	N	—	N
3	EOPD	M	49	10	39	R	0.0	Y	P	3	C	—	N	—	—	N	—	N
4	EOPD	M	51	7	44	R	0.0	N	—	1	I	—	Y	DK	—	N	—	N
5	EOPD	F	37	7	30	L	0.0	Y	P	2	C	—	Y	DK	—	N	—	N
6	EOPD	M	40	13	27	L	0.0	N	—	2	C	—	N	—	—	N	—	Y
7	EOPD	M	43	10	33	R	0.0	Y	P	1	C	—	Y	16	—	N	—	N
8	EOPD	M	49	6	43	R	0.0	N	—	1	I	—	Y	DK	—	Y	Dep	N
9	EOPD	M	50	9	41	L	0.0	N	—	3	C	Dep/DLP	N	—	—	N	—	N
10	EOPD	M	38	18	20	R	0.0	Y	P	1	I	—	Y	DK	—	Y	Dep	N
11	EOPD	F	35	8	27	R	0.0	Y	M	3	C	—	N	—	—	Y	GAD	Y
12	EOPD	M	37	4	33	L	0.0	N	—	2	C	HBP/RF	N	—	—	Y	HBP	N
13	EOPD	M	52	14	38	R	0.0	Y	—	3		—	N	—	—	N	—	N
14	EOPD	M	43	11	32	R	0.0	Y	P	2	I	bronchitis	N	—	—	N	—	N
15	EOPD	M	49	12	37	L	0.0	N	—	1	I	—	Y	17	—	N	—	N
16	EOPD	M	39	7	32	L	0.0	N	—	3	C	—	N	—	chemicals	N	—	N
17	EOPD	M	47	12	35	R	0.0	N	—	1	C	—	N	—	—	N	—	Y
18	EOPD	F	52	11	41	L	0.0	Y	M	2	C	—	N	—	—	N	—	N
19	EOPD	F	46	15	31	R	0.0	N	—	3	C	gest toxo	N	—	—	N	—	N
20	LOPD	M	57	10	47	L	0.1	N	—	1	C		Y	21	iron/alum.	Y	Dep	N
21	LOPD	M	58	4	54	L	0.0	N	—	2	I	—	Y	16	gasoline	N	—	N
22	LOPD	M	66	6	60	L	0.0	N	—	1	C	—	Y	DK	—	N	—	Y
23	LOPD	M	50	2	48	R	0.0	Y	M	3	C	Dep	N	—	—	Y	Dep	N
24	LOPD	F	57	12	45	L	0.0	Y	M	2	C	—	N	—	—	Y	HBP	Y
25	LOPD	M	58	5	53	R	0.0	N	—	1	C	HBP	Y	7	—	Y	HBP	N
26	LOPD	F	62	12	50	R	0.0	N	—	1		HBP	N	—	—	Y	GAD/HBP	N
27	LOPD	M	51	6	45	L	0.0	N	—	1		—	Y	4	—	N	—	N
28	LOPD	M	67	7	60	L	0.0	N	—	3	C	—	Y	13	—	N	—	Y

[a]ID, identification, PD subtype (EOPD or LOPD); sex; age; symptom duration in years; age of symptom onset; tested eye (right or left); VA, visual acuity (logMAR); previous history, family (Y-positive for relative with PD and N-negative for relative with PD); obs, observation (M, maternal line, P, paternal line, and B, brothers); edu, education (1, secondary; 2, high school; 3, college); obs, observation (I, incomplete and C, complete); diseases; rur, rural residence and number of years; occupational exposure; other diseases: pres, in the present; hal, hallucination; obs, observation; other abbreviations: Dep, depression; DLP, dyslipidemia; HBP, hypertension blood pressure; RF, rheumatic fever; gest toxo, gestational toxoplasmosis; GAD, general anxiety disorder; DK, don't know.

Table 2. Medications: Dosage of Medication in mg/day[a]

	Dopamines							Inhibitors		
	precursors			agon.	end.	antichol.		MAO-B		COMT
ID	LD	CD	BS	PP	AM	TF	BP	RS	SG	EC
1	200	–	50,0	3.00	450	–	–	–	10	–
2	375	37,5	–	3.00	200	–	–	–	–	–
3	600	–	150,0	2.50	–	–	–	–	10	800
4	400	–	100,0	3.00	–	–	–	–	–	–
5	200	–	50,0	1.50	–	–	–	–	5	–
6	–	–	–	3.00	300	–	6	–	–	–
7	1250	125,0	–	–	–	–	–	–	–	–
8	1000	100,0	–	–	–	–	6	–	–	–
9	400	100,0	–	2.00	–	–	–	1	–	800
10	500	50,0	–	3.00	–	–	–	–	–	–
11	–	–	–	2.00	–	5	–	–	–	–
12	–	–	–	3.00	–	–	6	–	–	–
13	750	75,0	–	4,00	300	–	–	–	–	–
14	400	–	100,0	3.00	–	10	–	–	–	–
15	850	75,0	25,0	1.50	300	–	6	–	–	–
16	375	75,0	–	0.75	–	–	12	–	–	–
17	1250	125,0	–	3,00	200	–	–	–	–	–
18	300	–	75,0	1.50	–	–	–	–	10	–
19	900	–	225,0	4.00	–	–	–	–	–	–
20	500	50,0	–	–	–	–	6	–	–	–
21	–	–	–	0.25	–	–	4	–	–	–
22	100	–	25,0	–	200	–	–	–	–	–
23	–	–	–	1,50	–	–	–	–	–	–
24	–	–	–	2.00	200	–	–	–	5	–
25	–	–	–	1,50	200	–	–	–	–	–
26	500	–	125,0	–	500	–	–	–	–	–
27	125	12,5	–	4,50	–	–	–	–	–	–
28	600	150,0	–	–	–	–	–	–	–	–

[a]Abbreviations: LD, levodopa; CD, carbidopa; BS, benserazide; PP, pramipexole; AM, amantadine; TF, trihexyphenidyl; BP, biperiden; RS, rasagiline; SG, selegiline; and EC, entacapone.

Treatment Diabetic Retinopathy Study) at a distance of 3 m. A fundus examination was performed using direct ophthalmoscopy or background biomicroscopy. Intraocular pressure was evaluated with a Goldmann aplanation tonometer.

Inclusion criteria for the present study were: no diagnosis of ocular pathology; corrected visual acuity of 0.2 logMAR or better; normal pupillary reflexes and ocular motility; normal intraocular pressure (12–20 mmHg); normal fundus in both eyes; biomicroscopy without media opacities, or at most 1 cortical opacity (C1), nuclear color (NC1) or nuclear opalescence (NO1) using the Crystalline III Opacity Classification System (LOCS III) [14]; absence of systemic diseases affecting the visual system such as diabetes and multiple sclerosis; absence of current alcoholism; minimal or no cigarette smoking (up to no more than five cigarettes/day).

A total of 28 PD patients (mean age = 50 ± 9 years, 22 male and 6 female; Table 1) and 28 age-matched controls (mean age = 45 ± 10 years, 13 male and 15 female) were evaluated. All patients were under medication for PD (Table 2).

The sample was composed of two PD subgroups: EOPD with symptom onset before 45 years of age (N = 19, mean age = 46 ± 6 years, 15 male and 4 female), and LOPD with symptom onset between 45 and 65 years of age (N = 9; mean age = 58 ± 6 years, 7 male and 2 female) (Table 1).

For the controls, subdivisions were made so that they were paired by age with the PD subgroups: 19 controls were compared with the EOPD group (40 ±5 years) and 9 were compared with the LOPD group (58 ± 10 years). There were no significant differences between the age of the controls and the age of the patients for both the EOPD and LOPD groups.

B. Psychophysical Measurements

The psychophysical tests were performed at the Vision Laboratory, Psychology Institute, University of São Paulo, Brazil.

For the CS test, the stimuli chosen had been previously used to test patients with Duchenne muscular dystrophy [15]. The stimuli with achromatic checkerboard squares were either low-spatial frequency (*low-SF*; 0.5 cpd) or high-spatial frequency squares (*high-SF*; 9 cpd) when viewed from 1 m, and with either a short duration (*high-TF*; 30 ms) or a long duration (*low-TF*; 1500 ms) (Fig. 1). The squares were presented as either luminance increments or luminance decrements relative to a

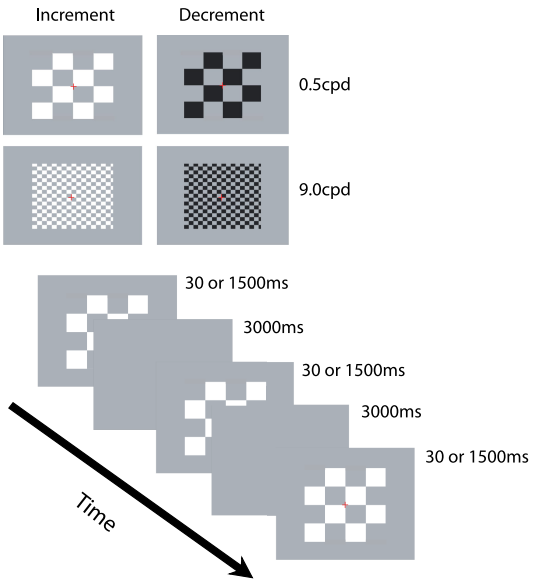

Fig. 1. Stimulus configuration. The upper checkerboards indicate the low-SF (0.5 cpd), and the lower checkerboards indicate the high-SF (9 cpd) for the increment (left) and decrement (right) conditions. The bottom portion of the figure illustrates the temporal configuration (low-TF, 1500 ms; high-TF, 30 ms) for presentation of the appearance-disappearance stimuli, with an interval interstimulus as 3000 ms.

homogeneous steady background of (CIE 1976 u' v' coordinates: 0.1977, 0.4698) (Fig. 1). A black cross in the center of the stimulus display was used as a fixation point.

Stimuli were generated on a XTC-600 microcomputer (Dell Dimension, Winston-Salem, NC) equipped with VSG graphics card (2/4, Cambridge Research Systems Ltd., Rochester, UK) using the psychophysical software, PSYCHO. The stimulus monitor was a 19", 12-bit Sony FD Trinitron (CPD-G420, Sony Electronics Inc., Tokyo, Japan), with a 100 Hz frame rate and 800 H × 600 V pixels for the spatial resolution. The monitor calibrations were measured with an Optical OP200-E photometer (Cambridge Research Systems Ltd., Rochester, UK).

Weber contrast thresholds were measured by the adjustment method, in which six measures were averaged to obtain each threshold estimate: three ascending series and three descending series for each test condition. The contrast started at 50% (±5%) for descending measurements and at 0.2% (±0.1%) for ascending measurements, with an interval interstimulus of 3000 ms. We started with an ascending trial followed by a descending trial in order to avoid adaptation to spatial frequencies.

The participant's task was to alert the experimenter when he or she first detected the appearance (ascending series) or disappearance (descending series) of the checkerboard. The experimenter controlled increases and decreases of contrast according to the verbal responses of the participant, patients and controls, as had been done in a prior study [16].

For the CV test, the stimuli were generated by the Cambridge Color Test (CCT, Cambridge Research Systems Ltd., Rochester, UK), which uses a design analogous to the Ishihara Pseudoisochromatic Plates (e.g., the Ishihara test, Kanehara & Co., Ltd, Tokyo, Japan, or the American Optical Hardy-Rand-Rittler Pseudoisochromatic Plates, AO HRR, Richmond Products, Boca Raton, FL). The stimulus to be detected in the CCT consisted of a Landolt "C" target comprising small circles of a given chromaticity with pseudo-random sizes, between 0.5 and 2 cm in diameter, i.e., from 0.05 to 0.38 deg of visual angle. The Landolt C was presented at a series of seven luminances between 8 and 10 $\mathrm{cd} \cdot \mathrm{m}^{-2}$, differing by six equal luminance steps. The Landolt C stimulus was presented on a background of similar circles having different chromaticity. The subject was positioned 2.6 m away from the monitor, resulting in 1 deg of visual angle for the gap in the Landolt C.

The test was performed using CCT version 2.0 (Cambridge Research Systems Ltd., Rochester, UK), running on a microcomputer XTC-600 (Dell Dimension, Winston-Salem, NC), equipped with a VSG5 graphics card (Cambridge Research Systems Ltd., Rochester, UK). The monitor was a Trinitron color monitor GDMF500T9 (Sony Electronics Inc., Tokyo, Japan) with 100 Hz frame rate and 800 H × 600 V pixels for the spatial resolution, and the monitor calibrations were performed with a CS1000 photometer (Konica Minolta Sensing Inc., Osaka, Japan).

We used the CCT Trivector test. This test measures color discrimination thresholds relative to the default background chromaticity (CIE 1976 u' v' coordinates 0.1977, 0.4698) as excursions in u' v' units along the protan, deutan, and tritan confusion axes. The three confusion axes were measured in the same test, with randomization of the testing order. A control target at maximum saturation was periodically presented.

Thresholds were measured by the staircase method. The testing procedure started with a presentation of the Landolt C target at a saturated chromaticity on a certain background and proceeded to a chromaticity closer to that of the background each time a subject responded correctly. Conversely, an incorrect response, or no response, was followed by the presentation of the target at a greater chromatic distance from the background. Color discrimination threshold was computed as the mean of 11 reversals.

The participant's task was to indicate to the experimenter the position of the Landolt C gap that appeared randomly in one of four orientations (up, down, left, or right). The response time limit was 6 s for each trial.

For both tests, CS and CV, stimuli were viewed monocularly, with the tested eye randomly chosen, and performed in a dark room with illumination provided only by the monitor used to present stimuli. We had just one experimenter evaluating all the participants. For the CS test, participants were tested in a single session, using a randomized testing order.

C. Statistical Analysis

The results were analyzed using the software Statistica 10 (StatSoft Inc., Tulsa, OK). The level of significance was set as $p \leq 0.05$. The data distribution was evaluated using the parametric Shapiro–Wilk test, confirming that they were normally distributed. A one-way repeated measure ANOVA, i.e., within-subject ANOVA, was applied between experimental subgroups (EOPD and LOPD) and the respective controls, considering

them as dependent variables; we applied the root mean square standardized effect (RMSSE), a standardized measure of effect size used in ANOVA to characterize the overall level of population effects. The required sample size was N = 8, with an actual power of 0.84. For the CS measures, statistical analyses were done with CS converted to Log(CS). Correlations were evaluated using the Pearson correlation, i.e., Pearson product-moment correlation coefficient (PPMCC); data distribution was close to the normal curve, and analyses of the residual values confirmed that data were relatively normal in distribution.

3. RESULTS

For the CS test, thresholds were significantly elevated in PD patients for all conditions (Table 3 and Fig. 2). For EOPD patients, CS thresholds were significantly elevated for all conditions compared to controls. For LOPD patients, CS thresholds were significantly elevated compared to controls only for the conditions with low-TF (Table 3 and Fig. 3), meaning that LOPD patients have better CS for high-TF, either with low-SF or high-SF. All participants completed all conditions.

For the CS test, correlations were found between the age of symptom onset and CS threshold for most of the conditions: low-SF/high-TF, increment ($r = -.46$; $p = .014$) and decrement ($r = -.67$; $p < .0001$), low-SF/low-TF, increment ($r = -.68$; $p < .0001$) and decrement ($r = -.60$; $p < .01$), for the high-SF/high-TF, increment ($r = -.40$; $p = .035$) and decrement ($r = -.44$; $p = .019$), and for the high-SF/low-TF, increment ($r = -.52$; $p < .01$) and decrement ($r = -.42$; $p = .03$). However, no correlation was found between symptom duration, positive family history for PD, or medications for the CS measures in any of the test conditions.

For the CV test, Trivector thresholds were significantly elevated in PD patients for protan and deutan confusion axes (Table 3 and Fig. 4). For EOPD patients, protan and deutan thresholds were significantly elevated compared to controls. For LOPD patients, thresholds were not significantly elevated

Table 3. Statistical Summary for Both CS and CV Tests: the Achromatic Spatiotemporal CS Test and the Trivector Test (CV) for 28 Overall PD Patients, 19 EOPD Patients, and 9 LOPD Patients (8 LOPD Patients for CV Test), Compared to Their Respective Controls[a]

		Overall PD		EOPD		LOPD	
Condition		**F**	**p-value**	**F**	**p-value**	**F**	**p-value**
low-SF/high-TF	inc.	**22.79**	**< .001**	**18.44**	**< .001**	3.73	.070
	dec.	**28.39**	**< .001**	**27.34**	**< .001**	3.99	.061
low-SF/low-TF	inc.	**26.51**	**< .001**	**11.56**	**.002**	**19.08**	**< .001**
	dec.	**20.86**	**< .001**	**11.10**	**< .001**	**9.53**	**.005**
high-SF/high-TF	inc.	**15.79**	**< .001**	**16.30**	**< .001**	1.00	.331
	dec.	**9.81**	**< .001**	**6.87**	**.013**	2.24	.154
high-SF/low-TF	inc.	**39.53**	**< .001**	**128.91**	**< .001**	**8.70**	**< .001**
	dec.	**37.21**	**< .001**	**28.86**	**< .001**	**5.56**	**.003**
Protan		**9.38**	**.003**	**7.79**	**.013**	3.02	.09
Deutan		**12.20**	**< .001**	**14.67**	**.002**	2.80	.10
Tritan		0.89	.35	0.87	.37	0.28	.60

[a]The statistically significant p-values < .05 are indicated in bold. Effect sizes for the CS test were .46 for overall PD, .59 for EOPD, and .66 for LOPD; for the CV test they were .33 for overall PD, .18 for EOPD, and .06 for LOPD.

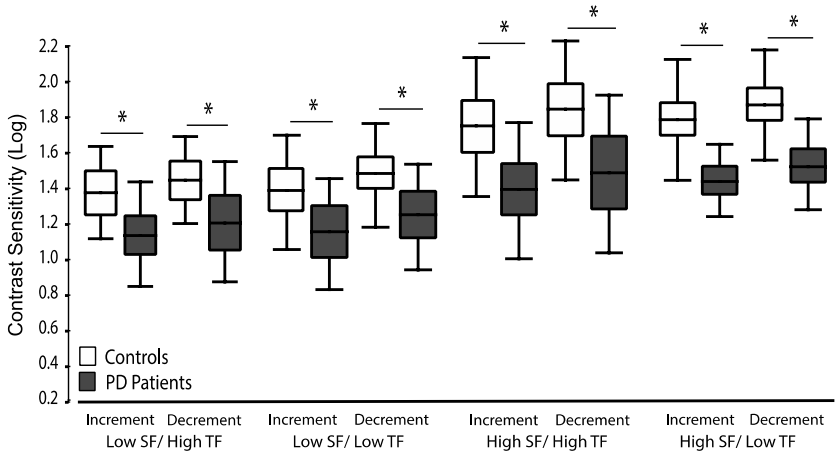

Fig. 2. Checkerboard CS results for all 28 PD patients (gray boxplots) compared with controls (white boxplots). The *y* axis shows CS in Log, and the *x* axis shows the stimulus configurations as a combination of low-SF (0.5 cpd) or high-SF (9 cpd), low-TF (1500 ms) or high-TF (30 ms), and increment or decrement conditions. Asterisks mark statistically significant results ($p < 0.05$); error bars mark ±2 standard errors.

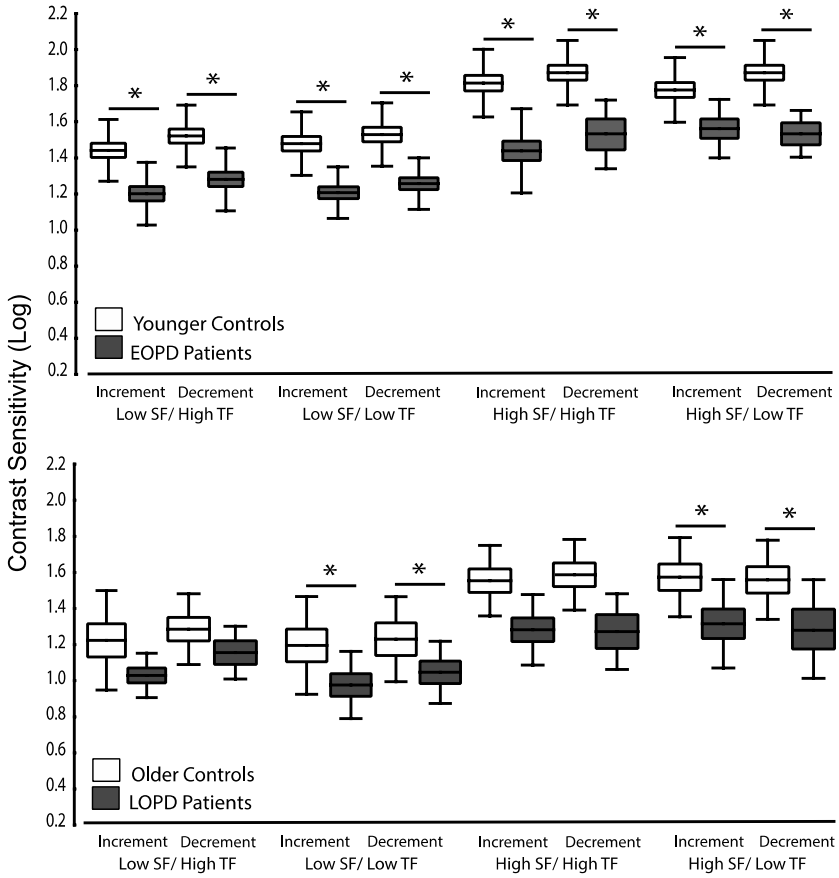

Fig. 3. Checkerboard CS results for the PD subtypes (19 EOPD and 9 LOPD patients in gray boxplots) compared with age-matched controls in white boxplots. The *y* axis shows CS in Log, and the *x* axis shows the stimulus configurations as a combination of low-SF (0.5 cpd) or high-SF (9 cpd), low-TF (1500 ms) or high-TF (30 ms), and increment or decrement conditions. Asterisks mark statistically significant results ($p < 0.05$); error bars mark ±2 standard errors.

compared to controls for all conditions (Table 3 and Fig. 4). All but one of the LOPD patients completed the test.

For the CV test, correlations were found between the age of symptom onset and the protan ($r = .40$; $p = .039$) and deutan ($r = .47$; $p = .013$) thresholds, but not for the tritan ($r = .35$; $p = .08$). No correlation was found between the symptom duration or positive family history for PD for the CV test measures in any of the confusion axes of the Trivector. For the medications, we found a positive correlation between the dosage of amantadine and the deutan ($r = .76$; $p = .018$) and tritan ($r = .76$; $p = .018$) thresholds, but not for protan ($r = .35$; $p = .36$) thresholds. No correlations were found for the other medications, e.g., levodopa (LD), carbidopa (CD), benserazide (BS), or pramipexole (PP). The total number of patients for the remaining drugs was not sufficient to perform any correlational analysis.

4. DISCUSSION

We evaluated CS and CV in patients with PD. Our data showed that CS and CV are significantly impaired in PD patients for all conditions tested. Given that these conditions are detecting the magnocellular (M) and parvocellular (P) pathways, either together or separately, mixed or isolated, the present study is consistent with most previous studies indicating that both M and P pathways are impaired by the disease [3,17–19].

To our knowledge, this is the first vision study to evaluate the effect of age of onset by testing both EOPD and LOPD patients. Our results show that losses in EOPD patients were greater than in LOPD patients when compared to their respective controls. For LOPD patients tested in our sample, the results for the CS test are in agreement with the literature, in that greater losses occur for conditions designed to be preferentially detected by the P pathway [18–23]. Although selective targeting of the P pathway by choice of spatial frequency is still debatable [22], there is a consensus that low-temporal-frequency contrast thresholds are more likely to be preferentially detected by the P pathway [18,21], and it was the low-TF CS that was affected in our LOPD sample. However, the CV results, presumably targeting the P pathway, were not affected in the LOPD group, suggesting that CS may be more dopamine-dependent than chromatic information [24]. For the EOPD patients, both M and P pathways seem to be affected, since all CS and CV test conditions were significantly different from the controls. Taken together, these results suggest that the age of symptom onset is an important factor in the etiopathology of PD.

Little is known about the differences in disease progression between EOPD and LOPD patients [25], but there is some

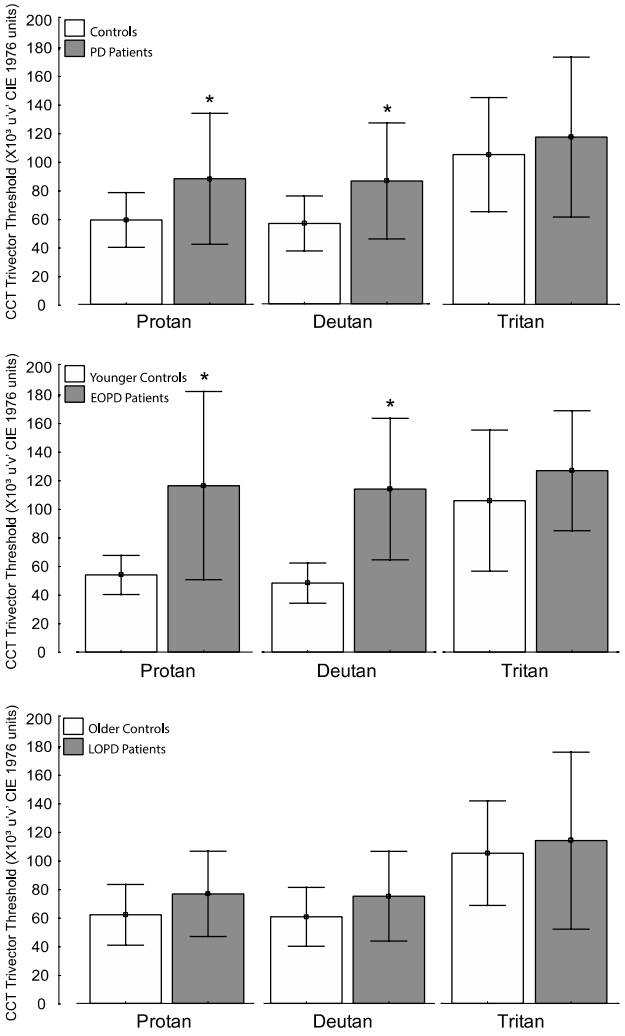

Fig. 4. Chromaticity discrimination thresholds for 27 PD patients (gray bars) and controls (white bars). Upper panel: data for all 27 PD patients. Middle panel: data for 19 EOPD patients. Bottom panel: data for 8 LOPD patients. The y axis shows CCT Trivector thresholds in u' v' CIE 1976 units, and the x axis shows the three subtests as follows: protan, deutan, and tritan. Asterisks mark statistically significant results ($p < 0.05$); error bars mark ±2 standard errors.

evidence that EOPD and LOPD may have distinct underlying etiopathological processes [12,13]. EOPD is more frequently associated with genetic mutations than LOPD, and this could explain a different profile of non-motor symptoms (such as sensory-perceptual deficits) in these patients [26,27].

One issue in the literature is the relationship between the patients' performance and the duration of symptoms, e.g., [28,29], as well as the age of symptom onset, e.g., [25,27,30]. In our study, no relationship was found between the duration of symptoms and the performance of patients. However, we found correlations between the age of symptom onset and the performance of the patients for both CS and CV tests.

Another issue in the literature is the relationship between medication and visual function, such as color discrimination and color vision. Most studies suggest that medications (e.g., dopamine precursors and agonists) impact visual function [31–37], suggesting that the abnormal visual function in PD patients is linked to dopaminergic deficiency. Some studies show that these functions are not impacted with the use of amantadine [38,39] leading them to hypothesize that this medication does not act via dopaminergic mechanisms. However, a severe visual impairment following the treatment with amantadine was recently reported [40], and our study found a positive correlation between the use of amantadine and color discrimination performance for the deutan and tritan confusion axes. Our findings, together with this case report [40], challenge the notion that amantadine does not impact vision and suggests that further studies are necessary to address the effects of amantadine on the visual system.

One limitation of our study was the small sample size in the LOPD group (for the CS test N = 9, and for the CV test N = 8). However, despite the small sample, our results for the LOPD group were in agreement with the literature on LOPD patients, the classical and most prevalent subtype of PD, with age of onset between 45 and 65 years old (e.g., [18,20,41,42]).

It is well known that clinical signs and symptoms in PD tend to increase in severity and develop more rapidly in LOPD patients compared to EOPD patients [13,26], in an apparent contradiction with the results we found in the present study. However, one prior study that evaluated dopamine neuronal loss [43] found a greater loss of dopamine density in the striatal areas in EOPD patients compared to LOPD patients with the same symptom duration and a similar PD severity. According to the authors [43], these findings may reflect greater activity of compensatory mechanisms in EOPD (younger age of symptom onset and greater plasticity) that allow them to adapt to the disease. However, such compensatory mechanisms in EOPD patients may not be adequate to compensate when the visual system is involved and, although our data do not identify the locus of visual losses, most visual studies found evidence that some loss can be attributed to the retina [3,4,6,34,44]. There are no other studies in the literature comparing the visual functions in EOPD and LOPD patients.

5. CONCLUSION

Visual losses occur in both EOPD and LOPD patients, with more pronounced losses occurring in EOPD than in LOPD patients, suggesting that the age of symptom onset is related to the pathophysiology of non-motor PD symptomatology. Future studies would permit earlier diagnosis and, perhaps, better management of the disease.

Funding. Fundação de Amparo à Pesquisa do Estado de São Paulo (05/053974-6, 08/58731-2, 14/26818-2); Conselho Nacional de Desenvolvimento Científico e Tecnológico (309409/2015-2, 523303/95-5); Sociedade Beneficente Israelita Brasileira Albert Einstein (52); Financiadora de Estudos e Projetos (01.06.0842-00); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (0019/01-1).

Acknowledgment. We are very thankful for the participants and their relatives for their support and contribution to this study. We also thank Egberto Reis Barbosa and Patricia Maria de Carvalho Aguiar for forwarding some of the participants to the study.

CFS, DFV, and MFC designed the study. ALM conducted the ophthalmologic exam. CFS collected data. CFS, MFC, and HBF analyzed data. CFS and RDH wrote the paper. All authors revised the paper.

Disclosures. The authors declare that they have no conflict of interest.

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