Parkinsonism and Related Disorders 92 (2021) 22–25

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

# Visual dysfunction is associated with cognitive impairment in Parkinson's disease

Rocío Del Pino, Ph.D [a,*], Marian Acera, MSc [a], Ane Murueta-Goyena, Ph.D [a], Olaia Lucas-Jiménez, Ph.D [b], Natalia Ojeda, Ph.D [b], Naroa Ibarretxe-Bilbao, Ph.D [b], Javier Peña, Ph.D [b], Paula Reyero, MSc [a], Jesús Cortés, Ph.D [c,d], Beatriz Tijero, MD, Ph.D [a,e], Marta Galdós, Ph.D [f], Juan Carlos Gómez-Esteban, MD, Ph.D [a,e,g,**], Iñigo Gabilondo, MD, Ph.D [a,e,h]

[a] Neurodegenerative Diseases Group, Biocruces Bizkaia Health Research Institute, Barakaldo, Bizkaia, Spain
[b] Department of Methods and Experimental Psychology, Faculty of Psychology and Education, University of Deusto, Bilbao, Spain
[c] Computational Neuroimaging Group, Biocruces Bizkaia Health Research Institute, Barakaldo, Spain
[d] Department of Cell Biology, University of the Basque Country (UPV/EHU), Leioa, Spain
[e] Neurology Department, Cruces University Hospital, Barakaldo, Bizkaia, Spain
[f] Ophthalmology Department, Cruces University Hospital, Barakaldo, Bizkaia, Spain
[g] Department of Neuroscience, University of the Basque Country (UPV/EHU), Leioa, Spain
[h] Ikerbasque: the Basque Foundation for Science, Bilbao, Spain

ARTICLE INFO

*Keywords:*
Cognition
Parkinson's disease
Visual cognition
Visual function

ABSTRACT

*Introduction:* Visual dysfunction and cognitive impairment are common in Parkinson's disease (PD) but the precise contribution of lower-level visual impairment to visual-input based cognitive performance has not been extensively characterized in PD.

*Methods:* We included 49 PD patients and 22 healthy controls (HC). Lower-level visual function tests [high and low contrast visual acuity (HCVA and LCVA) and contrast sensitivity (CS)] and a neuropsychological battery (involving visual cognition) were performed. Pairwise correlations between lower-level visual functions and visual cognition were computed and stepwise linear regressions were fitted introducing age, Geriatric Depression Scale, and lower-level visual functions in the model to calculate their predicted effect on visual cognition.

*Results:* Compared to controls, patients presented a significant impairment in all cognitive domains (visual attention, visual processing speed and visual perception, visuospatial abilities, visuoconstructive abilities, and visual memory), and lower-level visual functions. HCVA and LCVA were significantly associated with visual cognition in PD. HCVA explained up to 49.3% and 34.2% of the variability in visual perception and visuospatial abilities, respectively, whereas LCVA was mainly associated with short- and long-term visual memory and visuospatial abilities.

*Conclusion:* Lower-level visual dysfunction is highly associated with cognitive performance in PD, when cognitive tests are based on visual input. Our results support that lower-level visual functions should be considered when assessing cognitive status of PD patients and might be useful for predicting cognitive deterioration.

Interest in vision research in Parkinson's disease (PD) is gaining attention due to the cumulative evidence supporting visual dysfunction as an early predictive symptom for cognitive decline or dementia in PD [1–3]. Post-mortem and in-vivo studies in PD have consistently reported a specific injury of structures and networks participating in key steps of visual information perception and processing, from lower-level visual regions, such as the retina [4], to intracranial visual pathways involved in higher-level visual functions (visual cognition) [5].

Lower-level visual dysfunction, like visual acuity and contrast sensitivity impairment, has been extensively described in PD [4,6], and might have important implications for understanding cognitive deterioration, as most of the standard neuropsychological tests require visual

* Corresponding author. Neurodegenerative Diseases Group, Biocruces Bizkaia Health Research Institute, Plaza de Cruces 12, Barakaldo, Bizkaia, CP, 48903, Spain.
** Corresponding author.
*E-mail address:* delpinorocio@gmail.com (R. Del Pino).

https://doi.org/10.1016/j.parkreldis.2021.10.005
Received 15 February 2021; Received in revised form 2 September 2021; Accepted 3 October 2021
Available online 7 October 2021

inputs for assessing cognitive capabilities. Inversely, visual scenery generation and perception is tightly coupled with cognitive processes that are deteriorated in PD, such as attention [7], being the incoming visual information constantly regulated and tuned by top-down processes [8]. Previous studies have explored the link between visual alterations and cognitive impairment in PD, but the extent to which lower-level visual dysfunction could explain neuropsychological performance has not been deeply explored. In this work, we aimed to systematically examine the effect of lower-level visual functions on several vision-based neuropsychological tests.

## 1. Materials and methods

We performed a cross-sectional evaluation of 49 PD patients and 22 healthy controls (HC) recruited in the Department of Neurology of Cruces University Hospital. PD patients fulfilled Parkinson's UK Brain Bank criteria for PD diagnosis and were studied in their optimal *on*-motor situation. Participants with any ocular or systemic conditions that could potentially influence vision were excluded in an ophthalmological screening. These conditions included eye opacifications, retinal pathology or systemic diseases described elsewhere [9]. The study protocol was approved by the Ethics Committee of the Basque Health System (Spain). All subjects provided written informed consent prior to their participation in the study, in accordance with the tenets of the Declaration of Helsinki.

### 1.1. Demographics and PD-related features

Age, sex, and years of education were recorded for all participants. Two neurologists experienced in the field of movement disorders recorded disease duration, Hoehn & Yahr Scale score, Unified Parkinson Disease Rating Scale (UPDRS I-IV), and Levodopa equivalent daily dose (LEDD).

### 1.2. Neuropsychological evaluation and primary visual function

General cognition screening (Montreal Cognitive Assessment (MoCA)), depression symptoms (Geriatric Depression Scale (GDS)), and Instrumental Activities of Daily Living (IADL) were assessed. Additionally, we conducted neuropsychological tests for visual cognition (see Supplementary information), grouped in five domains: 1) visual attention; 2) visual processing speed and visual perception; 3) visuospatial abilities; 4) visuoconstructive abilities; 5) visual memory. The tests included in each domain are represented in Fig. 1.

Visual function assessment was performed binocularly with best-spectacle correction assessing distance high contrast visual acuity (HCVA), low contrast visual acuity (LCVA), and contrast sensitivity (CS) in high luminance lighting conditions (280 lux) at 1 m.

### 1.3. Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 20.0 (IBM-SPSS, Armonk, NY, USA). Group differences in demographical and clinical variables were analyzed with Student's t-test. Regarding the analysis of the relationship between visual function and cognition, we first transformed the raw data into Z-scores and computed pairwise correlations between lower-level visual function and visual cognition. Lastly, we performed stepwise linear regressions in PD patients and controls, separately, introducing age, GDS, HCVA, LCVA, and CS as independent predictors and, in each model, one visual

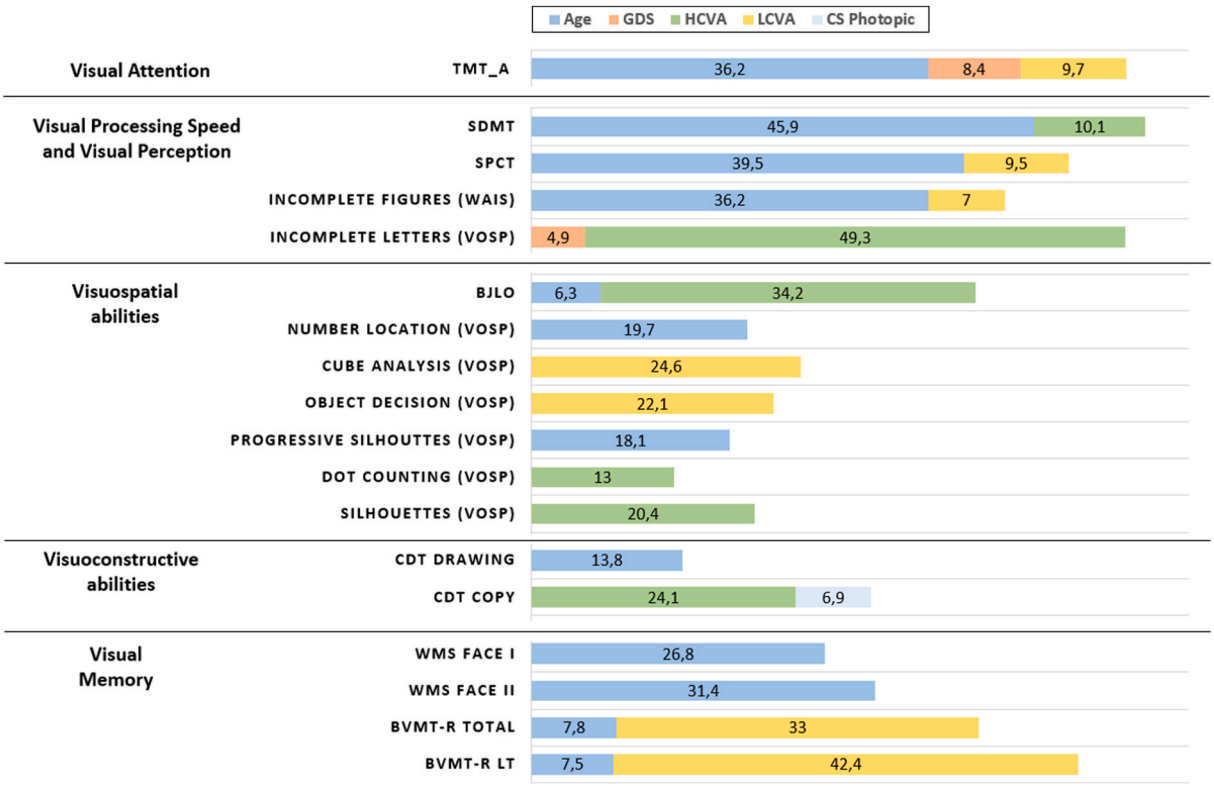


**Fig. 1. Predicted effects of age and lower-level visual variables in visual cognition tests in PD patients.** Horizontal bar plot showing predicted effects of age, GDS, HCVA, LVCA and CS in each visual cognition tests in PD, calculated by means of stepwise linear regressions. Only statistically significant ($p < .05$) coefficients of regression models are displayed. BJLO: Benton's Judgment of Line Orientation Test-H form; BVMT-R: Brief Visual Memory Test-Revised; BVMT-R LT: Brief Visual Memory Test-Revised Long Term; CDT: Clock Drawing Test; CS: Contrast Sensitivity; GDS: Geriatric Depression Scale; HCVA: High Contrast Visual Acuity; LCVA: Low Contrast Visual Acuity; TMT-A: Trail Making Test-A; SDMT: Symbol Digit Modality Test; SPCT: Salthouse Perceptual Comparison Test; VOSP: Visual Object and Space Perception Battery; WAIS-IV: Wechsler Adult Intelligence Scale-IV; WMS: Wechsler Memory Scale.

cognitive domain as the dependent variable. All regression analyses were checked for normality and homoscedasticity assumptions.

## 2. Results

The demographical data and clinical features of study participants are shown in Table 1. Overall, there were no statistically significant differences between groups in demographical parameters. Compared to controls, patients showed significant differences in general cognitive performance (MoCA), instrumental activities of daily living (IADL) and symptoms of depression (GDS). The mean disease duration of patients was 6.4 years scoring a median of 2 points in Hoehn & Yahr scale. Most patients (83.7%) met MDS criteria for multiple-domain MCI.

PD patients presented a significant impairment in all cognitive domains (visual attention, visual processing speed and visual perception, visuospatial abilities, visuoconstructive abilities, and visual memory), and in lower-level visual functions (HCVA, LCVA, and CS) compared to controls.

When the correlations between visual cognition and lower-level visual functions were calculated separately for controls and patients, we observed that HCVA, LCVA and CS significantly correlated with all cognitive domains in PD (Supplementary Table 1), observing moderate to strong positive correlation coefficients (up to r = .70; $p < .001$) while in controls no statistically significant correlations were found except for the Trail Making Test, part-A (CS, r = 0.73; $p < .001$), Symbols Digit Modality Test, and Salthouse Perceptual Comparison Test (HCVA, r = 0.48; $p = .02$ and r = 0.56; $p$=.009, respectively). In line with these findings, stepwise hierarchical regression analyses confirmed that lower-level visual functions predicted visual cognition (Fig. 1). In PD, HCVA explained between 10.1% and 49.3% of the variance of visual cognition tests, mainly of visual perception and visuospatial abilities (49.3% and 34.2%, respectively), whereas LCVA explained between 7% and 42.4% of the variance of visual cognition, being most significantly associated with short- and long-term visual memory (specifically, visuospatial memory) and visuospatial abilities.

## 3. Discussion

In the present study, the impairment of lower-level visual functions in PD was associated with the outcomes in a wide range of neuropsychological tests involving vision (visual cognition). More specifically, our results support that LCVA was related to the performance of several visual cognition tests, statistically explaining the impairment of visuospatial abilities, whereas HCVA was mainly related to visuospatial object location and visual orientation. In addition, as expected, age was also included in regression models of attention and visual processing speed in PD patients. Such associations were not observed in HC.

Several studies have consistently demonstrated impairment of lower-level visual functions and neuropsychological tests involving vision in PD [4,6]. However, few studies have specifically evaluated the association between lower-level vision and cognitive performance. A previous study including PD without dementia found that reduced CS contributed to deficits in spatial and motion perception and attention in PD patients [10]. Uc et al. (2005) found that impairment in visual memory, visuoconstructional abilities, executive functions, verbal memory and overall cognitive function correlated with the impairment in speed of visual processing and attention, CS, HCVA and spatial perception [10]. In their work, the authors demonstrated that line orientation and perception of structure from motion were independent predictors of cognitive status. Despite the innovative nature and comprehensive methodology of this study, the authors did not measure LCVA, which, according to our previous findings [2,4], is strongly associated with cognitive impairment in PD. Leyland et al. (2020) constructed a model to predict the risk of dementia in PD, including visual acuity and contrast sensitivity, but these authors did not include LCVA either [1]. Although the impact of lower-level vision on cognitive outcomes has been studied, to the best of

**Table 1**
Demographics and clinical characteristics of study participants.

| Demographic and clinical characteristics | | HC (n = 22) | PD (n = 49) | t ($p$) |
|---|---|---|---|---|
| | Age, years | 57.9 (6.0) | 60.5 (8.3) | −1.3 |
| | Males, n (%) | 10 (45.5) | 31 (63.3) | – |
| | Education, years | 12.0 (4.1) | 10.3 (4.1) | 1.4 |
| | IADL | 8.0 (0.0) | 7.4 (1.2) | −3.6 (.001) |
| | GDS | 1.4 (1.7) | 2.9 (2.7) | −2.7 (.008) |
| | MoCA Total score | 26,9 (2,5) | 24.3 (3.2) | 3.2 (.002) |
| | PD-MCI | – | 41 (83.7) | – |
| | Age at onset, years | – | 53.9 (7.9) | – |
| | Disease duration, years | – | 6.4 (3.9) | – |
| | Hoehn & Yahr | – | 2 (0–4.0) | – |
| | UPDRS I | – | 2.3 (1.8) | – |
| | UPDRS II | – | 12.2 (6.5) | – |
| | UPDRS III | – | 27.4 (11.2) | – |
| | UPDRS IV | – | 4.5 (3.7) | – |
| | LEDD | – | 648.2 (395.2) | – |
| **Functional domain** | | | | |
| Visual Attention | TMT-A | 42.5 (13.5) | 53.9 (23.1) | −2.6 (.01) |
| Visual Processing Speed and Visual Perception | SDMT | 49.0 (9.0) | 34.2 (14.3) | 5.2 (<.001) |
| | SPCT | 26.7 (7.4) | 23.3 (9.3) | 1.6 |
| | Incomplete Figures (WAIS-IV) | 11.3 (4.0) | 8.84 (4.2) | 2.4 (.02) |
| | Incomplete letters (VOSP) | 19.7 (0.7) | 18.2 (3.5) | 2.9 (.004) |
| Visuospatial abilities | BJLO-H | 24.6 (3.1) | 20.3 (5.9) | 3.9 (<.001) |
| | Number location (VOSP) | 9.2 (1.0) | 8.3 (2.0) | 2.6 (.01) |
| | Cube analysis (VOSP) | 9.8 (0.3) | 8.7 (1.9) | 3.9 (<.001) |
| | Object decision (VOSP) | 16.4 (2.5) | 16.1 (2.4) | 0.5 |
| | Progressive Silhouettes (VOSP) | 13.0 (2.5) | 13.2 (2.4) | −0.2 |
| | Dot counting (VOSP) | 9.8 (0.3) | 9.8 (0.4) | 0.3 |
| | Silhouettes (VOSP) | 21.7 (3.3) | 20.3 (4.5) | 1.3 |
| Visuoconstructive abilities | CDT Drawing | 9.1 (0.9) | 7.6 (2.3) | 3.9 (<.001) |
| | CDT Copy | 9.7 (0.4) | 8.7 (1.5) | 4.3 (<.001) |
| Visual Memory | WMS Face I | 36.0 (5.2) | 33.9 (4.2) | 1.8 |
| | WMS Face II | 35.9 (3.6) | 33.8 (4.8) | 1.8 |
| | BVMT-R total | 24.3 (5.6) | 16.9 (8.7) | 4.3 (<.001) |
| | BVMT-R LT | 9.8 (1.2) | 6.6 (3.5) | 5.7 (<.001) |
| Primary Visual Functions | HCVA | 61.6 (4.5) | 58.3 (6.7) | 2.1 (.04) |
| | LCVA | 37.9 (5.9) | 26.9 (12.5) | 3.8 (<.001) |
| | CS | 2.1 (0.1) | 1.9 (0.1) | 4.5 (<.001) |

The results are displayed as mean (standard deviation) except for sex, PD-MCI and Hoehn & Yahr score, which are shown, respectively, as number of males (% of males), number of participants with PD-MCI. Significant p-values are considered when (<.05). *Abbreviations:* BJLO-H: Benton's Judgment of Line Orientation Test H form; BVMT-R: Brief Visual Memory Test-Revised; CDT: Clock Drawing Test; CS: Contrast Sensitivity; GDS: Geriatric Depression Scale; HC: Healthy controls; HCVA: High Contrast Visual Acuity; IADL: Instrumental Activities of Daily Living; LCVA: Low Contrast Visual Acuity; LEDD: Levodopa Equivalent Daily dose; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease; PD-MCI: Parkinson's disease associated Mild Cognitive Impairment; SDMT: Symbol Digit Modalities Test; SPCT: Salthouse Perceptual Comparison Test; TMT-A: Trail Making Test part A; UPDRS: Unified Parkinson Disease Rating Scale; VOSP: Visual Object and Space Perception Battery; WAIS-IV: Wechsler Adult Intelligence Scale-IV; WMS-IV: Wechsler Memory Scale-IV. Units for all scores correspond to the total number of correct answers except for TMT-A (expressed in seconds), HCVA and LCVA (total number of correctly identified letters) and CS (log units).

our knowledge it has not systematically been stablished in PD to what extent the variability of neuropsychological tests that use visual inputs could be attributed to impairment in lower-level visual functions. Our findings support that some tests for assessing visual cognition are highly influenced by lower-level visual abilities, probably because poor lower-level vision acts as a confounder in object identification or in the time need to interpret visual sceneries.

One potential limitation of our study was the small sample size of the control group as compared to that of patients and the possible ceiling effect of lower-level vision and visual cognition tests in controls, which could have accounted for the lack of significant correlations in this group. Also, being a cross-sectional study, our results could not prove causality between lower-level visual dysfunction and cognitive disability, although a strong association in demonstrated. Lastly, the interindividual variability of "ON" medication state (between 1 and 4 h) remains a limitation of the current study. Future studies would benefit from using larger sample sizes and conducting longitudinal studies would help to unravel the interaction between lower-level and cognitive visual outcomes in PD.

In conclusion, our results support that neuropsychological performance of PD patients could be attributed to abnormalities in lower-level visual functions, especially to LCVA and HCVA. Since vision-related abnormalities are major predictors of cognitive deterioration in PD [1–3], our findings have important implications for understanding the predictive role of visual impairment in the prognosis of PD patients. Thus, being cognitive impairment a major determinant of disease outcome in PD, it is recommended to cautiously interpret neuropsychological performance when assessed using visual inputs, and to consider lower-level visual testing as part of the routine clinical care in PD patients.

## Author contribution statements

RDP contributed to research project, execution of the study, analysis and interpretation of data, initial drafting of the manuscript, and final approval. MA and OLJ contributed to the organization of the study, and execution of the study. AMG contributed to initial drafting of the manuscript, and final approval. NO, NIB and JP contributed to the execution of the study. PR contributed to the analysis of the study. JC contributed to the methodology and analysis of the study. BT and MG contributed to the execution of the study. JCGE and IG contributed to conception, organization and execution of the study, acquisition of data, critical revision of the manuscript, and final approval.

## Declaration of competing interest

The authors have no conflict of interest to report.

## Acknowledgments

The authors want to thank all the patients and participants involved in the study.

## Acknowledgments

The authors want to thank all the patients and participants involved in the study. This study was partially co-funded by Michael J. Fox Foundation [RRIA 2014 (Rapid Response Innovation Awards) Program (Grant ID: 10189)], by the Instituto de Salud Carlos III through the project"PI16/00005", the Juan Rodes grant "JR15/00008" (IG) (Co-funded by European Regional Development Fund/European Social Fund - "Investing in your future"), and by the Department of Health Basque Government through the project "2016111009", "2019111100" and "2020333033".

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2021.10.005.

## References

[1] L.-A. Leyland, F.D. Bremner, R. Mahmood, S. Hewitt, M. Durteste, M.R.E. Cartlidge, M.M.-M. Lai, L.E. Miller, A.P. Saygin, P.A. Keane, A.E. Schrag, R.S. Weil, Visual tests predict dementia risk in Parkinson disease, Neurol. Clin. Pract. 10 (2020), https://doi.org/10.1212/cpj.0000000000000719.

[2] A. Murueta-Goyena, R. Del Pino, M. Galdós, B. Arana, M. Acera, M. Carmona-Abellán, T. Fernández-Valle, B. Tijero, O. Lucas-Jiménez, N. Ojeda, N. Ibarretxe-Bilbao, J. Peña, J. Cortes, U. Ayala, M. Barrenechea, J.C. Gómez-Esteban, I. Gabilondo, Retinal thickness predicts the risk of cognitive decline in Parkinson disease, Ann. Neurol. 89 (2021), https://doi.org/10.1002/ana.25944.

[3] A. Zarkali, P. McColgan, L.A. Leyland, A.J. Lees, R.S. Weil, Visual dysfunction predicts cognitive impairment and white matter degeneration in Parkinson's disease, Mov. Disord. 36 (2021), https://doi.org/10.1002/mds.28477.

[4] A. Murueta-Goyena, R. del Pino, P. Reyero, M. Galdós, B. Arana, O. Lucas-Jiménez, M. Acera, B. Tijero, N. Ibarretxe-Bilbao, N. Ojeda, J. Peña, J. Cortés, J.C. Gómez-Esteban, I. Gabilondo, Parafoveal thinning of inner retina is associated with visual dysfunction in Lewy body diseases, Mov. Disord. 34 (2019), https://doi.org/10.1002/mds.27728.

[5] A. Arrigo, A. Calamuneri, D. Milardi, E. Mormina, L. Rania, E. Postorino, S. Marino, G. DiLorenzo, G.P. Anastasi, M.F. Ghilardi, P. Aragona, A. Quartarone, M. Gaeta, Visual system involvement in patients with newly diagnosed Parkinson disease, Radiology 285 (2017), https://doi.org/10.1148/radiol.2017161732.

[6] R.S. Weil, D.S. Schwarzkopf, B. Bahrami, S.M. Fleming, B.M. Jackson, T.J.C. Goch, A.P. Saygin, L.E. Miller, K. Pappa, I. Pavisic, R.N. Schade, A.J. Noyce, S.J. Crutch, A.G. O'Keeffe, A.E. Schrag, H.R. Morris, Assessing cognitive dysfunction in Parkinson's disease: an online tool to detect visuo-perceptual deficits, Mov. Disord. (2018), https://doi.org/10.1002/mds.27311.

[7] D.J. Norton, V.A. Nguyen, M.F. Lewis, G.O. Reynolds, D.C. Somers, A. Cronin-Golomb, Visuospatial attention to single and multiple objects is independently impaired in Parkinson's disease, PLoS One 11 (2016), https://doi.org/10.1371/journal.pone.0150013.

[8] C.D. Gilbert, W. Li, Top-down influences on visual processing, Nat. Rev. Neurosci. 14 (2013), https://doi.org/10.1038/nrn3476.

[9] P. Tewarie, L. Balk, F. Costello, A. Green, R. Martin, S. Schippling, A. Petzold, The OSCAR-IB consensus criteria for retinal OCT quality assessment, PLoS One 7 (2012), https://doi.org/10.1371/journal.pone.0034823.

[10] E.Y. Uc, M. Rizzo, S.W. Anderson, S. Qian, R.L. Rodnitzky, J.D. Dawson, Visual dysfunction in Parkinson disease without dementia, Neurology (2005), https://doi.org/10.1212/01.wnl.0000191565.11065.11.