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Cognitive Workload during Verbal Abstract Reasoning in Parkinson's Disease: A Pilot Study

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Abstract

Background: Pupillary response reflects cognitive workload during processing speed, working memory, and arithmetic tasks in Parkinson's disease (PD). Abstract reasoning, a higher-order cognitive function that relates different objects, events, or thoughts in a similar manner, may also be compromised in PD. The aim of this study was to compare pupillary response as a measure of cognitive workload while completing a verbal abstract reasoning test between patients with PD and age-matched controls.

Methods: Nineteen non-demented individuals with PD (66.6 ± 8.9 years) and 10 healthy controls (65.3 ± 7.3 years) were recruited. A remote eye tracker recorded the pupillary response at 60 Hz, while the participants were performing the Similarities test of Wechsler Adult Intelligence Scale-IV. Outcome measures included pupillary response, evaluated by the Index of Cognitive Activity (ICA), and behavioral responses of the Similarities test.

Results: The PD group (scaled scores = 8.9 ± 2.2) did not show impairment in behavioral performance on Similarities test compared with healthy controls (scaled scores = 8.8 ± 2.3; p = .91). However, the PD group (ICA = .32 ± .09) demonstrated significantly greater cognitive workload during the Similarities test compared to controls (ICA = .24 ± .08; p = .03).

Conclusions: Non-demented individuals with PD exerted greater cognitive workload to complete a verbal abstract reasoning task despite similar behavioral performance compared to healthy controls. Clinical utilities of pupillary response to detect and monitor early impairment in higher-order executive function will be the subject of further study in the PD population.

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AUTHORS' CONTRIBUTIONS

HD conceptualized the study. SM, MK, and HD drafted the manuscript and analyzed the data. HD, AEA, KEL, and RP made valuable suggestions and reviewed the manuscript.

DECLARATION OF INTEREST

Authors declare no conflict of interest.

Keywords

pupillary response; cognitive workload; cognition; Parkinson's disease; verbal reasoning; abstract reasoning

INTRODUCTION

Cognitive impairment is a common non-motor manifestation of Parkinson's disease (PD). Nearly 25% of individuals with newly diagnosed PD show cognitive deficits.[1] Among non-demented individuals with PD, between 17% and 30% are diagnosed with mild cognitive impairment.[2] Mild cognitive impairment in PD may eventually develop to PD-dementia.[3] Individuals with PD show approximately a six-fold greater risk of developing PD-dementia as their disease progresses compared with the healthy individuals.[4] Since dementia is considered to be an irreversible condition with substantial implications on an individual's quality of life and can cause significant socioeconomic burden, much effort has been invested in early detection of cognitive impairments.[5]

In PD, dopamine signaling dysfunction in the pre-frontal cortex (PFC) is linked to impaired executive functions.[6] Verbal abstract reasoning is an executive function involving higher-order and complex thought processes through the PFC expressed in verbal language.[7] The PFC is extensively interconnected with different parts of the brain through feedforward and feedback circuits. These associations enable the PFC to mediate multiple brain functions such as executive function, memory, intelligence, and language. The PFC is particularly associated with relational abstract reasoning, which is frequently used when one tries to integrate relationships between pieces of information that are not directly related (e.g., How are a cat and a dog alike? How are a bicycle and a car alike?). Furthermore, abstract reasoning is important in daily life since this cognitive ability helps people better understand complicated events, objects, and concepts by identifying them in a related manner.[8] Previous studies have shown that individuals with PD have significantly poorer verbal abstract reasoning compared to healthy individuals.[9, 10] However, it is possible that in the early stages of the PD, individuals might compensate for impairments in verbal abstract reasoning by executing higher cognitive workload to perform similarly to healthy controls.

Pupillary response is a reliable and valid measurement for cognitive workload that has been utilized in individuals with PD who have or are at risk of cognitive impairment.[11, 12] Pupils dilate when individuals perform cognitive tasks and subside quickly after the task is completed. Pupillary response induced by cognitive tasks is linked with the activation of locus coeruleus-norepinephrine system. The locus coeruleus primarily produces norepinephrine which plays an important role in the regulation of cognitive functions including attention, learning, memory, and decision making.[13] The underlying mechanism of the connection between pupil dilation and locus coeruleus activity is not fully understood, but neuroimaging showed correlations between pupil dilation and locus coeruleus activity during cognitive tasks.[14] The pupillary response can be accurately measured by pupillometric devices such as an eye tracker.[15] These eye tracking devices measure changes in pupil size, which in turn reflects changes in cognitive workload during cognitive

tasks.[16] Pupillary response during cognitive tasks has been investigated in different studies examining processing speed, attention, and arithmetic tasks in neurodegenerative conditions.[11, 17, 18] Abstract reasoning, however, includes the ability to relate different concepts on a complex level through evaluating and applying previous knowledge in problem-solving by using theories, metaphors, and complex analogies.[7]

In this pilot study, we investigated the difference in cognitive workload exertion measured by pupillary response in a verbal abstract reasoning task between non-demented individuals with PD and healthy controls. We hypothesized that non-demented individuals with PD would exert greater cognitive workload while performing equally well in a verbal abstract reasoning task when compared to performance of healthy controls on the same task.

METHODS

Participants

Non-demented individuals with PD were recruited from the Parkinson's Disease and Movement Disorders Center at the University of Kansas Medical Center. Diagnosis of idiopathic PD was based on the UK Parkinson's Disease Brain Bank Clinical Diagnostic Criteria.[19] Spouses of the non-demented individuals with PD or volunteers from the community were recruited as healthy controls. Dementia and mild cognitive impairment were ruled out by scoring within normative values on a standard cognitive assessment battery (Level II guideline).[20] All participants were considered non-demented.[17] The inclusion criteria for both groups were (1) Montreal Cognitive Assessment (MoCA) score > 25; (2) scores within two standard deviations from normative values or mean values of healthy controls of the cognitive battery to determine mild cognitive impairment; and (3) able to give voluntary consent. The exclusion criteria were (1) diagnosis of mild cognitive impairment or dementia; (2) atypical parkinsonism; (3) secondary parkinsonism; (4) history of unresolved neurological, visual (e.g., glaucoma, cataracts) or vestibular conditions unrelated to PD; (4) severe trunk and head dyskinesia or dystonia in the medication "ON" state; (5) blepharospasm; (6) deep brain stimulation; and (7) unpredictable motor fluctuations. This study was approved by the Institutional Review Board (ID: STUDY00004461). All participants gave written informed consent prior to enrollment in the study.

General testing

Demographics (e.g., age, sex, handedness, and education) and clinical characteristics (e.g., duration of disease and medication) of the participants were collected via questionnaires. For the non-demented individuals with PD, daily levodopa equivalent dosage (LED) was calculated. The calculation of LED was based on Tomlinson, Stowe [21]. The MoCA was administrated to all participants to assess global cognition. Non-demented individuals with PD were administered the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II (motor experiences of daily living) and Part III (motor examination), and modified Hoehn and Yahr (H&Y) stage scale. They also completed the Scales for Outcomes in Parkinson's Disease - Autonomic Dysfunction (SCOPA-AUT). This test was used to assess the possible effect of autonomic dysfunction on pupillary response.

The Similarities test of the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) was administered to assess verbal abstract reasoning from the Q-interactive iPad-based application. This test was endorsed by the Movement Disorder Society to assess verbal abstract reasoning in PD.[20] During the test, participants were asked to determine the similarity between two words or concepts. The highest score for this test is 36 points (scaled score range: 1 to 19), in which a higher score indicates better abstract thinking ability and verbal reasoning. After the testing, scaled scores were calculated based on the number of correct answers. The test was administered in a one-time session by a trained graduate research assistant. This study followed the STROBE guidelines (Supplementary Table 1).[22]

Assessment of cognitive workload

The amount of cognitive workload during the Similarities test was evaluated through pupillary response. Participants were asked to sit in front of a 9.7-inch iPad Air 2 (A1566, Apple Inc., 2014) which was mounted on a stand in an air-conditioned room. Lighting conditions were the same across evaluations. A height-adjustable table was used to place the center of the iPAD Air 2 at the level of participants' eyes. A remote eye tracker (FX3, SeeingMachines, Inc.) was placed right underneath the iPad and recorded raw pupil size at 60 Hz while participants were performing the Similarities test. The test administrator verbally asked each of the questions. Each question was shown on the iPad screen to ensure accurate capturing of the pupils. The participants were asked to verbally answer each of the questions. The answers of the participants were manually recorded on the Q-interactive application. EyeWorks™ Record software (EyeTracking, Inc., 2011) was used to record raw pupil size throughout the testing.

After the testing, raw pupil size data were transformed into the Index of Cognitive Activity (ICA). The ICA has been applied in different domains of cognition,[23] driving,[24-26] linguistic processing,[27] and cognitive-motor dual tasking.[28] The ICA is an algorithm, which measures cognitive workload through pupil dilation by filtering out the light reflex using a wavelet analysis.[16] The wavelet analysis removes large oscillations due to the light reflex and retains abrupt and short dilation that reflects cognitive workload.[25] The ICA is computed from the ratio of the number of abrupt and short pupil dilations in one second over the theoretical maximum. The ICA is then scaled to give a value between 0 (no cognitive workload) and 1 (maximum cognitive workload).[29] ICA values were averaged for each eye.

Statistical analysis

Demographic and clinical characteristics of non-demented individuals with PD and healthy controls were compared using unpaired *t* tests for continuous variables or by Chi-square test for categorical variables. The effect size (*d*) was calculated and interpreted using Cohen's criteria (small = .2-.5; medium = .5-.8; large ≥ .8).[30] The eye tracking data were normally distributed according to the Kolmogorov-Smirnov statistic. Unpaired *t* tests were used to compare the mean of the behavioral responses and the amount of cognitive workload spent during the Similarities test between non-demented individuals with PD and healthy controls. Pearson's correlation coefficients (*r*) were calculated for each group to examine relationships

between mean ICA and other variables including demographic, clinical, and Similarities test score, and interpreted as r = .25-.50, weak relationship; r = .50-.75, moderate relationship; and r > .75, excellent relationship.[31] The level of significance was set at .05. All statistical analyses were performed using IBM SPSS Statistics v24.

RESULTS

Demographic and clinical characteristics

Twenty-nine individuals participated in the study (19 non-demented PD and 10 healthy controls. Non-demented individuals with PD and healthy controls were matched based on age, years of education, and cognitive status (MoCA score). Non-demented individuals with PD had mild to moderate disease severity based on H&Y stage and MDS-UPDRS II and III scores. One individual was in H&Y stage I, 16 individuals were in H&Y stage II, and two individuals were in H&Y stage III. The mean disease duration was 5.7 years. A summary of the demographic and clinical characteristics of the groups are shown in Table 1.

Comparison of cognitive workload

Non-demented individuals with PD (.32 ± .09) exerted more cognitive workload indexed by ICA of the right eye during the Similarities test compared with healthy controls (.24 ± .08) (p = .03; Cohen's d = .93) (Figure 1). The left eye ICA values were not significantly different between the non-demented individuals with PD (.31 ± .07) and healthy controls (.27 ± .09) during the Similarities test (p = .19).

Behavioral responses

Non-demented individuals with PD (8.9 ± 2.2) and healthy controls (8.8 ± 2.3) performed similarly during the Similarities test (p = .91).

Relationship between cognitive workload and demographic, clinical, and behavioral variables

The left and right ICAs were significantly correlated (r = .50, p = .003). There was a weak correlation between right eye ICA and MDS-UPDRS II (r = .33, p = .17), MoCA (r = −.38, p = .11), SCOPA-AUT (r = .31, p = .18), and LED (r = .23, p = .35) in the PD group. In addition, there was a weak correlation between right eye ICA and years of education (r = −.30, p = .40), and a moderate correlation between right eye ICA and behavioral responses of the Similarities test (r = .52, p = .12) in the healthy controls.

DISCUSSION

This study investigated cognitive workload measured by pupillary response in non-demented individuals with PD and healthy controls during a task of verbal abstract reasoning. Our main findings demonstrated increased cognitive workload while performing verbal abstract reasoning tasks in individuals with PD compared to healthy controls, despite equal behavioral responses on the verbal abstract reasoning task.

Among various cognitive domains, executive dysfunctions in PD are considered the most profound impairment.[32] Abstract reasoning is a higher-order executive function built upon three cores of executive functions including working memory, inhibition, and cognitive flexibility.[33] In daily life, abstract reasoning function enables the generalization of multiple sources of information and apply the generalized information in novel but similar situations. Thus, when this ability is impaired, people may become less efficient in daily living. While conventional neuropsychological exams have shown inconsistent results in the verbal abstract reasoning domain in PD, pupillary response showed differences between individuals with PD and healthy controls.

Several studies have found increased cognitive workload in individuals with PD during simple speed of processing, arithmetic, and attention tasks. Ranchet, Orlosky [11] demonstrated that individuals with PD exerted more cognitive workload during a prosaccadic task. In addition, cognitive workload during the prosaccadic task was also greater in PD participants with mild cognitive impairment compared to non-demented PD. [11] Wang, McInnis [34] demonstrated disruptions of pupillary response modulation in anti-saccadic preparation in individuals with PD. A previous study also established the accuracy of pupillometry to discern changes in cognitive demand of a working memory and updating task in individuals with PD.[17] Similar observations have been reported in individuals with mild cognitive impairment.[35] However, two studies found no significant difference in pupillary response between individuals with multiple sclerosis and healthy controls.[36, 37] Therefore, further studies are warranted to compare pupillary response behaviors across different neurodegenerative diseases.

Interestingly, we found the ICA from the right eye to differentiate between PD and healthy controls during verbal abstract reasoning tasks, while no differences were found in the ICA from the left eye. Similar differences between right and left ICA data were found in other studies.[11, 17] Measurement error of the ICA may be the reason for differences in left and right ICA. Alternatively, a functional neuroimaging study of relational abstraction reported activation of left-lateralized PFC regions.[38] Furthermore, the abstract reasoning test used in this study was verbally administered. Thus, the task may engage more areas of the brain related to language, which is considered one of the most left-hemispheric lateralized functions of the brain.[39] This brain hemisphere lateralization could potentially contribute to asymmetry of pupillary responses.[38, 39] However, the underlying mechanism of this phenomenon is unclear and should be tested in future studies.

In our study, no significant difference was observed in the scores of verbal abstract reasoning test between individuals with PD and healthy controls. This finding is in accordance with previous findings suggesting normal abstract reasoning function in individuals with PD.[40, 41] By contrast, some other studies reported poorer abstract thinking and reasoning in PD compared to the healthy individuals.[9, 10] The difference in outcomes may be due to different inclusion criteria (e.g., PD-dementia included) or the use of different neuropsychological tests (e.g., Cambridge Cognitive Examination for Mental Disorders-Revised (CAMCOG-R)). In our study, individuals with non-demented PD performed similarly on verbal abstract reasoning test compared to the healthy controls, yet differences might be observed in the amount of cognitive workload that is exerted. Future

studies should investigate whether increased cognitive workload is a predictor of cognitive impairment.

Overall, our finding demonstrates the potential of using pupillary response as a more sensitive measurement tool for subtle cognitive changes and perhaps early detection of cognitive impairment in non-demented PD. Such knowledge will enable people to prepare an adequate treatment plan (e.g., cognitive therapies) capable of slowing down cognitive deterioration prior to actual manifestation of cognitive impairment associated with PD.

Although we found a significant difference in cognitive workload between non-demented PD and healthy controls (p =.03), the current results should be interpreted with caution due to the small sample size. While p-values are largely dependent on the number of samples [42], the effect size is dependent on the size of the sample and provides the magnitude of the study effect [43]. In this study, we found a strong effect size (Cohen's d = .93), providing a solid justification for future studies with larger sample size. In this study, all individuals with PD used medication to alleviate PD symptoms. Previous reports suggested that pupil dilation can be induced by acute overdose of levodopa[44] and indirectly elicited by levodopa therapy.[45] However, in our analysis, no significant relationship was found between pupillary response and LED in the PD group. In this pilot study, we only examined two groups, non-demented PD and healthy controls. However, future studies may have an additional group with de novo PD who are in the early stage of disease without taking levodopa. It is still controversial whether levodopa affects cognitive function and which cognitive domains are affected in individuals with PD [46-48]. Thus, future studies with de novo PD will provide further information in cognitive workload across the stages of PD and the levodopa use status. Other limitations included an unmatched sex distribution between groups, unequal participant numbers between PD and healthy control groups, and a lack of longitudinal analysis in verbal abstract reasoning due to the cross-sectional design, which should be addressed in future studies. In this study, we administered a verbal test recommended by the UPDRS task force to examine the abstract reasoning domain in non-demented PD. However, the abstract reasoning domain may also be tested through a graphical test such as the WAIS-IV matrix reasoning and the Halstead-Reitan category test. Future studies need to explore any differences in cognitive workload tested by both verbal and graphical formats that examine the same cognitive domain, which may offer additional insight into the role of the verbal component when solving abstract reasoning tasks.

In conclusion, this pilot study examined cognitive workload measured by pupillary responses during verbal abstract reasoning tasks. Pupillary response effectively distinguished between cognitive workload exerted by non-demented individuals with PD and healthy controls, despite equal performance in the conventional neuropsychological test. Our preliminary findings demonstrate the potential of pupillary response as a sensitive measure of cognitive workload that can possibly detect subtle cognitive changes in individuals with PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations:

H & Y	Hoehn and Yahr
ICA	Index of Cognitive Activity
LED	daily Levodopa Equivalent Dosage
MDS-UPDRS	Movement Disorder Society - Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PFC	Pre-frontal Cortex
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease - Autonomic Dysfunction
WAIS-IV	Wechsler Adult Intelligence Scale - Fourth Edition

REFERENCES

1. Muslimović D, et al., Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology, 2005. 65(8): p. 1239–1245. [PubMed: 16247051]
2. Aarsland D, Brønnick K, and Fladby T, Mild cognitive impairment in Parkinson's disease. Curr. Neurol. Neurosci. Rep, 2011. 11(4): p. 371–378. [PubMed: 21487730]
3. Meireles J and Massano J, Cognitive impairment and dementia in Parkinson's disease: Clinical features, diagnosis, and management. Front. Neurol, 2012. 3.
4. Aarsland D, et al., Risk of dementia in Parkinson's disease: A community-based, prospective study. Neurology, 2001. 56(6): p. 730–736. [PubMed: 11274306]
5. Weintraub D, Comella CL, and Horn S, Parkinson's disease - Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment. Am. J. Manag. Care, 2008. 14(2 Suppl): p. S40–48. [PubMed: 18402507]
6. Narayanan NS, Rodnitzky RL, and Uc E, Prefrontal dopamine signaling and cognitive symptoms of Parkinson's disease. Rev. Neurosci, 2013. 24(3): p. 267–278. [PubMed: 23729617]
7. Christoff K and Keramatian K, Abstraction of mental representations: Theoretical considerations and neuroscientific evidence, ed. Bunge SA and Wallis JD. 2007, Oxford, UK: Oxford University Press.
8. Wang L, et al., Characteristics of gray matter morphological change in Parkinson's disease patients with semantic abstract reasoning deficits. Neurosci. Lett, 2018. 673: p. 85–91. [PubMed: 29275185]

9. Athey RJ, Porter RW, and Walker RW, Cognitive assessment of a representative community population with Parkinson's disease (PD) using the Cambridge Cognitive Assessment–Revised (CAMCOG-R). Age Ageing, 2005. 34(3): p. 268–273. [PubMed: 15863411]
10. Huber SJ, Shuttleworth EC, and Freidenberg DL, Neuropsychological differences between the dementias of Alzheimer's and Parkinson's diseases. Arch. Neurol, 1989. 46(12): p. 1287–1291. [PubMed: 2590012]
11. Ranchet M, et al., Pupillary response to cognitive workload during saccadic tasks in Parkinson's disease. Behav. Brain Res, 2017. 327: p. 162–166. [PubMed: 28366772]
12. Wang CA, et al., Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease. Neuropsychologia, 2016. 80: p. 176–184. [PubMed: 26631540]
13. Sara SJ, The locus coeruleus and noradrenergic modulation of cognition. Nat. Rev. Neurosci, 2009. 10(3): p. 211–223. [PubMed: 19190638]
14. Murphy PR, et al., Pupil diameter covaries with BOLD activity in human locus coeruleus. Hum. Brain Mapp, 2014. 35(8): p. 4140–4154. [PubMed: 24510607]
15. Ranchet M, et al., Cognitive workload across the spectrum of cognitive impairments: A systematic review of physiological measures. Neurosci. Biobehav. Rev, 2017. 80: p. 516–537. [PubMed: 28711663]
16. Marshall SP, The index of cognitive activity: Measuring cognitive workload. Proceedings of the 2002 IEEE 7th Conference on Human Factors and Power Plants, 2002.
17. Kahya M, et al., Pupillary response to cognitive demand in Parkinson’s disease: A pilot study. Front. Aging Neurosci, 2018. 10: p. 90. [PubMed: 29692720]
18. Granholm EL, et al., Pupillary responses as a biomarker of early risk for Alzheimer's disease. J. Alzheimers Dis, 2017. 56: p. 1419–1428. [PubMed: 28157098]
19. Hughes AJ, et al., Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J. Neuro. Neurosurg. Psychiatry, 1992. 55(3): p. 181–4.
20. Litvan I, et al., Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov. Disord, 2012. 27(3): p. 349–356. [PubMed: 22275317]
21. Tomlinson CL, et al., Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord, 2010. 25(15): p. 2649–2653. [PubMed: 21069833]
22. von Elm E, et al., The strengthening the reporting of observational studies in epidemiology (strobe) statement: Guidelines for reporting observational studies. Ann. Intern. Med, 2007. 147(8): p. 573–577. [PubMed: 17938396]
23. Myers JS, et al., Pupillary response: cognitive effort for breast cancer survivors. Support. Care Cancer, 2019. 27(3): p. 1121–1128. [PubMed: 30097791]
24. Gangeddula V, et al., Effect of cognitive demand on functional visual field performance in senior drivers with glaucoma. Front. Aging Neurosci, 2017. 9(286).
25. Vogels J, Demberg V, and Kray J, The index of cognitive activity as a measure of cognitive processing load in dual task settings. Front. Psychol, 2018. 9(2276).
26. Niezgoda M, et al., Towards testing auditory–vocal interfaces and detecting distraction while driving: A comparison of eye-movement measures in the assessment of cognitive workload. Transp. Res. Part F Traffic Psychol. Behav, 2015. 32: p. 23–34.
27. Demberg V and Sayeed A, The frequency of rapid pupil dilations as a measure of linguistic processing difficulty. PLOS ONE, 2016. 11(1): p. e0146194. [PubMed: 26799065]
28. Kahya M, et al., Increased postural demand is associated with greater cognitive workload in healthy young adults: A pupillometry study. Front. Hum. Neurosci, 2018. 12: p. 288–288. [PubMed: 30072883]
29. Bartels M and Marshall SP, Measuring congitive workload across different eye tracking hardware platforms. Proceedings of the Symposium on Eye Tracking Research and Applications, 2012: p. 161–164.
30. Cohen J, A power primer. Psychol. Bull, 1992. 112(1): p. 155. [PubMed: 19565683]
31. Hinkle DE, Wiersma W, and Jurs SG, Applied statistics for the behavioral sciences. 2002, Boston, MA: Houghton Mifflin.

32. Kudlicka A, Clare L, and Hindle JV, Executive functions in Parkinson's disease: Systematic review and meta-analysis. Mov. Disord, 2011. 26(13): p. 2305–2315. [PubMed: 21971697]
33. Diamond A, Executive functions. Ann. Rev. Psychol, 2012. 64: p. 135–168. [PubMed: 23020641]
34. Wang C-A, et al., Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease. Neuropsychologia, 2016. 80: p. 176–184. [PubMed: 26631540]
35. Granholm EL, et al., Pupillary Responses as a Biomarker of Early Risk for Alzheimer's Disease. Journal of Alzheimer's disease, 2017. 56(4): p. 1419–1428.
36. de Rodez Benavent SA, et al., Fatigue and cognition: Pupillary responses to problem-solving in early multiple sclerosis patients. Brain and Behavior, 2017. 7(7): p. e00717. [PubMed: 28729927]
37. Devos H, et al., Cognitive performance and cognitive workload in multiple sclerosis: Two different constructs of cognitive functioning? Multiple sclerosis and related disorders, 2019. 38: p. 101505–101505. [PubMed: 31743847]
38. Nee DE, Jahn A, and Brown JW, Prefrontal cortex organization: Dissociating effects of temporal abstraction, relational abstraction, and integration with fMRI. Cereb. Cortex, 2014. 24(9): p. 2377–2387. [PubMed: 23563962]
39. Corballis MC, Left brain, right brain: facts and fantasies. PLoS Biol., 2014. 12(1): p. e1001767. [PubMed: 24465175]
40. Loranger AW, et al., Intellectual impairment in Parkinson's syndrome. Brain, 1972. 95(2): p. 405–412. [PubMed: 4655035]
41. Marinus J, et al., Assessment of cognition in Parkinson's disease. Neurology, 2003. 61(9): p. 1222–8. [PubMed: 14610124]
42. Kirk RE, The importance of effect magnitude. Handbook of research methods in experimental psychology: p. 83–105.
43. Schäfer T and Schwarz MA, The Meaningfulness of Effect Sizes in Psychological Research: Differences Between Sub-Disciplines and the Impact of Potential Biases. Frontiers in Psychology, 2019. 10(813).
44. Stuerenburg HJ and Schoser BGH, Acute overdosage and intoxication with carbidopa/levodopa can be detected in the subacute stage by measurement of 3-o-methyldopa. J. Neuro. Neurosurg. Psychiatry, 1999. 67(1): p. 122–123.
45. Weintraub MI, Gaasterland D, and Van Woert MH, Pupillary effects of levodopa therapy. N. Engl. J. Med, 1970. 283(3): p. 120–123. [PubMed: 5423148]
46. Cools R, Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. Neuroscience & Biobehavioral Reviews, 2006. 30(1): p. 1–23. [PubMed: 15935475]
47. Molloy SA, et al., Effect of levodopa on cognitive function in Parkinson's disease with and without dementia and dementia with Lewy bodies. Journal of neurology, neurosurgery, and psychiatry, 2006. 77(12): p. 1323–1328.
48. Poletti M and Bonuccelli U, Acute and chronic cognitive effects of levodopa and dopamine agonists on patients with Parkinson’s disease: a review. Therapeutic Advances in Psychopharmacology, 2013. 3(2): p. 101–113. [PubMed: 24167681]

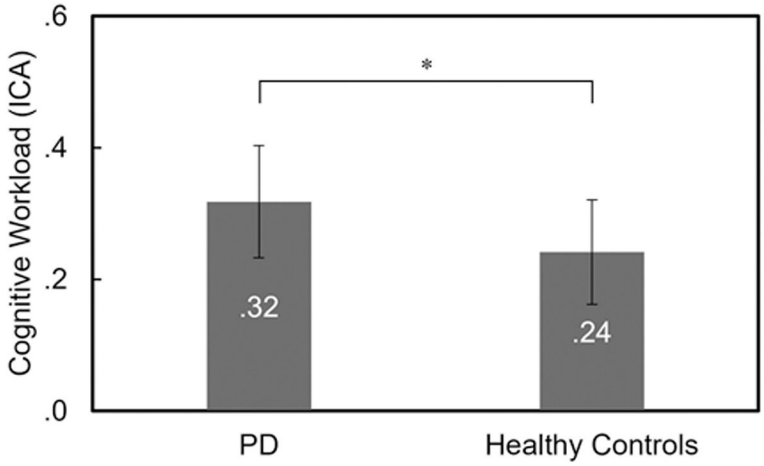

Figure 1.
Comparison of amount of cognitive workload among the groups based on ICA data from the right eye. ICA = Index of Cognitive Activity; PD = Parkinson's disease.

Table 1

Demographic and clinical characteristics

Variable	PD (n = 19)	Healthy controls (n = 10)	p-value
Age (years)	66.6 ± 8.9	65.3 ± 7.3	.70
Sex (female/male, n)	5/14	7/3	.03 *
Education (years)	17.5 ± 2.8	17.3 ± 3.9	.84
Handedness (R/L, n)	19/0	10/0	N/A
Cognitive status (MoCA score)	27.3 ± 1.4	27.6 ± 2.3	.69
Disease duration (years)	5.7 ± 3.0	N/A	N/A
MDS-UPDRS II	11.5 ± 6.8	N/A	N/A
MDS-UPDRS III	30.9 ± 11.5	N/A	N/A
Modified H & Y scale	2.1 ± .4	N/A	N/A
LED	749.3 ± 370.9	N/A	N/A
SCOPA-AUT	15.5 ± 6.6	N/A	N/A

Note: PD = Parkinson's disease; R/L = Right/Left; MoCA = Montreal Cognitive Assessment; MDS-UPDRS = Movement Disorder Society Unified Parkinson Disease Rating Scale; H &Y = Hoehn and Yahr; LED = Levodopa Equivalent Dose; SCOPA-AUT = Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; N/A = Not Applicable. The results are presented as mean ± standard deviation except for the sex variable.

* Significant value ($p < .05$).