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Color discrimination errors associate with axial motor impairments in Parkinson's disease

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Abbreviations: dihydrotetrabenazine, DTBZ; FMT, Farnsworth-Munsell 100 Hue Color Vision Test; LED, Levodopa Equivalent Dose; PD, Parkinson disease; positron emission

tomography, PET; TUG, timed up and go test; Movement Disorders Society Revised Unified Parkinson's Disease Rating Scale, MDS-UPDRS; VMAT2, vesicular monoamine transporter type 2.

Key Words: Color discrimination, dopamine, gait, Parkinson disease, PET, postural instability, retina, visual.

Running title: Visual functions and motor impairments in PD.

Abstract:

Background: Visual function deficits are more common in imbalance-predominant compared to tremor-predominant PD suggesting a pathophysiological role of impaired visual functions in axial motor impairments.

Objective: To investigate the relationship between changes in color discrimination and motor impairments in PD while accounting for cognitive or other confounder factors.

Methods: PD subjects (n=49, age 66.7±8.3 years; Hoehn & Yahr stage 2.6±0.6) completed color discrimination assessment using the Farnsworth-Munsell 100 Hue Color Vision Test, neuropsychological, motor assessments and [^{11}C]dihydrotetrabenazine vesicular monoamine transporter type 2 PET imaging. MDS-UPDRS sub-scores for cardinal motor features were computed. Timed up and go mobility and walking tests were assessed in 48 subjects.

Results: Bivariate correlation coefficients between color discrimination and motor variables were significant only for the Timed up and go (R_S=0.44, P=0.0018) and the MDS-UPDRS axial motor scores (R_S=0.38, P=0.0068). Multiple regression confounder analysis using the Timed up and go as outcome parameter showed a significant total model ($F_{(5,43)}$= 7.3, P<0.0001) with significant regressor effects for color discrimination (standardized β=0.32, t=2.6, P=0.012), global cognitive Z-score (β=-0.33, t=-2.5, P=0.018), duration of disease (β=0.26, t=1.8, P=0.038), but not for age or striatal dopaminergic binding. The color discrimination test was also a significant independent

regressor in the MDS-UPDRS axial motor model (standardized β=0.29, t=2.4, P=0.022; total model $t_{(5,43)}$= 6.4, P=0.0002).

Conclusions: Color discrimination errors associate with axial motor features in PD independent of cognitive deficits, nigrostriatal dopaminergic denervation, and other confounder variables. These findings may reflect shared pathophysiology between color discrimination visual impairments and axial motor burden in PD.

Introduction

Visual function deficits, including color discrimination changes, are common non-motor features in Parkinson's disease (PD) [1, 2]. Visual deficits in PD have been explained by retinal nerve fiber layer thinning, retinal dopaminergic denervation, and central nervous system pathologies [2-4]. Performance on a color discrimination task associates with cognitive deterioration in PD, in particular, executive function and visuospatial deficits [5]. Such cognitive deficits correlate also with postural instability gait difficulties (PIGD) motor features in PD [6, 7] through a common posterior visual network pathway. Interestingly, Bertrand *et al*. found that color discrimination errors in PD were associated with right (posterior) hemispheric white matter changes [5]. As right hemispheric connectivity changes, including the posterior visual network, have been associated with changes in gait in PD [8], we hypothesized that changes in color discrimination may also associate with worse axial motor features in PD.

The purpose of this study was to investigate the relationship between performance on a color discrimination task and cardinal motor impairments of PD while controlling for the degree of cognitive impairment and other potential confounder variables, such as degree of nigrostriatal dopaminergic deficits, age, and duration of motor disease.

Subject and Methods

Subjects and clinical test battery

PD patients, n=49 (M35/F15); mean age 66.7±8.3 (51-84) years old; duration of motor disease 6.7±4.6 (0.5-20) years; Hoehn & Yahr (HY) stage 2.6±0.6 (1-5); Montreal cognitive assessment (MOCA) score 26.4±2.2 (20-30), underwent color discrimination visual testing using the Farnsworth-Munsell 100 Hue Test (FMT) with binocular vision and identical room illumination [9]. The patient population consisted of a subset of subjects who completed the FMT as part of a larger study on non-motor symptoms in PD (ClinicalTrials.gov Identifier NCT01565473). The FMT assesses color discrimination and requires that patients place scrambled colored disks with varying order by hue. The main outcome parameter of this test was the FMT total error rate, with higher error rates reflecting greater color discrimination deficiency. We set no time limit for the FMT completion, as recommended for patients with neurological disorders [10]. Subjects with history of color blindness were excluded. A single patient had a history of benign visual hallucinations but no active hallucinations at the time of the study. Assessment of color discrimination was performed by a technician who was not involved in the analysis of the study.

Subjects met the UK PD Society Brain Bank clinical diagnostic criteria [11]. Abnormal striatal dopaminergic ([^{11}C]DTBZ) PET findings were consistent with the diagnosis of PD in all subjects. No subjects had a history of a large artery stroke or other significant intracranial disease. Most subjects had moderate severity of disease: one subject in modified HY stage 1, 11 in stage 2, 19 in stage 2.5, 15 in stage 3, 2 in stage 4, and 1 in stage 5. The median HY stage was 2.5. Although patients in HY stage 4 typically use a walking aid we examined them without the aid while providing very close supervision at arm length during the gait and balance tests. One subject who was unable to walk independently (HY stage 5).

All but two subjects were treated with dopaminergic agents; 23 subjects were taking a combination of dopamine agonist and carbidopa-levodopa medications, 17 were using carbidopa-levodopa alone, and 7 were taking a dopamine agonist alone. Mean levodopa equivalent dose (LED) was 660±491 mg [12]. Subjects on dopaminergic drugs underwent the MDS-UPDRS motor examination and gait assessments in the morning

after withholding dopaminergic drugs overnight. FMT was performed on usual dopaminergic drugs and with best corrected vision. Patients on anti-cholinergic or cholinesterase inhibitor drugs were not eligible for the study. Patients with contra-indication for MR imaging or claustrophobia were also not eligible for the study.

Motor testing was assessed using the MDS-UPDRS, mean total motor score (Part III) was 33.3±13.6 (13-72). Summed sub-scores for the cardinal motor features were computed: tremor (MDS-UPDRS items 3.15, 3.16, 3.17), rigidity (item 3.3), bradykinesia (items 3.4, 3.5, 3.6, 3.7, 3.8 & 3.14) and postural and mobility domains (items 2.12, 2.13, 3.10, 3.11, 3.12 & 3.13). During the same session, a measurement of the patient's 8.5-meter walking time, and timed up and go test (TUG) [13] were also performed in all subjects, except for one subject who was unable to walk independently. Each subject underwent a detailed cognitive examination following an approach previously reported to characterize cognitive impairment in PD [14]. These tests included measures of verbal memory: California Verbal Learning Test [15]; executive/reasoning functions: WAIS III Picture Arrangement test [16], and Delis-Kaplan Executive Function System Sorting Test [17]; attention/psychomotor speed as absolute time on the Stroop 1 test [18]; and visuospatial function: Benton Judgment of Line Orientation test [19]. A global composite cognitive Z-score was calculated based on normative data.

This study was approved by the Institutional Review Boards of the University of Michigan and VA Ann Arbor Healthcare System. Written informed consent was obtained from all subjects prior to any research procedures.

Imaging techniques

Subjects underwent brain MRI and [^{11}C]DTBZ vesicular monoamine transporter type 2 (VMAT2) PET imaging. [^{11}C]DTBZ PET imaging was performed in the morning after withholding dopaminergic medications overnight. MRI was performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands) and PET imaging was performed in 3D imaging mode with an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN) [20]. The imaging studies were generally completed within 1-2 days of the clinical and neuropsychological testing sessions.

[^{11}C]DTBZ was prepared as described previously [21]. Dynamic PET scanning was performed using an intra-venous bolus/infusion protocol for [^{11}C]DTBZ (15 mCi) in 60 minutes [22].

Analysis

All image frames were spatially coregistered within subjects with a rigid-body transformation to reduce the effects of subject motion during the imaging session [23]. Interactive Data Language image analysis software (Harris Geospatial Solutions, Broomfield, CO) was used to manually trace volumes of interest (VOI) on MRI images to include the caudate nucleus and putamen of each hemisphere. VOIs were bilaterally averaged. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal on the MRI scan [20].

[^{11}C]DTBZ distribution volume ratios (DVR) were estimated using the Logan plot graphical analysis method with the striatal time activity curves as the input function and the total neocortex as reference tissue (a region low in VMAT2 binding sites), with the assumption that the non-displaceable distribution is uniform across the brain at equilibrium [22].

Bivariate Spearman rank correlation coefficients were computed for the relationship between color discrimination errors and the motor and cognitive variables. Rank-normalized motor and color discrimination variables were used for multiple regression analysis to perform a confounder analysis of main effects, using nigrostriatal VMAT2 binding, HY motor disease stage, global cognitive Z-score, age, and duration of motor disease as covariates. Analyses were performed using SAS version 9.3 (SAS institute, Cary, North Carolina). Holm-Bonferroni correction for multiple testing was applied.

Results

Main findings

Table 1 provides a summary of the clinical cognitive, motor, and VMAT2 imaging findings.

Higher FMT error scores associated with higher total MDS-UPDRS motor scores (R_S=0.39, P=0.006) and lower global cognitive Z-scores (R=-0.30, P=0.037). Spearman rank correlation coefficients between color discrimination and the UPDRS cardinal domain and mobility sub-scores are listed in Table 2. Findings that remained significant after Holm-Bonferroni correction included the 3-meter TUG (R_S=0.44, P=0.0018) and the MDS-UPDRS axial motor scores (R_S=0.38, P=0.0068).

Multivariate confounder analysis of main effects

Multiple regression analysis using the rank-normalized TUG as outcome parameter showed a significant model ($F_{(5,43)}$= 7.3, P<0.0001) with significant regressor effects for FMT (standardized β=0.32, t=2.6, P=0.012), global cognitive Z-score (β=-0.33, t=-2.5, P=0.018), duration of disease (β=0.26, t=1.8, P=0.038), but not for age (β=0.11, t=0.8, P=0.42) or striatal VMAT2 binding (β=-0.15, t=-1.3, P=0.22). Figure 1 shows a scatter plot of FMT error rate and the covariate-adjusted TUG times.

Multiple regression analysis using the rank-normalized MDS-UPDRS axial motor scores as outcome parameter showed a significant model ($t_{(5,43)}$= 6.4, P=0.0002) with significant regressor effects for FMT error rate (standardized β=0.29, t=2.4, P=0.022), age (β=0.33, t=2.5, P=0.018), but not for duration of disease (β=0.24, t=1.9, P=0.07), global cognitive Z-score (β=-0.04, t=-0.3, P=0.77) or striatal VMAT2 binding (β=-0.18, t=-1.5, P=0.15).

Post hoc analysis: Effects of dopaminergic medications

As dopaminergic medications may affect vision we performed a *post hoc* regression analysis entering the LED in the TUG model, which confirmed the significant regressor effect for FMT error rate (standardized β=0.32, t=2.6, P=0.013; model

$F_{(6,41)}$=6.1, P=0.0001) independent from LED (β=0.18, t=1.2, p=0.23), and the other variables. A *post hoc* regression analysis entering LED in the MDS-UPDRS axial motor model showed similar findings: FMT error rate (standardized β=0.26, t=2.1, P=0.042; model $F_{(6,41)}$=6.2, P=0.0001) independent from LED (β=0.23, t=1.6, p=0.12), and the other variables.

Discussion

Our findings show that color discrimination errors associate with worse performance on the 3-meter TUG test and with more severe axial motor impairments in PD. There were non-significant trends of color discrimination performance with bradykinesia scores and straight walking times. There were no significant associations between color discrimination scores and rigidity or tremor motor features. Although there was a significant correlation between impaired color discrimination and more severe cognitive impairment [5], our multivariate analysis showed evidence of a selective association between color discrimination errors and axial motor impairments independent from the degree of cognitive impairment, nigrostriatal dopaminergic denervation or other covariates. These findings may reflect shared pathophysiology between color discrimination visual changes and axial motor features in PD.

We previously reported the lack of significant correlation between Rabin contrast sensitivity scores and UPDRS motor scores in PD [24]. Therefore, our present findings of a significant association between color discrimination errors and axial motor features suggest that retinal changes alone may not be the principal drivers of the association between color discrimination changes and axial motor features. This inference is also supported by recent findings that showed no significant correlation between FMT performance and photoreceptor thinning in PD [25].

Prior work reported strong correlations between FMT error rate and impaired performance on the grooved pegboard test, a visuomotor test that correlates well with overall motor dysfunction in PD. Visuospatial function deficits have been specifically

associated with axial motor impairments in PD [6]. Quick visuomotor adjustments are critical for safe ambulation to prevent falls and it is plausible that central and/or oculomotor mechanisms involved with color discrimination changes may contribute to axial motor or mobility dysfunctions in PD [26, 27]. It may need to be questioned whether the FMT, at least in part, is a visuomotor test requiring visual search functions. The FMT requires the use frequent short-range saccadic eye movements or fine oculomotor adjustments to allow more precise comparison of the hue of the different color disks that are spatially aligned on the test board and need to be reordered. It is possible that impairments of speed or accuracy of these fine oculomotor functions or related visual search mechanisms in PD may potentially contribute to more FMT errors. The exploration of the visual surround may be a common feature between the FMT and actual visual scanning of the environment for safe ambulation for patients with PD. Interestingly, our study findings showed that color discrimination changes were a more robust predictor of longer time to complete the TUG compared to straight hallway walking, a task that may require less complex visual exploration of the environment.

Visuomotor control changes in PD likely include visual cortical dysfunctions that may correlate with motor impairments in PD. We previously showed a relationship between asymmetry in finger tapping and visual cortical glucose hypometabolism in PD [28]. Bertrand *et al*. found that changes in color discrimination in PD were associated with right (posterior) hemispheric white matter changes, which may be indicative of disruption of visual networks [5, 8].

Performance on the FMT may also be affected by the effects of aging [29]. However, our primary findings were independent from the effect of age. Furthermore, the FMT is a cognitively demanding task but our findings were independent from cognitive performance scores in our study.

This study has limitations, including absence of a systematic ophthalmological or retinal assessment. None of our subjects, however, had a history of color blindness, diplopia, or known glaucoma, and all subjects had optimal (corrected) visual acuity. Our study is cross-sectional nature and no inferences regarding causation can be made. Another limitation of the study is the lack of genetic testing for the glucocerebrosidase (GBA) gene as patients with PD with GBA mutations have more prominent progression

of axial motor and non-motor impairments [30].

Color discrimination testing has been shown to be a predictor of PD in patients with dream enactment behavior [31]. Within the setting of symptomatic PD, color discrimination testing may also have the potential value as a screening tool to identify or predict more severe patterns of disease progression in PD. The cross-sectional nature of our study does not allow evaluation of this hypothesis. A longitudinal study will be necessary to determine if color discrimination evaluations could be used to predict the transition to more severe motor subtypes of PD.

We conclude that color discrimination errors selectively associate with axial motor features and mobility functions in PD. Our findings are not explained by a cognitive confounder effect or the degree of nigrostriatal degeneration, age, dopaminergic medication dose, or duration of disease. Assessment of visual functions, in particular color discrimination, may be important for future mobility studies in PD.

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Author roles:

1. Research Project: A. Conception, B. Organization, C. Execution
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique
3. Manuscript: A. Writing of the First Draft, B. Review and Critique

NB: 1A, 1B, 1C, 2A, 2B, 3A.
JH: 2B, 2C, 3A, 3B
VK: 2C, 3B
RA: 2C, 3B
KF: 1A, 1B, 1C, 2C, 3B
MM: 1B, 1C, 2C, 3B

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Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Legend

Figure 1: Scatter plot of the distribution of FMT color discrimination error scores and TUG times (cov. adj.: adjusted for co-variates of global cognitive Z-score, striatal VMAT2 binding, duration of disease, and age). Rank values are ordered from less to more severely abnormal scores on the test measures.

Table 1.

Summary of color discrimination, cognitive, motor, and VMAT2 imaging findings. Abbreviations: dihydrotetrabenazine, DTBZ; FMT, Farnsworth-Munsell 100 Hue Color Vision Test; LED, Levodopa equivalent dose; MCI, mild cognitive impairment; TUG, timed up and go test; Movement Disorders Society Revised Unified Parkinson's Disease Rating Scale, MDS-UPDRS; VMAT2, vesicular monoamine transporter type 2. MDS-UPDRS, TUG and gait testing was performed in the dopaminergic medication 'off' state.

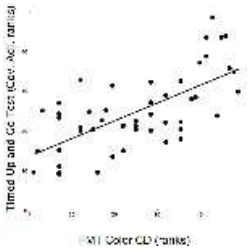
	Mean value (standard deviation / range)
Global cognitive Z-score	-0.27±0.72 (range -2.39-0.98)
MCI	17/49 (34.7%)
FMT errors	82.0±50.1 (range 4-228)
LED	660.3±490.8 (0-2,190)
Striatal [^{11}C]DTBZ VMAT2 distribution volume ratio	1.96±0.31 (range 1.38-3.03)
MDS-UPDRS part III (motor) score	33.7±13.0 (range 11-72)
MDS-UPDRS axial motor core	6.0±4.5 (range 1-24)
TUG (seconds; n=48)	9.1±2.8 (range 4.4-18.8)
8.5 meter walking test (seconds; n=48)	8.2±2.2 (range 5.1-17.2)

Table 2.

Spearman rank correlation coefficients between color discrimination and the UPDRS cardinal motor domain and timed mobility scores. Findings that remained significant after Holm-Bonferroni correction are depicted in bold font. MDS-UPDRS, Timed Up and Go and gait testing was performed in the dopaminergic medication 'off' state.

	Correlation coefficient with color discrimination scores
MDS-UPDRS domain sub-scores (n=49)	
Rigidity	R_S=0.22 (P=0.13)
Tremor	R_S=-0.06 (P=0.68)
Bradykinesia	R_S=0.35 (P=0.013)
Axial	**R_S=0.38 (P=0.0068)***
Timed mobility scores (n=48)	
3-meter Timed Up and Go	**R_S=0.44 (P=0.0018)***
8.5 meter walking test	R_S=0.32 (P=0.027)

* Significant after Holm-Bonferroni correction



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