Dopaminergic Basis of Spatial Deficits in Early Parkinson’s Disease

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Abstract

Dopaminergic mechanisms regulating cognitive and motor control were evaluated comparing visuoperceptual and perceptuomotor functions in Parkinson’s disease (PD). The performance of PD patients (n = 40) was contrasted with healthy controls (n = 42) across two separate visits (on and off dopaminergic medications) on computerized tasks of perception and aiming to a target at variable stimulus lengths (4, 8, 12 cm). Novel visuoperceptual tasks of length equivalence and width interval estimations without motor demands were compared with tasks estimating spatial deviation in movement termination. The findings support the presence of spatial deficits in early PD, more pronounced with increased discrimination difficulty, and with shorter stimulus lengths of 4 cm for both visuoperceptual and perceptuomotor functions. Dopaminergic medication had an adverse impact on visuoperceptual accuracy in particular for length equivalence estimations, in contrast with dopaminergic modulation of perceptuomotor functions that reduced angular displacements toward the target. The differential outcomes for spatial accuracy in perception versus movement termination in PD are consistent with involvement of the direct pathway and models of progressive loss of dopamine through corticostriatal loops. Future research should develop validated and sensitive standardized tests of perception and explore dopaminergic selective deficits in PD to optimize medication titration for motor and cognitive symptoms of the disease.

Key words: dopaminergic modulation, movement velocity, Parkinson Disease, spatial accuracy, visuoperceptual

Introduction

Parkinson’s disease (PD) is characterized by cardinal motor features of rigidity, bradykinesia, resting tremor, and postural instability (Jankovic 2008). In addition to the cardinal features of PD, there are other motor features of the disease that can aid in diagnostic accuracy such as freezing of gait, hypometria in aiming movements, and micrographia in writing and drawing (Heremans et al. 2015; Heremans et al. 2016; Thomas et al. 2017). Cognitive, motor, and limbic regions of the frontal cortex project topographically to the basal ganglia and thalamus, and have been characterized by segregated basal-ganglia-thalamocortical circuits (Middleton and Strick 2000). However, the neural mechanisms and cognitive-motor aspects underlying characteristic deficits in PD remain unclear (Hanakawa et al. 2017).

The role of dopaminergic modulation in motor control, implicit learning, and attention/executive functions has been...
extensively investigated in PD. Despite the focused research in this area, heterogeneity in PD presentation has challenged reconciliation of dopaminergic versus nondopaminergic deficits (Kish et al. 1988; Mattis et al. 2011). Other methodological factors can also complicate interpretation of contradictory results across studies such as unclear segregation of motor and cognitive task demands, and lack of consideration of how disease heterogeneity including dopaminergic asymmetries and disease progression impacts study findings. The complex role of dopamine in behavior and differential impact on subcomponent processes make it critical to discern precisely how dopamine regulates motor and cognitive control through careful development of paradigms designed to segregate task demands (Cools et al. 2001; Lee et al. 2002; Elsinger and Rosenbaum 2003; Lewis et al. 2007; Hanna-Pladdy and Heilman 2010; Macdonald and Monchi 2011; Ehgoetz Martens et al. 2013; Hanakawa et al. 2017; Merritt et al. 2017). Many PD investigations have focused on striatal dysfunction and dopaminergic depletion as the basis of clinical features of the disease. Because the clinical deficits cannot be exclusively explained by basal ganglia dysfunction and dopaminergic depletion alone, it is important to consider extranigral involvement in the full constellation of disease heterogeneity.

Investigative studies of dopaminergic modulation have demonstrated improvement in motor symptoms, but differential effect on cognition depending on the specific operations studied with a range of medication effects documented (improvement, no effect, or decline) (Lange et al. 1992; Jubault et al. 2009; Espay et al. 2011; Macdonald and Monchi 2011; Miah et al. 2012; Mongeon et al. 2013). Theoretically, this reflects progressive involvement of depleted dopaminergic circuits with early involvement of the dorsal striatum mediating motor functions, followed by depletion of the ventral striatum modulating cognitive operations that are more apparent later in the disease process (Cools 2006; Macdonald and Monchi 2011). Historically, degeneration of dopaminergic neurons of the dorsal striatal projections including the posterior putamen has been considered in the onset of motor symptoms, while it has remained unclear how degeneration relates to variable cognitive deficits in PD (Middleton and Strick 2000).

PD patients commonly experience cognitive and perceptual declines, although they may present variably in individual patients and may not be as distinctive as motor features of the disease. The presence of visual and visuoperceptual deficits in PD has been well documented, but the neural and behavioral underpinnings of these deficits remain elusive (Davidsdottir et al. 2005; Bak et al. 2006; Archibald et al. 2011; Bernardinis et al. 2018). More recent investigations have clarified the dopaminergic basis of retinal and other neurodegenerative pathology in PD related to visual alterations and reduced contrast sensitivity (Popova 1995; Lee et al. 2001a; Indrieri et al. 2020; Marrocco et al. 2020; Ortuno-Lizaran et al. 2020; Diaz-Santos et al. 2021). Also, visual acuity and contrast sensitivity deficits in visuoperceptual dysfunction or visual hallucinations are possible (Laudate et al. 2013; Diaz-Santos et al. 2021). In addition to dopaminergic depletion, other etiologies have been considered underlying these retinal changes including mitochondrial alterations and synucleinopathy all of which have been predictive of disease progression (Lee et al. 2001a; La Morgia et al. 2013; Jimenez et al. 2014; Satue et al. 2014; Li et al. 2015; Yang et al. 2016; Tugcu et al. 2020).

Separate from consideration of visual processing and proprioceptive deficits which are likely mediated by differential neural mechanisms, there is a need to further characterize the relationship between visuospatial or visuoperceptual deficits in PD and how they influence movement deficits. Visuoperceptual and visuospatial disorientation deficits in PD have been well documented and appear to correlate to disease progression (Boiler et al. 1984; Popova 1995; Davidsdottir et al. 2008; Indrieri et al. 2020; Marrocco et al. 2020; Ortuno-Lizaran et al. 2020). Furthermore, visuoperceptual deficits have been associated with visual hallucinations both of which are predictive of disease progression, but appear to be unrelated to changes in visual acuity (Gallagher et al. 2011). Specifically, pathological findings in PD patients with and without visual hallucinations did not reveal a significant association to ocular pathology. Conversely, patients with persistent visual hallucinations in PD revealed higher cortical and subcortical Lewy body counts in brain regions mediating executive and visuoperceptual functions (i.e., middle frontal, middle temporal, and transentorial and anterior cingulate cortices but not parietal cortex), therefore, there is a need to consider visuoperceptual functions related to dopaminergic basis and other disease-related characteristics, and clarify the connections between the basal ganglia and cortical regions such as prefrontal and parietal cortex (Middleton and Strick 2000, 2002; Schendan et al. 2009; Gallagher et al. 2011).

It is conceivable that hypometric movements and freezing of gait could be explained by problematic sensory and/or proprioceptive input guiding movement navigation modulated by dopamine (Ehgoetz Martens et al. 2013; Vitale et al. 2016). Accurate movement generation requires dynamic position updating beginning at the initiation of online positions and extending to visual tracking of path displacement relative to the target (Richards et al. 1993; Durgin et al. 2005b). Many previous investigations have relied on visuomotor adaptation and motor learning, thus, the distinct motor disorder may be more readily apparent than the visuoperceptual disorder (Mongan et al. 2013; Gama et al. 2014; Garcia-Diaz et al. 2018). This study aimed to evaluate dopaminergic modulation in an attempt to disambiguate motor and cognitive task demands, and clarify the impact of selective deficits in spatial disorientation on movement accuracy in PD. Variable outcomes regarding perceptuomotor deficits could reflect spatial selective deficits, and therefore, this study controlled for spatial presentation in all 4 quadrants because of evidence that variable orientation in PD and directional attentional bias may be present reflecting perceptuomotor asymmetries related to patterns of dopaminergic depletion (Lee et al. 2001a, 2001b, 2002; Harris et al. 2003; Milton et al. 2004; Wright et al. 2007). To further clarify the impact of perceptual impairments on movement, we created a model designed to evaluate variable distance estimations on spatial and movement accuracy at the same time selecting shorter distances in an attempt to restrict attentional demands modulated by dopamine (Ebersbach et al. 1996; Lee et al. 2002; Costa et al. 2003; Harris et al. 2003; Ehgoetz Martens et al. 2013).

The current study evaluated the role of dopamine in visuoperceptual accuracy versus spatial aspects of movement in idiopathic PD compared to age-matched healthy controls. In order to isolate dopaminergic medication effects on performance, subjects engaged in the experiment twice on and off medications counterbalanced across visits 1 and 2 (off and off for controls) with an 8-week interval between visits. Subjects were examined on computerized tasks of visuoperceptual judgments in vertical and horizontal orientations that were contrasted with spatial accuracy in cursor movement termination relative to targets in different locations. Experimental tasks were designed to segregate spatial accuracy in perception versus aiming movements of variable stimulus lengths (4, 8, and 12 cm lines).
Materials and Methods

Participants

A total of 40 individuals with PD and 42 age and education matched healthy controls (ages range 50–75) consented for participation in this study. There was no significant difference in age between PD patients (mean age = 66 years) and controls (see Table 1; mean age = 66.9 years).

Subjects were right-handed defined as a minimum score of 60 on the Edinburgh Handedness Inventory (Oldfield 1971). All subjects were initially screened for dementia, and were required to have a minimum score of 27 out of 30 on the Mini Mental Status Examination (Folstein et al. 1975), and no dementia was determined by a comprehensive neuropsychological evaluation (Table 1). Detailed neuropsychological assessment included alternate forms of The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al. 1998) for each visit, attention and working memory including subtests from the Wechsler Intelligence Scale—Fourth Edition (WAIS-IV), motor speed (finger tapping) and sensorimotor (grooved pegboard) integration (Reitan and Wolfson 1993; Wechsler 2008). Data for this sample have been previously published evaluating cognitive profiles and side of motor onset differences on and off medication states (Hanna-Pladdy et al. 2013; Hanna-Pladdy et al. 2015). Patients did not exhibit major psychiatric disturbance (including current alcohol or substance abuse), or history of significant ocular or neurologic disorder. Subjects were nondepressed based on screening with the Beck Depression Inventory-II using an adjusted cutoff of 18 for PD patients as well as patient interview (Visser et al. 2006). Depressive and anxiety scores for PD patients and healthy controls are provided in Table 1. Although enrolled participants were screened for current anxiety and depression, PD patients endorsed higher levels of both anxiety and depression consistent with nonmotor features of PD. However, they did not differ in self-reported measures of anxiety or depression between medication states as previously published for this sample (Hanna-Pladdy et al. 2013).

PD patients were evaluated by a movement disorder specialist and identified as having a diagnosis of idiopathic PD based on the United Kingdom PD Society Brain Bank Criteria and absence of dyskinesia based on neurological examination (Hughes et al. 1992). Patients included in the study had mild PD based on a Hoehn and Yahr (H & Y) rating of 2.5 or less and a Unified Parkinson’s Disease Rating Scale (UPDRS) motor score less than or equal to 20, or UPDRS total score less than or equal to 30 in the on-medication state (see Table 1). The groups were matched in terms of male to female ratio per group (control 25/17; PD 27/13) and did not differ in terms of racial/ethnic composition with only 2 ethnic minorities included in the sample. Also, there were no significant differences based on sex for the following variables: age, education, BAI, BDI-II, disease duration, levodopa dose equivalency (LED), or UPDRS values that might impact the results. Details of disease duration and UPDRS motor items by medication state and by side of motor onset were not significant as previously published for this sample in detail (Hanna-Pladdy et al. 2015).

Dominant motor symptoms were derived from left and right motor scores calculated from UPDRS part III items 22–26 resulting in more PD patients with right side motor onset (RMO = 25) relative to left motor onset disease (LMO = 15; Table 1). The disease duration based on date of symptom onset was 5.7 years (SD = 2.7 years) compared with duration since diagnosis which was 3.6 years (SD = 2.5). There was no significant difference between duration between examination and symptom onset duration since diagnosis for either the RMO (mean = 4.52, SD = 2.48; mean = 6.04, SD = 2.81) or LMO groups (mean = 3.6, SD = 2.48 mean = 5.1, SD = 2.50). All patients were prescribed levodopa as well as one of two dopamine agonists (pramipexole 47.5%; ropinirole 52.5%). The levodopa dose equivalency (LED) was calculated and taken with carbidopa that has similar effect and by adding together all LEDs to give the levodopa equivalent daily dose (LEDD mean = 744.4, SD = 360.27). LEDD equivalency for the LMO (mean = 687.5, SD = 428.48) and RMO (mean = 778.5, SD = 317.14) patients were not significantly different even though there was a trend for RMO patients to have higher LEDD equivalency associated with longer disease durations. Patients were asked to withhold all PD-related medications beginning at 5 pm the evening prior to their off medication visit and further doses were withheld until completion of the experiment at the end of their visit. Patients and caregivers were called to document and confirm discontinuation of medication usage prior to the off visit. Medication state was counterbalanced across visits 1 and 2 to account for practice-effects. Patients displayed significantly higher UPDRS total and motor scores (P < 0.0001) in the off medication state relative to the on medication state as previously reported for this sample (Hanna-Pladdy et al. 2013).

PD patients with previous history of deep brain stimulation (DBS) or taking the following medications were excluded from participation in the study: amantadine, monoamine oxidase inhibitors (MAOIs), catechol-O-methyl transferase (COMT), or stimulants. Control participants took fewer medications with only 3 participants receiving pharmacological treatment for depression at the time of the study. Significantly more PD patients (n = 15) were currently being treated for depression and/or anxiety or sleep disturbance. It is noteworthy that 3 of the PD patients were prescribed Xanax which could conceivably result in visual side effects.

Table 1. Means (standard deviations) for demographics and screening measures

| Group | N | M/F ratio | AGE | EDU | MMSE | BAI | BDI-II | UPDRS Total | UPDRS motor |
|-------|---|-----------|-----|-----|------|-----|--------|------------|------------|
| Control | n = 42 | 25/17 | 66.9 (4.6) | 16.3 (1.5) | 29.3 (.84) | 1.2 (1.4) | 3.3 (2.5) | ON 30.5 (11.1); OFF 43.5 (13.3) | ON 18.7 (6.2); OFF 29.4 (8.8) |
| PD | n = 40 | 27/13 | 66.0 (7.7) | 15.3 (2.6) | 28.6 (1.6) | 9.6 (8.3) | 9.5 (6.8) |

Note: M/F, Male/Female Ratio per group; EDU, Education, number of years; MMSE, Mini-Mental Status Examination; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; UPDRS, Unified Parkinson’s Disease Rating Scale; UPDRS Total, Score for all subscales; UPDRS Motor, Score for Section III Motor Subscale; ON, Parkinson Patients in the On-Medication State; OFF, Parkinson Patients in the Off-Medication State (washout of 15 h)
**Design**

A repeated measures model was utilized for the study with dopamine medication state (on, off) as the within-subjects factor and Group (Control, PD) as the between-subjects factor. All subjects received two assessments with an 8-week interval between visits to minimize practice effects. Medication state was counterbalanced across visits 1 and 2 with one-half of the subjects in the on-medication state for visit 1, while the other half of the subjects were in the off-medication state for visit 1, and vice versa.

The study was conducted in accordance with the Declaration of Helsinki criteria and was approved by the Institutional Review Boards of KUMC and Emory University School of Medicine. All the participants gave their written informed consent. Data analyses and write-up were finalized at the University of Maryland School of Medicine.

**General Experimental Procedure**

The experimental setup included a laptop, keyboard, mouse, and adjacent monitor connected to the laptop for the experimenter to control the paradigm and save the generated responses. Participants were evaluated with corrective lenses when applicable, and after screening for vision and perception on a training task requiring demonstration of comprehension as well as spatial accuracy. Subjects were evaluated on tasks segregating cognitive versus motor control of spatial accuracy across two visits with an 8-week interval. The cognitive task required subjects to make visuo perceptual judgments to estimate equivalence of lengths and width intervals in the absence of motor execution demands. The perceptuomotor task evaluated the spatial accuracy in movement termination when visual feedback was provided allowing for adjustments to spatial deviations from the target prior to a final decision of termination placement while aiming for the target. Prior to beginning the experiment, instructions and trial runs were provided to ensure the subject was able to view and perceive the visual display, control the computer, and comprehend the sample training repeated until 100% accuracy.

**Perceptual Discrimination of Length Equivalence and Width Intervals**

Presentation software (Neurobehavioral Systems www.neurobs.com) was utilized to present the perceptual stimuli, and also to collect the response data that were entered by the experimenter following the verbal response of the subject. This was designed to eliminate measurements of slowed motor responses that could potentially confound cognitive task demands. The first perceptual task required the subjects to compare two interval spaces between 3 horizontal lines, and make a determination as to whether the spaces between the lines were the same or different. The second task asked the subjects to evaluate length equivalence estimations of two lines in either a vertical or horizontal orientation, and to determine if they were the same or different (Fig. 1).

Subject responses were entered by the experimenter as same, different, or a miss (failure to respond) following a 4 s stimulus presentation. Each perceptual task contained 24 trials for interval comparisons and 24 trials for length estimations. The trials were randomized for each subject and varied on the basis of 3 stimulus measurements (4 cm, 8 cm, 12 cm) each presented across 4 levels of discrimination difficulty (same, easy, difficult, very difficult).

Shorter stimulus lengths and smaller intervals alternated positions between left and right lines, and top and bottom intervals across trials to account for perceptual asymmetries and vertical and horizontal orientations (Fig. 1A).

**Spatial Displacement from the Target**

Spatial accuracy was acquired from data during a computerized aiming task that quantified deviations from the final cursor position relative to the designated target on the screen. The subjects used their right hand to manipulate a track pointer to create line segments aimed toward the target. The start of the line and the location of target position were labeled and marked with a circle on a 17.2 x 17.2 cm white window on a dark gray screen. They were instructed to as quickly as possible reach the target with the cursor movement by drawing a line segment and accurately aiming for the target, but subjects could adjust lines to improve accuracy prior to ending the trial. Movement trials were presented in both horizontal and vertical orientations and both directions of various target distances (4, 8, 12 cm). The subjects were informed that a cursor would be located at the start position, which was randomized in position based on the orientation and direction relative to the target (Fig. 1B).

Subjects received visual feedback of the cursor movements in real time, and thus line segment orientations and lengths could be readjusted during aiming prior to final position termination relative to the target. Thus, subjects were capable of utilizing visual feedback-based error learning across trials to adjust cursor movements to optimize spatial accuracy prior to making the final decision to fix the final termination position once the desired distance and orientation were achieved. The computer program facilitated the generation of straight lines to eliminate the impact of tremor on the trajectory, and the length and orientation of the segments were determined by changes in exertion of pressure and rotation of the track pointer as opposed to changes in movement amplitude. The lengths of each line segment depended upon the timing of the release of the track pointer following a decision to terminate the line segment while aiming toward the target. Subjects received continuous visual feedback of created line lengths, position, and orientations to allow readjustment of the mouse spatial position (mouse path) prior to ending the trial in the final position (fixed path). Thus, subjects were capable of visual feedback-based error learning. Following adjustment of lines, the subject could make a decision to fix the line once achieving the correct orientation and final termination position with the goal of ending as close to the target as possible. Thus, spatial accuracy reflected both the mouse path trajectory as well as the final fixed line position.

A custom program developed in Matlab (version 7.7, MathWorks, Inc.) collected the time between readings such as the position of the cursor, time between locations, and the endpoint of the line segment generated. The position and time were recorded at 60 Hz while the pointer was in motion. Finally, an output file for each task was created with a time stamp; task ID, line segment length, and mouse track path and velocity (cm/sec) and fixed length (cm) and velocity. Based on the collected data several parameters were extracted reflecting spatial accuracy of the final fixed line segment following movement termination based on spatial deviations from the target position. The absolute spatial deviations from the target were calculated to determine the linear target deviation (cm), as well as angular displacement (radians) from the straight trajectory of the movement. The sign
A. Visuoperceptual (Length Equivalence and Width Interval) Estimations.

| Length Estimation | Width Interval Estimation |
|-------------------|--------------------------|
| Different         | Same                     |
| Same              | Different                |

Figure 1. Sample schematic of visuoperceptual and movement trajectory tasks. (A) Visuoperceptual Cognitive Task: visuoperceptual judgments of vertical line lengths and horizontal width intervals in the absence of motor execution demands. (B) Movement Termination Task: computerized track-pointer generated line segments for movement to a target while moving in either the vertical or horizontal plane.

of the angular displacement (radians) reflected the direction in clockwise (−) and counterclockwise (+) directions.

Results

Multivariate Model for Visuoperceptual Tasks

A multivariate mixed design evaluated within-subject factors for perceptual task (length equivalence, width interval), medication status (on, off medications), stimulus length (4, 8, 12 cm), and between-subject factors of group (Controls, PD).

The multivariate model revealed a significant effect for medication status, $F(1, 80) = 4.2, P < 0.05$, stimulus length, $F(2, 79) = 122.1, P < 0.0001$, and for stimulus length by group, $F(2, 79) = 3.4, P < 0.05$, perceptual task by stimulus length, $F(2, 79) = 75.1, P < 0.0001$, and perceptual task by stimulus length by medication, $F(2, 79) = 3.4, P < 0.05$ interactions. Between-group significance, $F(1, 80) = 9.07, P < 0.005$, revealed lower overall perceptual accuracy for PD patients relative to healthy controls.

Multivariate values for perceptual task, $F(1, 80) = 0.414, P = 0.522$, contrasting accuracy between length and width estimations were not significantly different. The following interactions were also insignificant: perceptual task by group, $F(1, 80) = 1.45, P = 0.231$, medication by group, $F(1, 80) = 0.909, P = 0.343$, perceptual task by medication, $F(1, 80) = 1.12, P = 0.284$, stimulus length by medication, $F(2, 79) = 0.071, P = 0.931$. The other interactions were insignificant for perceptual task by stimulus length by group, $F(2, 79) = 0.165, P = 0.848$, perceptual task by task by medication group, $F(1, 80) = 0.06, P = 0.807$, stimulus length by medication by group, $F(2, 79) = 2.39, P = 0.097$, and perceptual task by stimulus length by medication by group, $F(2, 79) = 0.321, P = 0.727$.

Univariates and Post hoc Analyses for Visuoperceptual Tasks

Univariates and post hoc analyses were conducted and post hoc analyses adjusted with Bonferroni correction to account for multiple comparisons (see Tables 2–3 significant univariate and post hoc values; and Figs. 2A and 2B for means).

Medication Status

Perceptual accuracy differed significantly based on medication status, $F(1, 80) = 4.2, P = 0.043$. There was higher accuracy in the off-medication state relative to the on-medication state (mean difference $= -0.925, P < 0.05$). This contrast should be interpreted considering counterbalanced on and off medication
Table 2. Results for visuoperceptual (length, width) tasks and discrimination difficulty

2A. Visuoperceptual estimations

| Length and width accuracy (percent correct) | F     | Sig.  | Partial Eta² |
|--------------------------------------------|-------|-------|--------------|
| **Within-subject effects**                 |       |       |              |
| Perceptual Task                            |       |       |              |
| Medication                                 |       |       |              |
| Length-Stimulus                            |       |       |              |
| Spatial deviations On < Off                | 4.2   | .043* | .05          |
| 4 cm < 8 cm, 12 cm                         | 4.14  | .522  | .005         |
| 8 cm < 12 cm                               | 152.4 | .0001 *** | .66         |
| **Length-Stimulus × Group**                |       |       |              |
| 4 cm [PD < Controls]                       | 4.03  | .02*  | .05          |
| 8 cm [PD < Controls]                       |       |       |              |
| 12 cm [PD vs Controls]                     |       |       |              |
| **Perceptual Task × Group**                |       |       |              |
| Length [PD < Controls]                     | 1.46  | .231  | .02          |
| Width [PD < Controls]                      |       |       |              |
| **Perceptual Task × Length-Stimulus**      |       |       |              |
| Length × Width [4 cm]                      | 112.4 | .0001*** | .58         |
| Length > Width [8 cm and 12 cm]            |       |       |              |
| **Task-Perceptual × Length × Medication**  |       |       |              |
| Length On and Off [4 < 8 < 12 cm]          | 4.16  | .017* | .05          |
| Length Off [8 < 12]                        |       |       |              |
| Width On and Off [4 < 8 < 12 cm]           |       |       |              |
| **Between-subject effects**                |       |       |              |
| PD < Controls                              | 9.07  | .003** | .10          |

2B. Visuoperceptual task difficulty

| Same, easy, difficult and very difficult items | F     | Sig.  | Partial Eta² |
|----------------------------------------------|-------|-------|--------------|
| **Within-subject effects**                   |       |       |              |
| Item Difficulty                              | 97.4  | .0001*** | .50         |
| Same < Easy                                  |       |       |              |
| [Easy < Difficult] and [Easy < Very Difficult] |       |       |              |
| Difficult vs Very Difficult                   |       |       |              |
| **Item Difficulty × Group**                  | 4.7   | .003** | .06          |
| Same and Easy [PD vs Controls]               |       |       |              |
| Difficult and very difficult items [PD < Controls] |       |       |              |
| **Item Difficulty × Length**                 | 109.2 | .0001*** | .58         |
| Same and Easy [No differences between lengths] |       |       |              |
| Difficult and Very Difficult [Differences between all lengths] |       |       |              |
| **Between-subject effects**                  | 2.09  | .053  | .03          |
| PD < Controls                                | 1.57  | .002** | .12          |

Notes: Group = Parkinson disease (PD) patients versus Healthy Controls; Stimulus Length and Target Distance = 4, 8, and 12 cm; Medication State = On or Off; Medication for PD, Sham On and Off or Controls. Item Difficulty based on 4 levels of discrimination (same, easy, difficult, very difficult). *P < 0.05. **P < 0.01. ***P < 0.001.

states across visit 1 and 2 to account for expected practice effects and interaction with the on-medication state, as well as the sham condition for the control group. Although the medication by group interaction was not significant, the accuracy for the PD group in the on-medication condition was the lowest, consistent with a detrimental effect of dopaminergic medication on visuoperceptual accuracy (see Table 2A for univariate results).

Stimulus Length

The stimulus length of the perceptual tasks significantly impacted perceptual accuracy, $F(2, 160) = 152.4, P < 0.0001$. Perceptual accuracy on trials with the shortest stimulus line lengths of 4 cm was lower than performance of longer stimulus lengths (8 and 12 cm; −6.4 and −7.6 mean differences, respectively; $P < 0.001$). The perceptual accuracy on trials of 8 cm lines resulted in lower scores than trials displaying 12 cm lines (mean difference = −1.23, $P = 0.01$).

**Stimulus Length by Group Interaction**

There was a significant interaction between group and stimulus length for the perceptual tasks, $F(2, 160) = 4.03, P = 0.02$. PD subjects had lower perceptual accuracy relative to healthy controls on trials of shorter stimulus lengths. Specifically, PD patients had the lowest scores relative to controls on trials presenting 4 cm lines (mean difference = −4.19, $P = 0.001$), followed by 8 cm lines (mean difference = −2.71, $P < 0.02$). However, PD patients did not differ significantly in their percent accuracy relative to controls when the stimulus length was 12 cm (mean difference = −1.53, $P = 0.12$). PD patients produced the highest
Table 3. Results for movement spatial deviations, movement trajectory and velocity

3A. Spatial deviation

| Linear distance (cm) angular deviation (radians) | F   | Sig. | Partial Eta² |
|-----------------------------------------------|-----|------|--------------|
| **Within-subject effects**                    |     |      |              |
| **Spatial task**                              |     |      |              |
| Distance > Angular Deviation                  | 5.25| .025 | .062         |
| **Medication**                                |     |      |              |
| On < Off                                      | 4.27| .042 | .051         |
| **Length-Target Distance**                    |     |      |              |
| 4 cm vs 8 cm                                  | 5.02| .008 | .059         |
| 4 cm vs 4 cm                                  |     |      |              |
| **Medication × Group**                        |     |      |              |
| On medication [Controls vs PD]                | 4.29| .041 | .051         |
| Off medication [Controls < PD]                |     |      |              |
| **Spatial Task × Medication**                 |     |      |              |
| Linear [On vs Off]                            | 4.17| .044 | .050         |
| **Spatial Task × Length-Target Distance**     |     |      |              |
| Linear [4 cm < 12 cm]                         | 6.67| .002 | .077         |
| Angular [4 cm > 8 cm]                         |     |      |              |
| Angular [4 cm > 12 cm]                        |     |      |              |
| **Length-Target Distance × Medication × Group**|     |      |              |
| 4, 8, and 12 cm [Controls, On vs Off]         | 3.07| .049 | .037         |
| 4 cm (PD; On < Off)                           |     |      |              |
| 4, 8, and 12 cm [PD; On vs Off]               |     |      |              |
| **Spatial Task × Length-Target Distance × Medication × Group** |     |      |              |
| PD Angulation deviation, 4 cm                 | 3.57| .03  | .043         |
| 8 cm [Controls × PD]                          |     |      |              |
| Controls Linear distance, 8 and 12 cm         |     |      |              |
| Controls Linear and Angular 4, 8, 12 cm       |     |      |              |
| Between-subject effects                       | 517 | .474 | .006         |

3B. Movement trajectory (Path, Fixed)

| Movement trajectory length (cm) | F   | Sig. | Partial Eta² |
|--------------------------------|-----|------|--------------|
| **Within-subject effects**     |     |      |              |
| **Target Distance**            |     |      |              |
| Path Length [4 and 8 < 12 cm]  | 75.5| .0001 | .485        |
| Fixed Length [4 < 8 < 12 cm]   | 277.5| .0001 | .776        |
| **Target Distance × Group**    |     |      |              |
| Path Length                    | .912| .398  | .011         |
| Fixed Length                   | 6.71 | .011  | .009         |
| 8 cm [Controls < PD]           |     |      |              |
| **Target Distance × Medication**|     |      |              |
| Path Length                    | 3.39| .036  | .041         |
| Fixed Length                   | 1.83 | .163  | .022         |
| 4 and 8 < 12 cm [On and Off]   |     |      |              |
| **Distance × Medication × Group**|     |      |              |
| Path Length                    | .024| .977  | .0001        |
| Fixed Length                   | 3.84 | .024  | .046         |
| 4 cm/Off [Controls < PD]       |     |      |              |
| 8 cm/On [Controls < PD]        |     |      |              |
| Between-subject effects        | 2.18 | .144  | .027         |
| **Movement velocity (cm/s)**   |     |      |              |
| Path Velocity [4 < 8 < 12 cm]  | 591.1| .0001 | .881        |
| Fixed Velocity [4 < 8 < 12 cm] | 443.3| .0001 | .847        |
| **Target Distance × Group**    |     |      |              |
| Path Velocity                  | 5.35| .006  | .063         |
| 12 cm [Controls > PD]          |     |      |              |
| 4 and 8 cm [Controls > PD]     |     |      |              |
| **Distance × Group**           |     |      |              |
| Path Velocity                  | 2.48 | .087  | .030         |
| 4, 8, 12 cm [Controls > PD]    |     |      |              |
| Fixed Velocity                 | 2.18 | .144  | .027         |
| Between-subject effects        | 8.08 | .006  | .092         |

Notes: Group = Parkinson disease (PD) patients versus Healthy Controls; Target Distance = 4, 8, and 12 cm; Medication State = On or Off; Medication for PD, Sham On and Off for Controls; Angular Deviation (radians) from movement termination to the target; Angular deviation in clockwise (−) and counterclockwise (+) directions; Distance from the target (cm) representing linear deviation from movement termination to the target.

* P < 0.05.
** P < 0.01.
*** P < 0.001.
Figure 2. Accuracy for visuoperceptual estimations (width, length) by group and medication status. (A). Length equivalence estimations (percent accuracy) across stimulus lengths. (B). Width interval estimations (percent accuracy) across stimulus lengths.

Table 4. Visuoperceptual results. Pair-wise comparisons with mean differences, standard errors

| Bonferroni comparisons | Mean Diff. | SE | Sig. |
|------------------------|------------|----|------|
| **Perceptual Task × Medication × Group** | | | |
| Line equivalence | | | |
| On PD < Controls | -4.00 | 1.41 | .006** |
| Off PD < Controls | -2.96 | 1.08 | .007** |
| Width interval | | | |
| On PD < Controls | -2.48 | 1.17 | .038* |
| Off PD vs Controls | -1.81 | 1.25 | .154 |
| **Perceptual Task × Length × Medication** | | | |
| Line equivalence | | | |
| 4 cm On vs Off | .909 | 1.14 | .427 |
| 8 cm On vs Off | -2.07 | .769 | .009** |
| 12 cm Off vs On | -3.97 | .597 | .508 |
| Width interval | | | |
| 4 cm On vs Off | -2.33 | .989 | .021* |
| 8 cm On vs Off | -1.34 | .10 | .206 |
| 12 cm On vs Off | -1.53 | 1.05 | .150 |

*p < 0.05.
**p < 0.01.
***p < 0.001.

Notes: Length equivalence estimations were lower for 4 cm lines relative to longer line lengths (P < 0.05). Width interval estimations were not significantly different across stimulus lengths (P = ns). Visuoperceptual accuracy was lower for PD for lengths of 4 and 8 cm (P < 0.05), but not for 12 cm. Visuoperceptual accuracy was lower on-medications relative to off-medications (P < 0.05).

Perceptual accuracy on 12 cm lines (mean_{control} = 89.1; mean_{PD} = 84.9) relative to 8 cm (mean difference = 1.82, P = 0.008) and 4 cm stimulus lines (mean difference = 8.96, P < 0.0001; see Tables 2A and 3; Fig. 3).

Perceptual Task by Stimulus Length Interaction

There was a significant interaction between stimulus length and perceptual task, F(2, 160) = 112.4, P < 0.0001. The test of length equivalence produced significantly different scores
depending on the length of the stimulus (P < 0.0001). Width interval perception was not significantly different in accuracy across the range of stimulus lengths (mean difference between 0.01 and 0.027). Length equivalence accuracy was lower for the trials presenting 4 cm stimuli relative to trials presenting longer stimulus lengths (mean difference 8 vs 12 cm = −12.8; mean difference 12 vs 12 cm = −15.22), and width accuracy perception for 4 cm lines (mean difference = −8.97), P < 0.0001. Conversely, the length equivalence accuracy was higher for 12 cm lines relative to 8 cm lines (mean difference = 2.45), and length equivalence for 8 and 12 cm lines displayed higher accuracy than width equivalence for the longer line lengths (see Table 2A for summary results).

Perceptual Task by Stimulus Length by Medication Interaction

There was a significant 3-way interaction between stimulus lengths, perceptual task, and medication status, F(2, 160) = 4.16, P = 0.017 (Table 2A; Table 3, and Figs. 2A and 2B). Medication effects were evident for 8 cm length equivalence (mean difference = −2.07, P = 0.009), and for 4 cm width interval perception (−2.32 mean difference, P = 0.021) consistent with lower performance in the on-medication state (Table 3). The other stimulus lengths were not significantly different between medication states on-medications versus off-medications states for length equivalence (mean difference 8 vs 12 cm = −0.908; mean difference 12 vs 12 cm = −0.397) or width interval (mean difference 8 vs 12 cm = −1.134; mean difference 12 vs 12 cm = −1.53) perception estimation, but there was a trend for lower performance in the on-medication state for all but one contrast. The interpretation of the medication effect is supported by greater differences between PD patients and controls in the on-medication state for perceptual accuracy, reflecting a medication and not-practice effect influencing accuracy. However, PD patients width interval estimations were not significantly different from controls overall, although PD patients had lower accuracy in the on-medication state (P = 0.038). Length equivalence accuracy revealed that PD patients were lower than controls in both on and off medication states (P = 0.006, and P = 0.007, respectively) although the differences were greater for the on-medication state (reflecting a detrimental effect of medication; see Table 3).

Perceptual Task Difficulty

Analyses were conducted to evaluate how perceptual task difficulty impacted perceptual accuracy across stimulus lengths (4, 8, 12 cm). The multimodal task revealed significance for perceptual difficulty, F(3, 78) = 192.06, P < 0.0001, as well as the following interactions: difficulty level by group, F(3, 78) = 3.64, P = 0.016, difficulty level by perceptual task, F(3, 78) = 36.9, P < 0.0001, and difficulty level by length, F(6, 75) = 54.88, P < 0.0001. Effects for difficulty level by medication, F(3, 78) = 1.01, P = 0.392, difficulty by group by medication, F(3, 78) = 1.09, P = 0.360, difficulty by length by group, F(6, 75) = 1.47, P = 0.201, difficulty by medication by group, F(6, 75) = 1.58, P = 0.164, and difficulty by medication by length by group, F(6, 75) = 1.55, P = 0.172 were not significant. Between-subjects effects were significant for group, F(1, 80) = 10.57, P = 0.002. Significant univariate tests are presented below and in Tables 2B.

Item Difficulty

Difficulty based on 4 levels of perceptual discrimination (same, easy, difficult, very difficult) between stimuli significantly influenced accuracy, F(3, 240) = 97.4, P < 0.0001. The following stimulus difficulty-discrimination results were identified: (i) perceptual items with the same lengths (i.e., equivalent lines) resulted in lower accuracy than easy items (mean differences = −2.56, P < 0.0001), (ii) same items resulted in higher accuracy than difficult items (mean differences = 20.2, P < 0.0001) and very difficult items (mean differences = 219.8, P < 0.0001), (iii) easy items resulted in higher accuracy than difficult items (mean differences = 227.7, P < 0.0001), and finally (iv) difficult and very-difficult items were not significantly different (mean differences = −377, P = ns).

Item Difficulty by Group Interaction

Perceptual performance for healthy controls was significantly higher than PD patients, and the between-group difference was moderated by task difficulty, F(3, 470) = 4.7, P = 0.003. The interaction revealed that PD patients had significantly lower accuracy on difficult and very difficult items (mean difference difficult = −8.85, P = 0.005; mean difference easy = −11.27, P = 0.012) than healthy controls resulting in significantly greater perceptual discrimination. Conversely, the same or easy items were not discriminating between PD patients and controls (mean difference same = −1.46, P = 0.117; mean difference easy = −3.22, P = 0.280).

Item Difficulty by Length Interaction

There was a significant difficulty by length interaction, F(6, 480) = 109.2, P < 0.0001. The interaction revealed significant differences in perceptual estimations across stimulus lengths (4, 8, 12 cm) with lower accuracy for shorter lengths for difficult items (mean difference 4 vs 8 cm = −51.9, P < 0.0001; mean difference 4 vs 12 cm = −55.07, P < 0.0001; mean difference 4 vs 12 cm = −3.08, P < 0.05) and very difficult items (mean difference 4 vs 8 cm = −23.79, P < 0.0001; mean difference 4 vs 12 cm = −34.81, P < 0.0001; mean difference 4 vs 12 cm = −11.01, P < 0.0001). The interaction revealed there were no significant differences in perceptual estimations across stimulus lengths (4, 8, 12 cm) for same (mean difference 4 vs 8 cm = −1.06; mean difference 4 vs 12 cm = −0.774; mean difference 4 vs 12 cm = −0.290) and easy items (mean difference 4 vs 8 cm = −0.312; mean difference 4 vs 12 cm = 0.007; mean difference 4 vs 12 cm = 0.320).

Item Difficulty by Length by Group Interaction

At the univariate level, the difficulty by length by group interaction approached significance, F(6, 480) = 2.09, P = 0.053.

Multivariate Model for Spatial Deviations from the Target

A multivariate mixed design evaluated within-subject factors for spatial deviations to the target (linear distance, angular deviation), medication status (on and off medications), target distance (4, 8, 12 cm), and between-subject factors of group (Controls, PD).

The multivariate model revealed a significant effect for the variables estimating spatial deviation from the target, F(1, 80) = 5.25, P = 0.025, medication status, F(1, 80) = 4.27, P = 0.042, target distance, F(2, 79) = 3.55, P = 0.033, medication by group, F(1, 80) = 4.29, P = 0.041, spatial deviation by target distance, F(2, 79) = 4.92, P < 0.01, and spatial deviation by medication interaction, F(1, 80) = 4.17, P = 0.044 (see Table 4–5 and Fig. 3 for means, univariate tests, and pair-wise comparisons).
The between-group comparison was not significant, F(1, 80) = 0.517, P = 0.47, and spatial deviations to the target were not significantly different between PD patients and healthy controls. Multivariate values for spatial deviations by group, F(1, 80) = 1.17, P = 0.284, target distance by group, F(2, 79) = 0.27, P = 0.764, target distance by medication, F(2, 79) = 1.72, P = 0.187, spatial deviation by target distance by group, F(2, 79) = 0.476, P = 0.623, spatial deviation by medication by group, F(1, 80) = 2.26, P = 0.137, spatial deviation by medication by group, F(2, 79) = 2.29, P = 0.08, spatial deviation by target distance by medication, F(2, 79) = 1.62, P = 0.205, spatial deviation by target distance by medication by group, F(2, 79) = 2.55, P = 0.085 were insignificant.

**Univariate and Post hoc Analyses for Spatial Deviation from the Target**

Univariate and post hoc analyses were conducted and follow-up post hoc analyses were adjusted with Bonferroni correction (see Table 4A for significant univariates).

Spatial Deviations

Spatial accuracy was significantly different between distance to the target relative to angular deviations, F(1, 80) = 5.25, P = 0.025. There were greater deviations for distance from the target relative to angular deviations from the target (mean difference = 0.035, P < 0.025).

Target Distance

Target distance significantly impacted extent of spatial deviation when aiming to the target, F(2, 160) = 5.02, P < 0.01. Spatial deviations on trials with the shortest target distance of 4 cm were significantly greater than the longest target distance (mean difference = 0.05, P = 0.028). Spatial deviations were not significantly different on trials of 4 cm versus 8 cm target distances (mean difference = 0.043, P = 0.08), and 8 cm versus 12 cm target distances (mean difference = 0.007, P = ns) were not significantly different.

Medication Status

Spatial deviations differed significantly based on medication status, F(1, 80) = 4.27, P < 0.05. Spatial deviations were reduced (i.e., accuracy in spatial aiming improved) in the on-medications state relative to the off-medications state (mean difference = 0.029, P < 0.05).

Medication by Group

There was a significant group by medication interaction, F(1, 80) = 4.29, P < 0.05. The interaction revealed that PD patients and healthy controls did not differ in spatial deviation in the on-medications state (mean difference = −0.019, P = 0.402), but PD patients displayed greater spatial deviations than healthy controls in the off-medications state (mean difference = −0.04, P = 0.029). Spatial deviations were reduced in the on-medications relative to the off-medications state only for the PD patients (P < 0.05).

Spatial Deviation by Medication Interaction

There was a significant medication by spatial deviation interaction, F(1, 80) = 4.17, P < 0.05. In the off-medications state, spatial deviations were not significantly different (mean difference = 0.004, P = 0.80), but there was a difference in the on-medications state with distance from the target greater than angular deviation (mean difference = 0.066, P < 0.014). In the on-medications state there was a reduction in angular deviation (mean difference = −0.061, P = 0.04), but not for distance from the target (mean difference = 0.002, P = ns).

**Spatial Deviation by Target Distance Interaction**

There was a significant spatial deviation by target distance interaction, F(2, 160) = 6.68, P < 0.005. Spatial deviations were not significantly different for distance to target versus angular deviations for trials containing 4 cm target distances (mean difference = 0.037, P = 0.29). Distance from the target was significantly greater than angular deviations for 8 and 12 cm target distances (mean difference = 0.063; mean difference = 0.079, P < 0.005).

Linear deviations to the target were significantly smaller for 4 cm relative to 12 cm target distances (mean difference = −0.009, P = 0.016). Angular deviation between 4 and 8 cm (mean difference = 0.093, P = 0.053) and 8 and 12 cm target distances (mean difference = 0.015, P = ns) were not significantly different. Linear deviations to the target were not significantly different between 4 and 8 cm target distances (mean difference = 0.007, P = 0.166), and 8 and 12 cm target distances (mean difference = −0.002, P = ns).

**Target Distance by Medication by Group Interaction**

This interaction was not significant at the multivariate level, but was significant at the univariate level, F(2, 160) = 3.07, P < 0.05. PD patients in the off-medications state displayed greater deviations for 4 cm target distances relative to 8 cm (mean difference = 0.119, P = 0.006) and 12 cm (mean difference = 0.119, P = 0.012). There were no other significant differences for controls or PD patients for this interaction.

**Spatial Deviation by Target Distance by Medication by Group Interaction**

This interaction was not significant at the multivariate level, but was significant at the univariate level, F(2, 160) = 3.57, P = 0.03. Linear deviation was significantly different between PD and controls at both on-medications and off-medications states for both 4 and 8 cm target distances. Controls had less linear deviation relative PD patients for 4 cm target distances (mean difference = 0.026, P = 0.006) and 8 cm target distances (mean difference = 0.022, P = 0.042) in both medication states. For 12 cm target distances, controls had significantly lower linear deviation relative to PD patients only for the off-medications state (mean difference = 0.022, P = 0.006) and 8 cm target distances (mean difference = 0.022, P = 0.042). There were no significant differences for angular deviation for this interaction.

**Multivariate Model for Movement Trajectory Length**

A multivariate mixed design evaluated within-subject factors for medication status (on, off medications), target distance (4, 8, 12 cm), and between-subject factors of group (control, PD). The multivariate model revealed a significant effect for trajectory length across target distances, F(4, 320) = 72.97, P < 0.0001, and
Table 5. Spatial deviations: Pair-wise comparisons with mean differences, standard errors, and pair-wise significance corrected with Bonferroni presented for interactions

| Bonferroni comparisons | Mean Diff. | SE | Sig. |
|------------------------|------------|----|------|
| **Group × Medication × Spatial Deviation** |            |    |      |
| Control                 |            |    |      |
| On                     | Linear vs Angular | .027 | .037 | .469 |
| Off                    | Linear vs Angular | .010 | .022 | .634 |
| Parkinson disease       |            |    |      |
| On                     | Linear > Angular | .105 | .038 | .006** |
| Off                    | Linear vs Angular | −.002 | .022 | .912 |
| **Spatial Deviation × Target Distance × Medication** |            |    |      |
| Linear deviation        |            |    |      |
| 4 cm                   | On vs Off  | .002 | .006 | .725 |
| 8 cm                   | On vs Off  | −.003 | .007 | .662 |
| 12 cm                  | On vs Off  | .005 | .007 | .419 |
| Angular displacement    |            |    |      |
| 4 cm                   | On < Off   | −.164 | .079 | .042* |
| 8 cm                   | On vs Off  | −.024 | .038 | .529 |
| 12 cm                  | On vs Off  | .006 | .032 | .842 |

*P < 0.05.
**P < 0.01.
***P < 0.001.

Notes: Linear deviation estimations were greater than angular deviations (P < 0.05). Spatial deviations were greatest for 4 cm relative to 12 cm target distances (P < 0.05). Spatial deviations were lower for PD patients on relative to off medications (P < 0.05).

Figure 3. Spatial deviations following movement termination to the target by group. (A). Linear deviation (cm) from the target across distances. (B). Angular displacement (radians) to the target [clockwise (−) and counterclockwise (+)].

For interactions for target distance by group, F(4, 320) = 3.29, P = 0.011, and target distance by medication, F(4, 320) = 2.67, P = 0.032. Movement trajectory length was not significant for medication status, F(2, 79) = 2.57, P = 0.083, medication by group, F(2, 79) = 1.78, P = 0.176, or target distance by medication by group, F(4, 320) = 1.88, P = 0.113.

The between-group comparison was significant for movement trajectory length between groups, F(2, 79) = 3.69, P < 0.03.
Figure 4. Mouse created lengths contrasting path and fixed movement trajectories. (A). Path lengths (cm) across trials of target distance. (B). Fixed lengths (cm) across trials of target distance.

Univariate and Post hoc Analyses for Trajectory Length

Univariate and post hoc analyses were conducted and follow-up post hoc analyses were adjusted with Bonferroni correction for multiple comparisons (see Table 4B and Figure 4).

Group

The between-group comparison was significant for fixed movement trajectory length, $F(1, 80) = 7.45, P = 0.008$, but not for path movement trajectory, $F(1, 80) = 2.18, P = 0.144$. Controls displayed shorter fixed movement trajectories length than PD patients (mean difference = $-0.379$, $P = 0.008$) and path movement trajectories (mean difference = $-0.577$, $P = 0.144$) compared with PD patients.

Target Distance

Movement trajectory was significantly different across target distances for both path length, $F(2, 160) = 75.47, P < 0.0001$, and fixed length, $F(2, 160) = 277.48, P < 0.0001$. Path trajectory length was shorter for movements with 4 cm target distances relative to 12 cm distances (mean difference $4\text{ cm} < 12\text{ cm} = -4.50, P < 0.0001$), and 8 cm relative to 12 cm (mean difference $8\text{ cm} < 12\text{ cm} = -3.89, P < 0.0001$). There was no significant difference between 4 and 8 cm target distances for path length (mean difference $4\text{ cm} < 8\text{ cm} = -0.611, P < 0.283$). Fixed trajectory length was shorter for 4 cm compared with 8 cm (mean difference $4\text{ cm} < 8\text{ cm} = -2.15, P < 0.0001$) and 12 cm target distances (mean difference $4\text{ cm} < 12\text{ cm} = -3.99, P < 0.0001$), and 8 cm compared with 12 cm (mean difference $8\text{ cm} < 12\text{ cm} = -1.85, P < 0.0001$).

Target Distance by Group Interaction

There was a significant target distance by group interaction for fixed trajectory length, $F(2, 160) = 6.71, P = 0.002$, but not for path trajectory length, $F(2, 160) = 0.912, P = 0.404$. Controls produced shorter fixed trajectory lengths than PD patients for 8 cm target distances (mean difference $8\text{ cm} = -1.09, P = 0.01$), but not for other target distances (mean difference $4\text{ cm} = -0.012, P = 0.174$; mean difference $12\text{ cm} = -0.028, P = 0.071$).

Target Distance by Medication Interaction

There was a significant target distance by group interaction for path trajectory length, $F(2, 160) = 3.39, P = 0.036$, but not for fixed trajectory length, $F(2, 160) = 1.83, P = 0.163$. Path trajectory length was greatest between 4 and 12 cm target distances in both on and off-medication states (mean difference $\text{on}/4\text{ cm} < 12\text{ cm} = -5.12, P = 0.0001$; mean difference $\text{off}/4\text{ cm} < 12\text{ cm} = -3.89, P = 0.0001$), followed by differences between 8 and 12 cm target distances (mean difference $\text{on}/8\text{ cm} < 12\text{ cm} = -4.49, P = 0.0001$; mean difference $\text{off}/8\text{ cm} < 12\text{ cm} = -3.28, P = 0.0001$). Path trajectory length was not significantly different between 4 and 8 cm.
target distances in either on or off-medication states (mean difference on/4 cm vs 8 cm = −0.615, \( P = 0.278 \); mean difference on/4 cm vs 8 cm = −0.607, \( P = 0.288 \)). Fixed trajectory length was significantly different between target distances in both on and off-medication states, \( P < 0.0001 \).

**Target Distance by Medication by Group Interaction**

There was a significant target distance by group interaction for fixed trajectory length, \( F(2, 160) = 3.84, P = 0.024 \), but not for path trajectory length, \( F(2, 160) = 0.024, P = 0.977 \). Controls produced shorter fixed trajectory lengths relative to PD patients in the off-medication state for 4 cm target distances (mean difference on/off 4 cm = −0.026, \( P < 0.02 \)), and on-medication state for 8 cm target distances (mean difference on/off 8 cm = −1.66, \( P < 0.005 \)). All other contrasts were insignificant.

**Multivariate Model for Velocity**

A multivariate mixed design evaluated within-subject factors for medication status (on, off medications), target distance (4, 8, 12 cm), and between-subject factors of group (control, PD) on path and fixed velocities. The multivariate model revealed a significant effect for velocity across target distances, \( F(4, 320) = 63.62, P < 0.0001 \), and a target distance by group interaction, \( F(4, 320) = 2.91, P = 0.022 \). Velocity was not significant for medication, \( F(2, 79) = 2.4, P = 0.097 \), medication by group, \( F(2, 79) = 0.005, P = 0.995 \), target distance by medication, \( F(4, 320) = 0.888, P = 0.471 \), or target distance by medication by group interactions, \( F(4, 320) = 1.01, P = 0.403 \).

The between-group comparison was significant for group for velocity, \( F(2, 79) = 4.16, P = 0.019 \), demonstrating significantly higher differences for controls relative to PD patients.

**Univariate and Post hoc Analyses for Velocity**

Univariates and post hoc analyses were conducted and follow-up post hoc analyses were adjusted with Bonferroni correction for multiple comparisons (see Table 4B and Figure 5).

**Group**

The between-group comparison was significant for both path velocity, \( F(1, 80) = 4.57, P = 0.036 \), and fixed velocity, \( F(1, 80) = 8.08, P = 0.006 \) demonstrating significant differences between controls and PD patients. PD patients displayed lower velocities for both path (mean difference = −0.201, \( P = 0.036 \)) and fixed (mean difference = −0.208, \( P = 0.006 \)) trajectories compared with healthy controls.

**Target Distance**

Velocity for path movement trajectory was significantly different across target distances, \( F(2, 160) = 443.3, P < 0.0001 \). Also, velocity for fixed movement trajectory was significantly different across target distances, \( F(2, 160) = 591.12, P < 0.0001 \). Velocities increased across target distance lengths (4 cm < 8 cm < 12 cm) for both path and fixed velocities (\( P < 0.0001 \)).
### Table 6. Step-wise multiple regression coefficients for PD patients

| Dependent variable                  | Predictors                                      | Beta | SE  | T    | P    |
|-------------------------------------|-------------------------------------------------|------|-----|------|------|
| **Perception**                      | **ON—Length equivalence**                       |      |     |      |      |
|                                     | 1. ON—RBANS Line Orientation                    | .582 | .316| 4.98 | .0001*** |
|                                     | 2. ON—Grooved Pegboard Asymmetry                | .344 | .06 | 2.95 | .006** |
| **OFF—Length equivalence**          | 1. OFF—Letter Number Sequencing                  | .401 | .189| 2.23 | .008** |
|                                     | 2. OFF—RBANS Line Orientation                   | .313 | .272| 2.21 | .054*  |
| **Spatial deviation**               | **OFF—Linear deviation**                        |      |     |      |      |
|                                     | 1. OFF—RBANS Line Orientation                   | −.541| .003| −4.2 | .001***|
|                                     | 2. OFF—Disease Duration                         | .324 | .003| 2.52 | .016*  |
| **ON—Angular deviation**            | 1. ON—UPDRS Total                               | .374 | .003| 2.68 | .011** |
|                                     | 2. Disease Duration                             | .362 | .014| 2.59 | .013*  |
| **OFF—Angular deviation**           | 1. OFF—Digit Span Total                         | −.505| .004| −3.56| .001** |

**Movement velocity**

| Dependent variable                  | Predictors                                      | Beta | SE  | T    | P    |
|-------------------------------------|-------------------------------------------------|------|-----|------|------|
| **ON—Path velocity**                | 1. ON—UPDRS Motor                               | −.360| .10 | −2.49| .017* |
|                                     | 2. Levodopa Dose Equivalency                    | .308 | .00 | 2.14 | .039* |
| **OFF—Path velocity**               | 1. Levodopa Dose Equivalency                    | .556 | .00 | 4.58 | .0001***|
|                                     | 2. OFF—UPDRS Total                              | −.418| .004| 3.44 | .002**|
| **ON—Fixed velocity**               | 1. ON—UPDRS Total                               | −.343| .005| −2.25| .03*  |
| **OFF—Fixed velocity**              | 1. Levodopa Dose Equivalency                    | .570 | .001| 4.55 | .0001**|
|                                     | 2. OFF—UPDRS Total                              | −.354| .004| −2.83| .008**|

**Movement trajectory**

| Dependent variable                  | Predictors                                      | Beta | SE  | T    | P    |
|-------------------------------------|-------------------------------------------------|------|-----|------|------|
| **ON—Path length**                  | 1. ON—Grooved Pegboard Asymmetry                 | −.465| .004| −3.24| .002**|
| **OFF—Fixed length**                | 1. OFF—RBANS Line Orientation                   | −.523| .003| −3.73| .001**|

*P < 0.05.  **P < 0.01.  ***P < 0.001.

Notes: Stepwise criteria presenting significant predictor variables entered in the equation:

Levodopa dose daily equivalency, disease duration, UPDRS motor and total score, RBANS Letter Number Sequencing (LNS), RBANS Line Orientation, RBANS Digit Span Total, Finger Tapping and Grooved Pegboard hand asymmetries.

Excluded dependent variables without significant predictors entered in the equation include the following:

On and Off Perceptual Width Interval, On and Off-Linear Deviation, Off-Path Length, On-Fixed Length.

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**Target Distance by Group Interaction**

There was a significant target distance by group interaction for path trajectory, \( F(2, 160) = 5.35, P = 0.006 \). PD patients displayed lower velocities relative to healthy controls only for the longest target distance (mean difference\( \_{\text{ON}} \) = -0.347, \( P = 0.016 \)), but not for 4 cm (mean difference\( \_{\text{OFF}} \) = -0.102, \( P = 0.107 \)), or 8 cm (mean difference\( \_{\text{OFF}} \) = 0.155, \( P = 0.109 \)).

There was no significant target distance by group interaction for fixed trajectory, \( F(2, 160) = 2.48, P = 0.087 \), with PD patients displaying lower velocities for all target distances (\( P < 0.01 \)) relative to healthy controls.

**Step-Wise Regression Analyses**

Several step-wise forward multiple regression analyses were conducted utilizing the predictors of levodopa dose, UPDRS motor and total subscors, disease duration, neuropsychological assessment scores for attention and visuo-perceptual functioning, and sensorimotor asymmetries for grooved pegboard and finger tapping speed on dependent variables of PD spatial deviations and velocity on and off medications (see Table 6 for coefficients).

**Visuo-perceptual Accuracy**

**Length Equivalence Perception**

Length equivalence estimation accuracy in the on-medication state was best predicted by RBANS line orientation in the on-medication state \( F(1, 38) = 23.71, P < 0.0001, R^2 = 0.384 \) explaining 36.8% of the variance, and grooved pegboard asymmetry in the on-medication state \( F(2, 37) = 18.59, P < 0.0001, R^2 = 0.501 \), adding an additional 10.6% to 47.4% overall variance explained. Similarly, in the off-medication state length equivalence was best predicted by Letter Number Sequencing \( F(1, 38) = 8.64, P < 0.0001, R^2 = 0.189 \) explaining 16.7% of the variance, and line orientation \( F(1, 38) = 7.22, P = 0.002, R^2 = 0.296 \) from the RBANS in the off-medication state explaining an additional 8% of the 24.7% overall variance explained.

**Width Interval Perception**

In the on and off-medication state, none of the predictors significantly adjusted for the variance in width interval perception accuracy.

**Spatial Deviation from Movement to the Target**

**Linear Distance to Target**

In the on-medication state, none of the predictors significantly adjusted for the variance in linear distance and were not entered into the equation. In the off-medication state, linear distance to the target was predicted by RBANS line orientation in the off-medication state \( F(1, 38) = 15.82, P < 0.0001, R^2 = 0.299 \) explaining 28.1% of the variance, followed by disease duration \( F(2, 37) = 6.35, P < 0.0001, R^2 = 0.405 \) explaining an additional 9% of the 37.1% of the overall variance.

**Angular Deviation**

Angular deviation in the on-medication state was best predicted by the UPDRS total \( F(1, 38) = 6.74, P = 0.013, R^2 = 0.151 \) explaining 12.8% of the variance, followed by disease duration contributing...
an additional 11.5% of the variance \(F(2, 37) = 7.25, P = 0.002, R^2 = 0.282\) to the overall 24.3% of the overall variance explained. Angular deviation in the off-medication state was best predicted by the Digit Span total in the off-medication state \(F(1, 37) = 12.67, P = 0.001, R^2 = 0.255\) explaining 23.5% of the overall variance.

**Movement Trajectory (Path, Fixed) for Length and Velocity**

**Trajectory Length**
Path trajectory length in the on-medication was best predicted by grooved pegboard asymmetry in the on-medication state \(F(1, 38) = 10.51, P = 0.002, R^2 = 0.217\) explaining 19.6% of the variance. Path trajectory length in the off-medication was not significantly predicted by any of the predictors entered into the equation.

Fixed trajectory length in the off-medication was not significantly predicted by any of the predictors entered into the equation. Fixed trajectory length in the off-medication was best predicted by RBANS line orientation in the off-medication state, \(F(1, 38) = 13.92, P = 0.001, R^2 = 0.273\] explaining 25.4% of the variance.

**Velocity**
Path velocity in the on-medication state for PD patients was best predicted by the UPDRS motor accounting for 11.4% of the variance \(F(1, 38) = 6.02, P = 0.019, R^2 = 0.137\] and levodopa dose adding an additional 7.6% \(F(2, 37) = 4.56, P = 0.039, R^2 = 0.232\] of the overall 19% variance explained by both predictors in the model. Path velocity in the off-medication state for PD patients was best predicted by levodopa dose accounting for 27.6% of the variance \(F(1, 38) = 15.47, P = 0.0001, R^2 = 0.295\] and UPDRS total in the off-medication state \(F(2, 37) = 15.89, P = 0.0001, R^2 = 0.469\] adding an additional 16.3% of the overall 43.9% variance explained by both predictors.

Fixed velocity in the on-medication state was best predicted by the UPDRS total in the on-medication state \(F(1, 38) = 5.07, P = 0.03, R^2 = 0.118\] explaining 9.4% of the variance. Similar to path velocity, fixed velocity in the off-medication state was best predicted by levodopa dose accounting for 29.3% of the variance \(F(1, 38) = 16.77, P = 0.0001, R^2 = 0.312\] and UPDRS total in the off-medication state \(F(2, 37) = 13.96, P = 0.0001, R^2 = 0.437\] adding an additional 11.2% of the overall 40.5% variance explained by both predictors.

**Discussion**
Models of frontostriatal circuitry posit direct and indirect pathways from the striatum to the output nuclei of the basal ganglia, considered to produce opposing effects to facilitate and suppress cortically initiated activity (Middleton and Strick 2000). Although neuroanatomical models propose functional segregation of motor and cognitive domains, the aspects of PD disordered behavior attributable to dopamine depletion remain unspecified (Cools et al. 2001; Macdonald and Monchi 2011). The connections between the basal ganglia and cortical regions such as prefrontal cortex and parietal and posterior cortex should be considered related to regions subserving visual hallucinations, visuoperceptual and visuconstructional functions (Middleton and Strick 2000, 2002; Schendan et al. 2009; Gallagher et al. 2011). Therefore, there is a need to develop sensitive and specific assessment of visuoperceptual and visuospatial functions with validated dopaminergic and neuroanatomical basis, and capable of clearly segregating cognitive and motor task demands.

Characterization of how dopamine regulates sequential movements requires determination of how dopamine modulates specific cognitive-motor components that can eventually drive perceptuomotor integration and influence movement accuracy. However, investigations focused on evaluation of spatial deviations in extra-personal space in PD have resulted in contradictory findings, in particular related to the extent that aberrations in perceptual processing impact spatial deviations during movement trajectories (Miller et al. 2004; Wright et al. 2007; Seidler et al. 2015).

This study aimed to disambiguate motor and cognitive task demands in PD, and clarify the impact of dopaminergic modulation on spatial orientation and perceptual processing in movement accuracy. Previous investigations evaluating perceptuomotor functioning in PD have been contradictory and have not clearly segregated different aspects of either motor or cognitive control. Different outcomes could reflect a number of cognitive components including selective deficits including spatial presentation in different quadrants or directional bias, or reflecting dopaminergic asymmetries related to attentional or working memory functions (Lee et al. 2001a, 2001b, 2002; Harris et al. 2003; Miller et al. 2004; Wright et al. 2007). To further clarify the impact of perceptual impairments on movement, we designed a study including different directional aspects of perception in visuoperceptual processing as well as movement trajectory. The experimental paradigm presented stimuli in all possible quadrants and directions, and varied across shorter distances in an attempt to restrict attentional demands modulated by dopamine (Ebersbach et al. 1996; Lee et al. 2002; Costa et al. 2003; Harris et al. 2003; Eghgoetz Martens et al. 2013).

**Presence of Spatial Deficits in Early Parkinson’s Disease**
Our study findings reveal that patients with early PD demonstrated visuoperceptual deficits, but overall did not display significant spatial deviations in cursor movement when aiming to the target. After controlling for dopaminergic medication state, spatial accuracy during cursor movement with visual feedback was adequate when compared with healthy controls. There is substantial evidence for early perceptual and motor dysfunction in PD, although the paradigms included in prior investigations were not capable of specifying the aspects of PD-disordered behavior that ultimately translated into aberrant movement trajectories. In one study, one-third of nondemented PD patients reported perceiving spatial inaccuracy in everyday life, and actively engaging in visuoperceptual strategies to overcome movement deficits (Daviddottir et al. 2005). The presence of higher order perceptual dysfunction in movement disorders independent of basic motor control have received minimal attention, although it has implications for prediction of functioning as well as disease progression (Mosimann et al. 2004).

Our results concur with previous investigations confirming the presence of visuoperceptual deficits in patients with early-stage PD (Hovestadt et al. 1987; Bodis-Wollner 2003; Hanna-Pladdy et al. 2013). Directional differences in dopaminergic modulation were also evident, suggesting greater modulation for length perception compared with width interval perception. Similarly, length perception had greater specificity for PD-related perceptual deficits, and was predicted not only by standardized line perception but also sensorimotor asymmetry with sensitivity to dopaminergic modulation (Hanna-Pladdy et al. 2015). Overall, the findings highlight the importance of segregating perception from movement, and the need to develop.
and validate sensitive tests of spatial accuracy relevant to movement disorders and neurodegeneration. Distinct structural MRI markers have been associated with visual hallucinations in PD, emphasizing that early identification of patients with visual hallucinations and visuoperceptual deficits could assist in prediction of disease course (Gama et al. 2014; Goldman et al. 2014). A longitudinal study evaluating neuropsychological and neuropathological progression across 3 years in PD identified age, visuoperceptual deficits, and posterior cortical hypometabolism as risk factors for more rapid cognitive decline (Shoja et al. 2014). Also, patients with dementia secondary to PD and Lewy body disease present with visual hallucinations and perceptual deficits that exceed what is observed in typical cases of Alzheimer’s disease (Mosimann et al. 2004). There is evidence for reduced retinal thickness in PD associated with visual alterations and reduced contrast sensitivity which should be explored further as potential early markers in PD (Inzelberg et al. 2004; Armstrong 2011; Bertrand et al. 2012; Adam et al. 2013; Li et al. 2015; Polo et al. 2016; Yang et al. 2016; Shi et al. 2020). Furthermore, the role of visual processing deficits in faulty depth perception should be considered in their potential contribution to deficits in aiming and impacting postural control in PD (Durgin et al. 2005a, 2005b; Wright et al. 2007; Davidsdottir et al. 2008; Ehgoetz Martens et al. 2013; Vitale et al. 2016).

Therefore, the development of specific posterior cortical biomarkers could improve disease differentiation. This can be guided by structure to function relationships such as association of visuospatial deficits with atrophy in parietal and superior occipital regions, and visuoperceptual deficits with atrophy in fusiform, parahippocampal, and middle occipital gyri (Pereira et al. 2009).

**Dopaminergic Modulation of Spatial Accuracy**

Moreover, it is critical to more clearly delineate cognitive and motor aspects of movement that are modulated by dopamine to elucidate the pathophysiology of PD and guide future treatment approaches. In this study, movement spatial accuracy was adequate when compared with healthy controls, although the medication state significantly impacted findings. Dopaminergic medication had opposing effects on spatial accuracy depending on whether the task involved actual movement. That is, dopaminergic medication improved spatial accuracy during the cursor movement task, but did not improve visuoperceptual estimations. Since many investigations do not carefully control for medication state, the findings have implications for interpretation of variable outcomes in PD with careful consideration of the methodologies employed (Jones et al. 2008). Overall, the findings are consistent with the well-established role of dopamine in minimizing movement aberrations in PD, but emphasize that subtle impairments may not be detectable under peak medication doses early in the disease process (Jones et al. 2008; Joubault et al. 2009; Espay et al. 2011; Mongeon et al. 2013). Conversely, the results revealed an adverse impact of dopaminergic medication on visuoperceptual performance, with the lowest perceptual performance in the on compared with the off medication state in PD relative to healthy controls. These findings substantiate clear dissociation in dopaminergic modulation of spatial accuracy depending on the cognitive versus motor task demands. Movement linear deviations from the target more closely related to line perception and did not demonstrate clear improvement with medication in contrast to angular deviations from the target that improved with medication, supporting differential components of spatial movement. The relationship of sensory-motor asymmetries to length perception and linear deviation from the target support results from our previous investigations, concluding that basal levels of dopamine asymmetries can predict response (Hanna-Pladdy et al. 2015). Cognitive and motor deficits in PD are widespread and apart from attention, working memory and motor dysfunction, cannot be explained by dopamine depletion alone (Mollon et al. 2003; Cools et al. 2008; Hanna-Pladdy et al. 2013; Mongeon et al. 2013; Hanna-Pladdy et al. 2015). Therefore, dopaminergic medication capable of ameliorating movement deficits could reduce visuoperceptual accuracy because of over-dosing, since dopamine depletion is evident earlier in dorsolateral than ventral areas (Cools et al. 2001; Cools 2006).

These conclusions are supported by previous investigations documenting effects of medication in early PD, with improvement in working memory and executive functions, but demonstrating a detrimental effect on pattern recognition and visual memory (Fournet et al. 2000; Costa et al. 2003; Beato et al. 2008; Costa et al. 2009; Miah et al. 2012). Furthermore, the short and long time scales of dopaminergic modulation in the prefrontal cortex display a u-shaped curve, with the duration of the post-synaptic effect contributing to differences in cognitive performance (Dreher et al. 2002). Future research should explore optimal medication titration to produce desired improvement of motor features of the disease while minimizing adverse impact on cognition.

**Influence of Distance Estimation on Spatial Accuracy**

Systematic examination of perceptual differences in PD including those driven by task demands has been documented, and has revealed that perception can be altered depending on distance estimation, spatial direction as well as orientation (Ebersbach et al. 1996; Harris et al. 2003; Amick et al. 2006; Ehgoetz Martens et al. 2013). Consequently, in order to evaluate the impact of distance estimation on spatial accuracy, our novel visuoperceptual and motor control paradigms included different lengths and controlled for presentation of stimuli in both vertical and horizontal orientations. The novel tasks developed in this investigation were designed to improve sensitivity in detecting spatial deficits during focused attention, while simultaneously controlling for the spatial location of targets during discrimination determinations (Ebersbach et al. 1996; Montse et al. 2001; Nys et al. 2010). To eliminate the effects of motor impersistence on movement and related to hemispatial inattention, the perceptual task only required a verbal response (Heilman et al. 1985; Coslett et al. 1990). The predictive results as well as dissociations across task demands support distinct differences between angular spatial deviations to the target and perceptual length equivalence estimations. Angular spatial deviations are more closely aligned with movement velocity parameters in terms of relationship to LED, disease duration, and UPDRS scores. Conversely, visuoperceptual equivalence is more closely related to standardized tests of judgment of line perception, working memory, as well as sensorimotor asymmetries. Also, directional and spatial attentional influences were considered by placing targets and discrimination points in every possible quadrant and movement trajectories in all directions consistent with critical visual attentional demands sensitive to PD deficits (Heilman et al. 1985; Schneider et al. 1992; Pitzalis et al. 1997; Tarig et al. 2020). Therefore, our novel experimental tasks were carefully designed to isolate spatial accuracy and evaluate the role of dopaminergic modulation...
by controlling for focused visual attention as well as kinetic properties during visual tracking in space.

Visuoperceptual processing requires varying resources and effort for either focused attention or configurations. To eliminate global attentional demands, we presented stimuli in the mid-line and maintained very short lengths. Several task differences influenced discrimination from healthy individuals in our study, and in addition to the two perceptual tasks of length and width estimation, we controlled for variable stimulus line lengths (4, 8, 12 cm) and varying degrees of discrimination difficulty required for task accuracy. The comparison of our path trajectory to fixed movement trajectory following visual feedback and decision of spatial placement indicate that path trajectory and not fixed trajectory is influenced by medication and distance effects. However, PD patients off-medications displayed differences on the shortest lengths for fixed placement. These findings were upheld for both spatial trajectories and velocities, suggesting similar impact of dopaminergic modulation and distance on cognitive decisions impacting movement performance. Importantly, our stimulus properties included lengths that were significantly shorter than those utilized in studies of hemispatial attention as well as shorter than standardized tests of visuoperceptual function of line orientation (Barrett et al. 2001; Nys et al. 2010; Elgoetz Martens et al. 2013).

Study results revealed that spatial discrimination was significantly influenced by the length of the stimulus as well as item difficulty. This was evident in increased discrimination for trials presenting the shortest lines (4 cm lines) and requiring the greatest discrimination. These differences were accentuated by dopaminergic medication that demonstrated greater impact on spatial accuracy during both length equivalence discriminations and angular deviations to the target. Conversely, PD patient's performed comparable to healthy controls on trials displaying the longest line lengths and requiring the least amount of discrimination. However, perceptive discrimination was reduced when the degree of difficulty required too fine a discrimination, resulting in decreased accuracy for all participants. In terms of practice effects, the medication by difficulty interaction revealed significant differences in the repeated testing factor for the easy items reflective of some learning from repeated testing, but this was not present for the more difficult items. In summary, introducing visual adaptation in PD has potential to increase functionality, but will require detailed consideration of distance and discriminative details impacting attentional and spatial demands.

Overall, the results highlight the critical need to closely develop and standardize perceptual diagnostic tests that emphasize which essential task demands are capable of optimizing discriminative and predictive validity. Our previous investigations evaluating cognitive deficits in this same PD sample confirmed the presence of visuoperceptual deficits based on judgment of line orientation utilizing a standardized neuropsychological test, although it could not detect significant influence of dopamine even when accounting for motor asymmetric features of the disease (Hanna-Pladdy et al. 2013, 2015). The line orientation test included in our neuropsychological battery displayed 20 cm lines in a radial display to determine selective orientation deficits based on the original Benton test but which is administered as a part of the RBANS (Benton et al. 1975; Benton et al. 1994; Randolph et al. 1998). Specific stimulus indices such as distance and discrimination significantly contribute to sensitivity and specificity in visuoperceptual functioning. Therefore, there is a need to develop experimental and standardized visuoperceptual tests with improved sensitivity in detecting cognitive deficits in early PD, eventually resulting in improved management of medication titration to reduce adverse effects.

The Role of Visual Feedback in Spatial Navigation

Sensory-motor deficits in PD have been characterized as imperceptible movement errors of gradual onset involved primarily in implicit learning processes. The role of dopamine in dynamic visuoperceptual functioning that impacts tracking and navigation during movement is unclear with some studies implying there is only a minor role (Jones et al. 1996). Moreover, controlling for visuoperceptual task demands with respect to tracking has not ameliorated PD deficits, causing some researchers to conclude visuoperceptual components influencing movement control in PD are minor factors (Mongeon et al. 2013). However, other studies more closely evaluating differences in movement tracking through manipulation of both dopamine and implicit/explicit task demands, demonstrate there is likely a complex interplay between sensory information and the planning and execution of movement trajectories (Durgin et al. 2005b; Davidsdottir et al. 2008; Hanna-Pladdy and Heilman 2010; Mongeon et al. 2013).

In this investigation we aimed to more clearly delineate the role of dopamine in spatial aspects of navigation by controlling for multiple aspects of task demands in the planning and execution of movement trajectories. This was accomplished by adjusting for the direction of movement toward the target, as well as counterbalancing the location of the target in all quadrants previously identified as important in characterizing spatial movement parameters in PD (Wright et al. 2007). Taken together, our findings and those of previous investigations supports that the critical dopaminergic deficit in PD is linked to ineffective integration of sensory information in the planning and execution of movement trajectories. That is, dopaminergic medication improved the spatial accuracy of aiming during the movement trajectory as quantified by the discrepancy between the selected endpoint following feedback-based adjustments, and the designated target location. However, spatial accuracy differed depending on the actual distance to the target, with the greatest spatial deviations evident for the shortest distances (i.e., 4 cm). This is consistent with our visuoperceptual discrimination findings which varied by stimulus length, although the influence of dopamine was in the opposite direction demonstrating an adverse effect. Overall findings are in line with studies of spatial navigation in PD that indicate visual-feedback influences navigation, and that specific visual input and visuoperceptual information can impact navigation and veering in PD (Davidsdottir et al. 2008). Dopaminergic medication improved spatial accuracy in PD patients so that their performance was comparable to healthy controls. Specifically, angular deviations measured from the final cursor endpoint to the target location were more accurate in the on relative to the off-medications state. Importantly, the computerized paradigm facilitated reliance on visually guided feedback allowing for continuous adjustment of the spatial location of the cursor prior to making a final decision regarding endpoint placement relative to the target. This is further supported by the dissociation between dopaminergic modulation of angular displacement from the target but absence of dopaminergic influence on the distance from the target.

Since the experiment controlled for bidirectional and horizontal and vertical movements modulated by dopamine, the target displacement could be isolated from the temporal and spatial components of the trajectory. These findings are supported by a previous investigation examining the role of dopamine in
cognitive strategies that facilitated visuomotor learning accuracy in reaching in PD, through perturbation manipulations of timing and size of visuomotor errors in virtual reality (Mongeon et al. 2013). Moreover, the findings are in accordance with our previous investigation utilizing an earlier version of this computerized program (replication of Archimedes square utilizing visual feedback (Hanna-Pladdy and Heilman 2010)). This paradigm isolated dopaminergic modulation to the planning aspects of skill acquisition, which is supported by the current findings demonstrating a group by medication interaction for the fixed trajectory following visual feedback and decision of final line position (Hanna-Pladdy and Heilman 2010). Movement trajectories during aiming movements can improve spatial accuracy through adjustments to visual feedback, and there is evidence that PD patients may preferentially respond to feedback in a delayed fashion (Foerde and Shohamy 2011; Mongeon et al. 2013). Theories of dopaminergic function highlight a central role in detecting reward prediction errors, and therefore dopamine may have a key function in updating actions through corticostriatal modulation including both visual and visuoperceptual feedback (Pessiglione et al. 2006). These findings raise the question of whether there is preferential processing of adaptive behavior in particular for immediate outcomes by the striatum (Shohamy et al. 2004).

In summary, the findings demonstrate variable effects of dopaminergic medication on distinct processes dependent upon the extent to which task demands have reliance on either the ventral or dorsal striatum (Kish et al. 1988). Furthermore, the cursor movement task findings emphasize the involvement of the direct pathway and models of progressive loss of dopamine through corticostriatal loops, in line with previous findings isolating dopaminergic modulation of the planning aspects of movement (Hanna-Pladdy and Heilman 2010). Overall, the study findings highlight the importance of perceptual deficits in early PD, and emphasize the need to develop valid and sensitive measures relevant to movement disorders to evaluate for potential to detect adverse medication effects and serve as markers for cognitive decline.

Notes
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