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Paradoxical Effect of Dopamine Medication on Cognition in Parkinson's Disease: Relationship to Side of Motor Onset

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Abstract

Parkinson's disease (PD) is characterized by asymmetric motor symptom onset attributed to greater degeneration of dopamine neurons contralateral to the affected side. However, whether motor asymmetries predict cognitive profiles in PD, and to what extent dopamine influences cognition remains controversial. This study evaluated cognitive variability in PD by measuring differential response to dopamine replacement therapy (DRT) based on hemispheric asymmetries. The influence of DRT on cognition was evaluated in mild PD patients (n = 36) with left or right motor onset symptoms. All subjects were evaluated on neuropsychological measures *on* and *off* DRT and compared to controls (n = 42). PD patients were impaired in executive, memory and motor domains irrespective of side of motor onset, although patients with left hemisphere deficit displayed greater cognitive impairment. Patients with right hemisphere deficit responded to DRT with significant improvement in sensorimotor deficits, and with corresponding improvement in attention and verbal memory functions. Conversely, patients with greater left hemisphere dopamine deficiency did not improve in attentional functions and declined in verbal memory recall following DRT. These findings support the presence of extensive mild cognitive deficits in early PD not fully explained by dopamine depletion alone. The paradoxical effects of levodopa on verbal memory were predicted by extent of fine motor impairment and sensorimotor response to levodopa, which reflects extent of dopamine depletion. The findings are discussed with respect to factors influencing variable cognitive profiles in early PD, including hemispheric asymmetries and differential response to levodopa based on dopamine levels predicting amelioration or overdosing.

Keywords

Cognition; Dopamine; Memory; Motor asymmetry; Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder identified by cardinal motor features of tremor, rigidity, bradykinesia and postural instability, with initial unilateral motor symptom presentation for at least half the patients persisting long after the disease becomes bilateral (Djaldetti, Ziv, & Melamed, 2006; Uitti, Baba, Whaley, Wszolek, & Putzke, 2005). This motor asymmetry has been attributed to asymmetric degeneration of dopaminergic neurons of the dorsal striatal projections including the posterior putamen, with a close relationship between side of motor onset and motor dysfunction (Haaxma et al., 2010; Middleton & Strick, 2000a, 2000b). Although there are additional ventral striatal dopaminergic projections connected to orbitofrontal, dorsolateral prefrontal, anterior cingulate and inferotemporal cortices, it remains controversial how asymmetric dopaminergic depletion influences cognition (Verreyt, Nys, Santens, & Vingerhoets, 2011). In part, this controversy has been maintained by differences in response to dopamine replacement therapy (DRT) based on cognitive task demands, and disagreement regarding whether the laterality of motor impairment predicts cognitive profiles in PD (Cools, 2006; Poletti et al., 2012; Verreyt et al., 2011).

There is substantial evidence documenting the presence of mild cognitive deficits early in PD, although the underlying neuropathology remains controversial. Recent evidence suggests that cognitive impairment present in the early stages of PD cannot be fully explained by dopamine depletion alone (Hanna-Pladdy, Jones, Cabanban, Pahwa, & Lyons, 2013; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007). In addition to dopamine, many other contributing factors to cognitive deficits in PD have been considered including structural changes in both cortical and subcortical regions, genetic variation in the COMT gene, amyloid plaques, alpha-synuclein, tau protein, and involvement of other neurotransmitter systems including GABA (Beyer, Janvin, Larsen, & Aarsland, 2007; Braak et al., 2003; Buongiorno, Compta, & Marti, 2011; Gomperts et al., 2013; Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011; Luciana, Collins, & Depue, 1998). Nonetheless, since therapy with levodopa has been demonstrated to modify cognition, it is critical to first clarify the role of dopamine in cognitive functioning to discriminate pathophysiological mechanisms mediating motor and nonmotor features of PD (Cools, 2006; Verreyt et al., 2011).

Numerous investigations have evaluated cognition in PD, and have attempted to explain differential DRT effects based on task demands, although the disease duration and dopamine dose have not been well accounted for across studies (Beato et al., 2008; Cools, Barker, Sahakian, & Robbins, 2001, 2003; Fera et al., 2007; Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000; Gotham, Brown, & Marsden, 1986; Jahanshahi, Wilkinson, Gahir, Dharmarinda, & Lagnado, 2010). Since dopamine depletion is evident earlier in dorsolateral areas than in ventral areas (Kish, Shannak, & Hornykiewicz, 1988), it has been suggested that DRT that ameliorates motor dysfunction might have a detrimental effect on specific cognitive tasks related to overdosing (Cools, 2006; Cools et al., 2001). Thus, it has been hypothesized that variable effects of dopamine treatment on distinct cognitive processes relate to differential reliance on dorsal and ventral striatum.

Dorsal striatum tasks including planning, switching, set shifting, and category judgments have demonstrated enhancement following dopaminergic therapy (for review, see Macdonald & Monchi, 2011). Most of these studies have focused on attentional and executive tasks, with very few studies evaluating memory encoding and retrieval *on* and *off* medications and with inconsistent findings (Drag, Bieliauskas, Kaszniak, Bohnen, & Glisky, 2009; Edelstyn, Shepherd, Mayes, Sherman, & Ellis, 2010; MacDonald et al., 2013). However, detrimental effects for ventral striatum tasks involving implicit and explicit learning and reversal learning have been also been documented (Cools et al., 2001; Jahanshahi et al., 2010). While memory encoding can rely on attentional and executive functions which might be influenced by dopamine, the effects of dopamine replacement on memory retrieval and VTA innervated regions such the limbic system remain unclear.

Other investigations have tried to explain the variability in cognitive presentation in PD through examination of patterns of cognitive dysfunction reflective of hemispheric asymmetries in dopamine depletion based on the side of motor symptom onset (Amick, Grace, & Chou, 2006; Katzen, Levin, & Weiner, 2006; Tomer et al., 2007; Verreyt et al., 2011). If asymmetric nigral cell loss implicated in asymmetric motor presentation is also responsible for cognitive deficits, then differential patterns of cognitive impairment based on hemispheric specialization could be evident. However, the literature has revealed a wide range of cognitive profiles based on motor symptom onset, in particular for patients in the early stages of the disease (Poletti et al., 2013; Tomer et al., 2007; Williams et al., 2007). In fact, contrary to other studies suggesting greater cognitive deficits with left hemisphere involvement, some studies have suggested there is greater cognitive impairment with right hemisphere involvement and after dopamine replacement for tasks mediated by the less affected side, suggesting a detrimental overdosing effect (Bentin, Silverberg, & Gordon, 1981; Tomer et al., 2007; Tomer, Levin, & Weiner, 1993). It is conceivable that medication effects may interact with asymmetry to determine cognitive outcomes although the complexity of this interaction remains uncertain (Cools, 2006; Gotham et al., 1986; Gotham, Brown, & Marsden, 1988).

The specific role of dopamine in cognition remains controversial since previous investigations have revealed both improvement and detrimental effects in PD depending on task demands, as well as differential profiles related to side of motor onset (Cools et al., 2001, 2003; Gotham et al., 1986; Jubault, Monetta, Strafella, Lafontaine, & Monchi, 2009; Verreyt et al., 2011). We hypothesized that in addition to cognitive task demands, motor asymmetries (reflective of dopamine asymmetries) might predict differential response to medications. To explore interaction effects between cognitive task demands and basal level of dopamine in corticostriatal circuitry, we evaluated differential effects of DRT on neuropsychological performance based on side of motor onset reflective of differences in hemispheric specialization.

MATERIALS AND METHODS

Subjects

A total of 78 subjects (36 PD and 42 controls) were recruited from Kansas University School of Medicine (KUMC). Healthy controls were recruited from the Landon Center on

Aging database which maintains the contact information and demographics of potential research subjects primarily comprised of KUMC alumni. Patients were recruited from the PD and Movement Disorder Center at KUMC. Enrolled subjects were 50–75 years of age, right handed, and free of dementia, significant anxiety or depression.

Subjects were screened before enrollment to determine study eligibility, and all subjects were strongly right hand dominant based on the Edinburgh Inventory. Subjects were excluded on the basis of history of other neurologic disorder; major psychiatric disorder; significant alcohol or substance abuse; concurrent, unstable, or serious medical condition; or major head trauma. An attempt was made to match controls to PD subjects in terms of age and education, although control subjects had slightly higher educational levels. Subjects were free of dementia based on a minimum score of 27 out of 30 on the Mini Mental State Examination (MMSE) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; see Table 1) (Folstein, Folstein, & McHugh, 1975; Oldfield, 1971; Randolph, Tierney, Mohr, & Chase, 1998). Potential subjects with minimum scores of 27 on the MMSE were administered the RBANS. The RBANS scores were evaluated by a clinical neuropsychologist, and patients with global impaired scores (greater than –2 *SD*) were excluded from the study. Subjects were also free of clinically significant anxiety based on the Beck Depression (BDI-II) and Anxiety Inventories (BAI; see means in Table 1) (Beck, Epstein, Brown, & Steer, 1988; Steer, Rissmiller, & Beck, 2000). The study was conducted in accordance with the Declaration of Helsinki criteria and was approved by the Institutional Review Boards of KUMC, where all participants gave their written informed consent. Table 1 reports means (*SD*) for each group for demographics and screening measures.

PD subjects were in the mild stage of the disease as defined by the presence of stable unilateral or bilateral motor symptoms without motor fluctuations. Selection criteria for PD subjects included a diagnosis of idiopathic PD based on the United Kingdom PD Society Brain Bank Criteria, 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, and absence of dyskinesia. PD patients included in the study had a disease severity [Hoehn and Yahr (H&Y) rating of 2.5 or less, with the following distribution of severity in the sample: (i) H&Y of 1–1.5 = 40%, (ii) H&Y of 2 = 48.6 %, and H&Y rating of 2.5 = 11.4%. The dominant side of motor symptoms was based on clinical examination and asymmetry indices derived from the UPDRS both *on* and *off* medications. The UPDRS left and right motor scores were calculated by combining scores from the UPDRS part III, items 22–26, and revealed significantly more PD patients with right side motor onset than left motor onset disease (RMO $n = 23$; LMO $n = 13$). The two PD groups did not differ significantly in age, global cognitive screening, anxiety or depressive measures. However, while education was not significantly different based on side of motor onset, the RMO group had slightly lower educational levels than the control group [$F(2,75) = 3.72$; $p < .029$]. Similarly, the two PD groups were comparable on measures of anxiety and depression, although both groups reported significantly more symptoms than controls on the BDI–II [$F(2,75) = 16.35$; $p < .001$] and BAI [$F(2,75) = 20.26$; $p < .001$]. Means and standard deviations of demographics

and screening measures for each of the PD groups based on side of motor onset are provided in Table 1.

All PD patients were prescribed levodopa as well as one of two dopamine agonists (pramipexole = 50%; ropinirole = 50%). Patients taking amantadine, monoamine oxidase inhibitors (MAOI), catechol-O-methyl transferase (COMT), stimulants, or those with deep brain stimulators (DBS) were excluded from the study. Calculated levodopa dose equivalency (LED) did not reveal significant differences between the PD groups, $F(2,34) = .110$, $p = .742$, although there was a trend for LMO patients to have higher LED (LMO = 775 mg; RMO = 740 mg). Similarly, there were no differences between disease duration, $F(2,34) = .613$, $p = .439$, although RMO patients tended to have longer durations despite their lower LED (LMO = 47.1 months; RMO = 55.3 months; see Table 1). The two PD groups did not differ in the following UPDRS items: (i) posture *on* [$F(1,35) = .339$; $p = .564$] or *off* medications [$F(1,35) = .952$; $p = .336$], (ii) gait *on* [$F(1,35) = .566$; $p = .457$] or *off* medications [$F(1,35) = .745$; $p = .394$], or (iii) body bradykinesia and hypokinesia *on* [$F(1,35) = 2.22$; $p = .146$] or *off* medications [$F(1,35) = 1.28$; $p = .266$]. PD patients were asked to withhold their medication beginning at 5pm the evening before their *off* medication visit, and further doses were withheld until completion of the experiment at the end of their visit.

Procedure

A repeated measures model was used for the study with levodopa medication state (*on* and *off*) as the within-subjects factor, and Group (Control, LMO, RMO) as the between-subjects factor. All subjects received one of two alternative forms of the RBANS (A or B) with an 8 week interval imposed to minimize practice effects. Medication state was counter-balanced across visits 1 and 2 (i.e., half of the subjects were in the *on* state for visit 1, while the other half of the subjects were in the *off* medication state for visit 1 and vice versa).

The neuropsychological assessment included the RBANS Form A or Alternate Form B that provide subtest scores for Immediate Memory (List Learning, Story Memory), Visuospatial/ Constructional (Figure Copy, Line Orientation), Language (Picture Naming, Semantic Fluency), Attention (Digit Span, Coding) and Delayed Memory (List Learning Free Recall and Recognition, and Story Memory Free Recall, Figure Free Recall) domains (Randolph et al., 1998). Additional measures of attention and inhibition were included from subtests from the Wechsler Intelligence Scale-Fourth Edition (WAIS-IV) Digit Span and Letter-Number Sequencing (Wechsler, 2008), and the Stroop test (Golden, 1978). Several subtests measuring visuomotor integration and cognitive flexibility (Trails 1–5), fluency and switching, and planning functions (Tower Test) from the Delis Kaplan Executive Function System (D-KEFS) were administered (Delis, Kramer, Kaplan, & Holdnack, 2004).

Fine motor control was measured with two standardized tests, the Finger Tapping Test (FT) and the Grooved Pegboard Test (GP) (Reitan & Wolfson, 1993). On the FT task, subjects were required to tap with each hand across 5 trials in a 10-s period. The GP is a more complex test of manipulative dexterity with randomly positioned slots and pegs with a key along one side that must be rotated to be inserted correctly.

Statistical Analyses

Analyses evaluating the two PD groups in terms of cognitive and motor function were conducted using SPSS (Version 22) to determine differences based on the presenting motor features of the disease. All raw scores were converted into *Z*-scores based on the mean and standard deviations of normal controls for each neuropsychological measure. *Z*-score conversions maintain the distribution of raw scores while allowing the advantage of comparison of impairment across several cognitive domains. Several repeated measures analyses were conducted for the domains of attention/executive, language, memory, and visuospatial and visuomotor functions with group as the between-subject's factor (Control, LMO, RMO) and medication state (*on* and *off*) as the within subjects factor. Six multivariate analysis of variance (MANOA) measuring cognitive domains of interest and one motor model were evaluated. Separate univariates were evaluated in step-down analyses when the MANOVA was significant. Significant univariates were followed up with *post hoc* analyses with Bonferroni correction for multiple comparisons, while all univariates are presented for review in Table 2 given the small sample size. Age and education were evaluated as covariates for all multivariate models, but only used in the equation when one of the variables significantly adjusted for the variance.

RESULTS

Dopaminergic Medication States

To confirm dopaminergic washout between *on* and *off* medication states, a repeated measures model with side of motor onset as the between-subjects measure, and medication as the within-subjects measure was evaluated for UPDRS total and UPDRS motor subscores. The model was not significant for side of motor onset, $F(2,34) = .333$, $p = .719$, but was significant for a medication effect, $F(2,34) = 60.13$, $p < .001$ (see Table 1 for means). There was no significant medication by group interaction, $F(2,34) = 1.78$, $p = .185$. Medication effects were significant for both UPDRS total scores, $F(1,35) = 123.5$, $p < .001$, and UPDRS motor subscores, $F(1,35) = 109.6$, $p < .001$, consistent with more impaired UPDRS scores in the *off* medication state (UDPRS total *on* = 30.14, *off* = 44.54; UDPRS motor *on* = 18.47, *off* = 30.08), confirming sufficient medication washout (Table 1).

Attention

Education was not significant in the multivariate model for attention, while age significantly adjusted for the multivariate model and was used as a covariate [between-subjects, $F(4,71) = 7.46$; $p < .001$]. Overall, the multivariate model was not significant between-subjects, $F(8,144) = 1.76$, $p = .091$ (Table 2). The multivariate model was insignificant for within-subjects effects for medication, $F(4,71) = .613$, $p = .654$, but revealed a significant medication by group interaction, $F(8,144) = 2.77$, $p = .007$ (Table 3). The interaction was significant for Digit Span Total ($p = .002$) and Digits Span Forward ($p = .007$). *Post hoc* comparisons with Bonferroni correction revealed that the LMO group improved attentional performance in Digit Span Total and Forward during the *on* medication state, while there was no difference between medication states for the RMO group (Table 4). No significant medication by group interactions were identified for Digit Span Backwards, Digits Sequencing, or Letter Number Sequencing.

Table 2 reports descriptive statistics and significance between-subjects for cognitive tasks by group. Table 3 reports significant within-subject significance based on response to medications. Table 4 reports mean differences and significance for medication by group interaction effects.

Executive

Executive subtests were evaluated and education was not significant in the multivariate model, but age significantly adjusted for the variance and was used as a covariate, [between-subjects, $F(6,69) = 5.82$; $p < .001$]. The multivariate model revealed between-subjects significance, $F(12,140) = 2.38$, $p < .01$ (Table 2), but the within-subjects effects were not significant for either medication, $F(6,69) = .246$, $p = .960$, or for a medication by group interaction, $F(12,140) = .837$, $p = .613$. The between-subjects univariates revealed significance for Tower Total Time, and Stroop Word but not for the other executive subtests (see Table 2 for statistical values). *Post hoc* pairwise contrasts revealed the RMO (mean difference = .885; $p = .003$) and LMO groups (mean difference = .839; $p = .027$) required more time than controls to complete the Tower. However, only the RMO group was significantly more impaired than controls on Stroop Word (RMO mean difference = –.791; $p < .007$; LMO mean difference = –.685; $p = .086$). The two PD groups did not differ from each other on any of the subtests.

Fluency

Age and education were evaluated in the multivariate model, and education was not entered in the equation since it was not significant. Age was used as a covariate because it significantly adjusted for the variance in fluency between-subjects, $F(3,72) = 6.98$, $p = .001$. However, after adjusting for age, the multivariate model did not reveal significant between-subject, $F(6,146) = 1.98$, $p = .071$, or within-subject effects [medication, $F(3,72) = .561$, $p = .642$; medication by group interaction, $F(6,146) = .881$, $p = .511$; Table 2].

Verbal Memory

Covariates were evaluated in the multivariate model and age [between-subjects, $F(4,70) = 9.31$, $p = .001$; within-subjects, $F(4,70) = 2.91$, $p = .027$] and education were significant [between-subjects, $F(4,70) = 2.2$; $p = .077$; within-subjects, $F(4,70) = 3.54$; $p = .011$]. After controlling for age and education, the multivariate model was significant between-groups, $F(8,142) = 3.44$, $p = .001$ (Table 2), and within-groups for medication by group interaction [medication $F(4,67) = 1.96$; $p < .11$; medication by group interaction, $F(8,142) = 2.34$; $p = .022$; Table 3]. Between-subjects effects were significant for RBANS List Learning ($p < .001$), Story Memory ($p < .05$), List Recall ($p < .001$), and Story Recall ($p < .001$; Table 2). *Post hoc* comparisons with Bonferroni revealed that both groups performed lower than controls on RBANS List Learning ($p < .05$), RBANS List Recall ($p < .005$), RBANS Story Recall ($p < .005$), but the two PD groups were not significantly different from each other. The RMO group was also more impaired on RBANS Story Memory relative to controls ($p < .05$; Table 2).

The medication by group interaction was significant for Story Immediate and Story Delayed Memory Recall (Table 3). Both groups had different scores on RBANS Story Memory (i.e.,

immediate recall) between medication states (LMO, $p = .05$; RMO $p = .022$), and RBANS Story Recall (LMO, $p = .041$; RMO $p = .020$; Table 4). However, the LMO group improved recall in the *on* relative to the *off* medication state, while the RMO group displayed the opposite response to medications with lower Story Memory Recall in the *on* medication state relative to the *off* state.

Visuospatial

Age and education were tested in the model, and age was used as a covariate since it was significant between-subjects, $F(4,71) = 7.12$, $p < .001$. After controlling for age, the multivariate model was significant between-subjects for visuospatial functions, $F(8,144) = 3.05$, $p < .005$. However, within-subjects effects for medication $F(4,71) = .592$, $p = .669$ and the medication by group interaction were insignificant, $F(8,144) = .614$, $p = .765$. Univariates revealed between-subject differences for RBANS Coding $F(2,74) = 11.11$, $p < .001$, and RBANS Figure Copy $F(2,74) = 3.78$, $p < .05$, but not for RBANS Line Orientation or Figure Recall (Table 2). *Post hoc* comparisons with Bonferroni corrected revealed that both the RMO and LMO groups were more impaired than controls on Coding (RMO mean difference = –1.27; $p < .001$; LMO mean difference = .959, $p < .05$), but only the RMO group was significantly impaired on Figure Copy (mean difference = –.747; $p < .05$). The RMO and LMO groups were not significantly different from each other on any of these measures.

Visuomotor Control

Age, but not education, significantly adjusted for the variance in Trails performance between-subjects and was used as a covariate in the model, $F(5,69) = 5.57$, $p < .001$. The multivariate model was significant between-subjects, $F(10,140) = 2.84$, $p < .005$. However, within-subjects effects were insignificant for the multivariate model [medication, $F(5,69) = .293$; $p = .915$; medication by group, $F(10,140) = .613$; $p = .817$]. Univariate between-subjects effects were significant for Trails 1–5 ($p < .001$; see Table 2). The RMO group was significantly more impaired across Trails 1–5 ($p < .001$) relative to controls, while the LMO group was only more impaired than controls for Trails 2 ($p < .05$) and Trails 5 ($p < .005$). The RMO and LMO groups were not significantly different from one another on any of the Trails tasks.

Fine Motor Control

Six subjects (two controls, three LMO, and one RMO subjects) were excluded from the motor analyses because they had missing motor data for one hand from one of the visits. Age and education were evaluated as covariates, but only age was used because it was significant between-subjects, $F(2,67) = 5.45$, $p < .01$. The multivariate model was significant between subjects, $F(4,136) = 12.57$, $p < .001$, and within-subjects for hand by group [$F(4,136) = 6.74$; $p < .001$] and medication by group [$F(4,136) = 3.18$; $p = .016$] interactions. Within-subjects effects for medication, hand, or medication by hand by group interactions were insignificant. Between subjects univariate effects were significant for both Finger Tapping (FT) and Grooved Pegboard (GP; $p < .001$; Table 2). Pairwise comparisons with Bonferroni correction revealed the RMO (mean difference = –.789; $p = .016$) and LMO

groups (mean difference = –1.52; $p < .001$) were significantly more impaired than controls on FT speed. Similarly, on the GP task, the LMO (mean difference = –3.23; $p < .001$) and RMO groups (mean difference = –3.52; $p < .001$) were significantly slower than controls. There was no significant difference between the PD groups.

Within-subjects interactions for hand by group were significant for both FT and GP ($p < .001$) consistent with the expected greater impairment based on side of motor onset. However, the medication by group interaction was only significant for GP (GP; $p < .005$; FT; $p = .64$; Table 3). Pairwise comparisons for GP revealed medication effects for the LMO (mean difference = –1.58; $p < .001$) and RMO groups (mean difference = –.666; $p < .05$; Table 4).

DISCUSSION

Our results revealed the expected PD related cognitive deficits in executive functioning (planning), memory, and motor speed for all PD patients irrespective of the initial side of motor onset (Hanna-Pladdy et al., 2013). However, patients with greater left hemisphere dysfunction displayed more extensive cognitive deficits including additional deficits of selective attention and inhibition, verbal memory, and visuomotor integration. Patients with relatively greater right hemisphere dysfunction displayed greater fine motor impairment and greater response to dopamine replacement therapy on tasks of sensorimotor integration, attention and verbal memory. Conversely, there was a detrimental effect of medication for patients with left hemisphere dysfunction in terms of verbal memory recall. Overall, the findings do not support the premise that the degree of motor impairment predicts the extent of cognitive impairment, but suggests differential response to dopamine medications for cognitive functions which are predicted by basal level of dopamine.

Dopamine Asymmetries

Theories of neurochemical asymmetries propose that the right striatum may have lower quantities of dopamine than the left, which may result in heightened vulnerability to nigrostriatal denerveation (Glick, Ross, & Hough, 1982; Haaxma et al., 2010; Toga & Thompson, 2003). Evidence supporting dopamine asymmetries is based on postmortem studies, behavioral asymmetries and human nuclear imaging studies consistent with a leftward shift in dopamine levels (Glick et al., 1982; Toga & Thompson, 2003; van Dyck et al., 2002; Wagner et al., 1983). A left hemisphere dopamine activating system is theoretically linked to specialization of complex motor programming including right hand preference, speech and other skilled movements (Toga & Thompson, 2003; Tucker & Williamson, 1984). Therefore, replacement therapy may more readily ameliorate these depleted networks early in the disease process (Haaxma et al., 2010). This hypothesis is corroborated by our results of higher medication doses for PD patients with greater right hemisphere involvement, and subsequent improvement following levodopa on tasks of sensorimotor integration, attention, and verbal memory. Furthermore, patients with greater left hemisphere involvement in our study had relatively lower levodopa doses despite a trend for longer disease durations, consistent with the premise that higher levels of basal dopamine might eventually result in slower disease progression.

Conversely, the higher incidence of right motor onset symptoms in our study and other studies and recent evidence for lower dopamine transporter uptake in the left posterior putamen for PD, are consistent with a left and not right hemisphere predominance of nigrostriatal dysfunction (Riederer & Sian-Hulsmann, 2012; Scherfler et al., 2012). In summary, the predictors of motor lateralization in PD remain elusive despite speculation that dopamine asymmetries and handedness may play a role in predicting dominant side of motor onset (Melamed & Poewe, 2012; Riederer & Sian-Hulsmann, 2012; Uitti et al., 2005; van der Hoorn, Bartels, Leenders, & de Jong, 2011). Additional research is needed to reconcile the higher incidence of right motor onset disease despite some evidence for leftward dopamine asymmetry. Future studies should better control for disease severity, disease duration, and subtypes of PD, which are all likely to influence basal level of dopamine and cognitive profiles.

Motor Deficits and Dopamine

Previously it has been argued that the best motor control predictors of dopaminergic responsiveness, motor disability and UPDRS values, were alternating finger tapping measures of motor speed reflective of bradykinesia (Taylor Tavares et al., 2005). Despite these correlations, our findings did not reveal a statistically significant influence of DRT on finger tapping speed in early PD. The group with greater right hemisphere involvement displayed more impairment in fine motor control. Even on selective tasks segregating specific aspects of visuomotor integration, the patients with right hemisphere impairment were selectively impaired on the tasks isolating processing speed and motor speed, as opposed to those requiring greater cognitive flexibility or visual search. However, the findings revealed little change between *on* and *off* medication conditions for finger tapping speed, irrespective of side of motor onset. This partly can be explained by the repetitive nature of the index finger tapping test used in our study that did not involve a sequential or finger-alternating component (Taylor Tavares et al., 2005). Additionally, the findings may be related to the long-duration response of levodopa, which has been demonstrated to only decline following 24 hr (exceeding the 15-hr washout period), but can potentially extend even beyond a 2-week washout phase, as well as the early stage of the patients (Kang & Auinger, 2012; Nutt, Carter, & Woodward, 1995).

Dopaminergic modulation was selective in improving the grooved pegboard task which required sensorimotor integration and manual dexterity. Patients with right hemisphere disease displayed greater reductions in fine motor speed and correspondingly displayed the greatest response to DRT. The grooved pegboard task's response to medications is consistent with its potential role as a biomarker of nigrostriatal denervation, and indicates it is a sensitive and reliable measure of degree of dopamine depletion in early stage PD (Bohnen, Kuwabara, Constantine, Mathis, & Moore, 2007; Bohnen, Studenski, Constantine, & Moore, 2008). This hypothesis is also supported by the trend for right hemisphere disease patients to display higher levodopa doses. Conversely, the patients with left hemisphere disease displayed relatively lower levodopa doses, less fine motor impairment and less pronounced response to levodopa in terms of both cognitive and motor functions. Overall, these findings reflect how basal level of dopamine may predict response to levodopa in particular early in the disease process.

Dopamine and Attention

On the majority of neuropsychological tests, both patient groups displayed impairment irrespective of side of motor onset, substantiating extensive mild cognitive deficits in early PD. Bilateral hemispheric contribution to tasks evaluating higher levels of cognitive flexibility, such as planning, were evident. These findings indicate that both medicated and unmedicated PD patients display greater cognitive impairment than age-matched controls irrespective of motor presentation, and highlights the role of other-disease related variables in cognitive presentation (Hanna-Pladdy & Heilman, 2010; Jubault et al., 2009). Nonetheless, limited medication effects emerged for attentional functions. That is, levodopa improved performance on the WAIS-IV Digit Span (DS) forward and total for the patients with greater right hemisphere dopamine deficiency. DS forward is a component of DS total that also revealed improvement in the *on* medication state. Working memory was tested using the DS tests and patients with greater right hemisphere disease exhibited poorer attention in the *off* state than *on* state in DS forward and, collectively, in the DS total, which measures attention, concentration, and mental control (Wechsler, 2008). Consistent with our findings, levodopa has previously demonstrated improvement in attention and working memory mediated by the dorsal frontal-striatal circuitry, which is depleted early in PD (Cools, 2006; Torta, Castelli, Zibetti, Lopiano, & Geminiani, 2009). The positive influence of levodopa in patients with greater right hemisphere dopamine deficiency further supports the bilateral distribution of attention/executive functions, and highlights the role of dopamine in attention/executive functions. Our findings of sensorimotor and attentional responsiveness to levodopa substantiate this premise, while the selective improvement in patients with greater right hemisphere disease supports theories of dopamine asymmetries predicting amelioration for the more depleted hemisphere.

Nonetheless, patients with left hemisphere disease had greater impairment on tasks of selective inhibition, verbal memory, visuospatial functions and visuomotor integration consistent with previous reports in the literature, but these deficits did not improve with levodopa (Drag et al., 2009; Tomer et al., 2007). The results indicate that cognitive tasks are potentially less sensitive to phasic changes in dopamine than motor tasks, which may partly be explained by the greater severity of dopamine depletion in motor *versus* cognitive areas (Drag et al., 2009). Additionally, lateralization influences on cognitive profiles are likely contributory and have been well documented. Greater cognitive impairment in patients with left hemisphere disease has also been documented in both left hemisphere stroke and left asymmetric neurodegenerative disease, and emphasizes the role of hemispheric specialization in influencing extent of cognitive deficits and cognitive profiles (Mesulam et al., 2014; Shprakh & Suvorova, 2010). The dissociation between dopaminergic denervation and degree of cognitive impairment is in line with the growing body of literature reviewing extranigral sources of cognitive impairment in early PD (Aarsland, Bronnick, & Fladby, 2011; Buongiorno et al., 2011; Gomperts et al., 2013; Hanna-Pladdy & Heilman, 2010; Ibarretxe-Bilbao et al., 2011).

Paradoxical Effects of Dopamine

While dopamine replacement therapy has established improvement for PD motor deficits, depending on the frontostriatal circuit involved and the nature of the task, it can improve or

impair cognitive performance (Cools et al., 2001, 2003; Macdonald & Monchi, 2011). The proposed imbalance of dopamine levels in different cognitive systems relying on different areas of prefrontal cortex as well as the dopamine asymmetry hypothesis, may explain the selective improvement in cognition following dopamine replacement for patients with greater right hemisphere disease (Macdonald & Monchi, 2011). In addition to attentional functions, this group improved in the encoding of verbal information following medication. While this could have conceivably been potentiated by improved attentional functions, verbal memory delayed recall also improved suggesting there is dopaminergic influence on declarative memory retrieval operations. Conversely, in patients with greater left hemisphere deficiency, dopamine had a detrimental effect on verbal memory encoding and memory retention.

The paradoxical effect of levodopa has been reported previously for cognition in PD, in particular early in the disease process when the dopamine deficit is mild and optimal medication for treatment of motor dysfunction may involve over-medication of circuits that are non-depleted (Jahanshahi et al., 2010; Jubault et al., 2009; Macdonald & Monchi, 2011; Torta et al., 2009). These studies, however, have focused almost exclusively on attention and executive functions that are highly influenced to some extent by dopaminergic dysfunction (Lange et al., 1992). Most studies examining how dopaminergic transmission influences learning and memory in early PD have focused primarily on working memory, incremental learning, and reward based learning, with few investigations focusing on the role of dopamine in declarative memory (Cools et al., 2003; Cools, Stefanova, Barker, Robbins, & Owen, 2002; Costa et al., 2003; Cropley et al., 2008; Fera et al., 2007; Fournet et al., 2000; Gotham et al., 1986; Jahanshahi et al., 2010; Kelly et al., 2009; Lange et al., 1992; McClure, Laibson, Loewenstein, & Cohen, 2004; Nagano-Saito et al., 2008; Reiss et al., 2005; Sawamoto et al., 2008; Seo, Beigi, Jahanshahi, & Averbeck, 2010; Shohamy, Myers, Geghman, Sage, & Gluck, 2006). Nonetheless, there have been several investigations evaluating the role of dopamine in memory recall and retention. Despite the focus on hippocampal atrophy as the source of memory impairment in PD, some evidence points to striatal dopaminergic depletion and caudate volume loss as a strong predictor of verbal memory impairment (Jokinen et al., 2009). There is also emerging evidence endorsing dopaminergic modulation of hippocampal-dependent learning and memory consolidation, in particular for the auditory domain (Blonder et al., 2013; Halbig et al., 2008; O'Carroll, Martin, Sandin, Frenguelli, & Morris, 2006; Pezze & Bast, 2012; Schicknick et al., 2008). Furthermore, similar to our findings, several studies have reported a paradoxical effect of levodopa withdrawal on verbal memory retention (Blonder et al., 2013; Brusa et al., 2005; Halbig et al., 2008). Taken together, these studies describe a key role for dopamine transmission in hippocampal synaptic plasticity, and emphasize the role of dopamine in learning and memory.

SUMMARY

In summary, the response to dopamine replacement in PD may be complicated not only by the staging of the disease and task demands, but also related to differential profiles based on hemispheric asymmetries influencing basal level of dopamine. These factors can influence cognitive profiles, and can partly explain the inconsistent results and the variable cognitive

outcomes in the PD literature. Finally, while our results provide support for the role of dopaminergic modulation of attention and memory functions, many of the cognitive deficits characterized appear to be regulated by other pathological mechanisms. Thus, the neuropathological basis of cognitive impairment in PD appears to be multifactorial, and future research should focus on teasing apart dopaminergic from extranigral sources of cognitive deficits in PD, and identifying predictors of cognitive progression.

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Table 1

Means (standard deviations) for each group for demographics and screening measures

Group	Age	EDU	MMSE	BDI-II	BAI	LED	UPDRS Motor On	UPDRS Motor Off	DUR
Control (*n* = 42)	66.9 (4.6)	16.3 (1.5)	29.3 (0.9)	3.29 (2.46)	1.17 (1.40)				
LMO PD (*n* = 13)	65.9 (6.5)	15.8 (2.9)	29.3 (0.9)	9.96 (4.67)	9.89 (5.49)	775 (47.1)	18.3 (3.9)	31 (7.9)	47.1 (29.9)
RMO PD (*n* = 23)	65.9 (8.3)	14.8 (2.4)	28.3 (1.6)	8.80 (7.02)	9.07 (9.48)	740 (55.3)	18.4 (7.0)	29.1 (9.4)	55.3 (30.4)

Note. EDU = education, number of years; MMSE = Mini-Mental Status Examination, EDIN = Edinburgh Handedness Inventory, LED = levodopa equivalent dose; LMO = left motor onset; RMO = right motor onset: UPDRS = Unified Parkinson's Disease Rating Scale; DUR = duration of diagnosis in months.

Table 2

Descriptive statistics of cognitive tasks by PD group and multivariate and univariate significance

	LMO (n = 13)	M	Adj. M	SD	RMO (n = 23)	M	Adj. M	SD	F	p	np^2
Attention											
Multivariate between subjects									1.76	.091	.09
WAIS-IV Digit Span Total		–.43	–.46	1.06		–.64	–.66	1.20	3.35	.040	.08
WAIS-IV Digit Span Forward		–.12	–.14	1.10		–.35	–.36	1.05	.96	.387	.03
WAIS-IV Digit Span Backward		–.42	–.44	1.09		–.58	–.59	.94	3.28	.043	.08
WAIS-IV Digit Span Sequence		–.68	–.74	1.56		–.83	–.85	2.04	3.77	.028	.09
WAIS-IV Letter Number Sequence		–.71	–.81	1.52		–.89	–.94	1.61	7.40	**.001**	.17
Executive											
Multivariate between subjects									2.38	**.008**	0.17
DKEFS Tower Total Achievement		–.12	–.11	.93		–.47	–.47	.59	2.26	.111	.06
D-KEFS Tower Rule Violations		–.03	–.07	.70		–.40	–.42	1.34	1.52	.225	.04
D-KEFS Tower Time		–.77	–.81	1.29		–.84	–.86	1.04	7.50	**.001**	.17
Stroop Word		–.59	–.65	.97		–.74	–.76	1.09	5.92	**.004**	.14
Stroop Color		–.20	–.27	.84		–.31	–.34	.90	1.72	.186	.04
Stroop Color-Word		–.05	–.12	.89		–.33	–.36	1.09	1.44	.244	.04
D-KEFS Fluency											
Multivariate between subjects									1.98	.071	.08
Letter Fluency		–.05	–.01	1.31		–.32	–.35	1.42	.93	.399	.03
Category Fluency		–.44	–.53	1.22		–.43	–.46	1.29	2.85	.064	.07
Switching Fluency		–.52	–.60	1.19		–.63	–.67	1.58	4.07	**.021**	.09
RBANS Verbal Memory											
Multivariate between subjects									3.44	**.001**	.19
List Learning		–1.17	–1.27	1.33		–.96	–.89	1.88	8.65	**.001**	.19
Story Immediate Memory		–.78	–0.74	1.48		–1.08	–.84	1.76	4.02	**.022**	.10
List Recall		–1.02	–1.12	1.34		–.98	–.91	1.64	8.47	**.001**	.18

	LMO (n = 13)	M	Adj. M	SD	RMO (n = 23)	M	Adj. M	SD	F	p	np^2
Story Recall		–1.49	–1.52	1.97		–1.43	–1.25	2.01	10.53	**.001**	.22
Visuomotor											
Multivariate between subjects									2.84	**.003**	.17
D-KEFS Trails 1 (Visual)		–.66	–.78	2.12		–1.17	–1.22	1.89	7.28	**.001**	.17
D-KEFS Trails 2 (Number)		–1.32	–1.49	3.09		–1.79	–1.87	2.46	11.9	**.001**	.25
D-KEFS Trails 3 (Letter)		–1.19	–1.36	3.12		–2.30	–2.38	4.06	9.05	**.001**	.19
D-KEFS Trails 4 (Number Letter)		–0.97	–1.13	2.62		–2.42	–2.49	4.02	9.07	**.001**	.19
D-KEFS Trails 5 (Motor)		–1.42	–1.55	2.15		–1.66	–1.72	2.48	11.9	**.001**	.25
Visuospatial											
Multivariate between subjects									3.05	**.003**	.15
RBANS Coding		–.79	–.90	1.32		–1.16	–1.21	1.66	11.11	**.001**	.23
RBANS Line Orientation		–.09	–.11	0.73		–.44	–.45	1.07	1.84	.166	.05
RBANS Figure Copy		–.65	–.67	2.13		–0.73	–.74	1.55	3.78	**.027**	.09
RBANS Figure Recall		–.17	–.19	.02		–.16	–.17	.03	.65	.524	.02
FIne Motor											
Multivariate between subjects									12.57	**.001**	0.27
Finger Tapping		–1.47	–1.51	1.20		–0.78	–0.78	1.31	9.99	**.001**	0.23
Grooved Pegboard		–2.81	–3.14	3.18		–3.41	–3.43	2.71	29.95	**.001**	0.47

Note. Comparisons based upon MANCOVA adjusted means controlling for age, and education for Verbal Memory. RMO < controls; RMO & LMO < controls. WAIS-IV = Wechsler Adult Intelligence Scale IV; DS = digit span; LNS = Letter Number Sequencing; D-KEFS = Delis-Kaplan Executive Function System; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; LMO = left motor onset; RMO = right motor onset.

▲ RMO < controls; ◯ RMO & LMO < controls.

Table 3

Significant results and descriptive statistics for within-subjects effects (medication and medication by group interaction)

Source	SS	df	MS	F	*p*	np^2
Attention						
Multivariate tests						
Medication by group interaction		8, 144		2.77	**.007**	.133
Univariate tests						
Medication by group						
WAIS-IV Digit Span Total	1.98	2, 74	.99	6.79	**.002**	.155
WAIS-IV Digit Span Forward	2.33	2, 74	1.17	5.39	**.007**	.127
RBANS Verbal Memory						
Multivariate tests						
Medication by group interaction		8, 142		2.34	**.022**	.116
Univariate tests						
Medication by group						
Story Immediate Memory	9.01	2, 73	4.51	4.54	**.014**	.111
Story Memory Recall	14.99	2, 73	7.49	4.89	**.010**	.118
FINE Motor Control						
Multivariate model						
Medication by group interaction		4, 136		3.18	**.016**	.085
Hand by group interaction		4, 136		6.74	**.001**	.165
Univariate Tests						
Medication by group						
FT	.412	2, 68	0.206	.454	.637	.013
GP	20.48	2, 68	10.24	6.21	**.003**	.154
Hand by group						
FT	17.53	2, 68	8.76	8.60	**.001**	.202
GP	97.49	2, 68	48.74	14.51	**.001**	.299

Note. Comparisons based upon multivariate analysis of variance adjusted means controlling for age, and education for Verbal Memory.

WAIS-IV = Wechsler Adult Intelligence Scale IV; DS = Digit Span; LNS = Letter Number Sequencing; D-KEFS = Delis-Kaplan Executive Function System; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

Table 4

Multiple comparisons and mean differences in medication by Group interactions

				95% Confidence	
Source	**Mean diff**	***SE***	**Sig**	**Lower**	**upper**
Attention					
WAIS-IV Digit Span Total					
LMO	.54	.150	**.001**	.241	.839
RMO	.12	.113	.274	–.100	.349
WAIS-IV Digit Span Forward					
LMO	.57	.183	**.002**	.208	.937
RMO	.09	.137	.495	–.179	.368
RBANS Verbal Memory					
Story Immediate Memory					
LMO	.780	.392	**.05**	–.001	1.56
RMO	–.709	.304	**.022**	–1.32	–.103
Story Recall					
LMO	1.01	.486	**.014**	.041	1.98
RMO	–.899	.378	**.020**	–1.65	–.146
Grooved Pegboard					
LMO	–1.58	.412	**.000**	–2.40	–.755
RMO	–.666	.274	**.018**	–1.21	–.119

Note. Comparisons based upon estimated marginal means controlling for age, and education for Verbal Memory. $p < .05$, where *p*-values are adjusted using the Bonferroni method.

WAIS-IV = Wechsler Adult Intelligence Scale IV; DS = Digit Span; LNS = Letter Number Sequencing; D-KEFS = Delis-Kaplan Executive Function System; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. LMO = left motor onset; RMO = right motor onset.