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Differential susceptibility to motor impulsivity among functional subtypes of Parkinson's disease

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Abstract

Background and objectives—Parkinson's disease patients with predominant postural instability and gait difficulties (PIGD) may experience unique cognitive difficulties compared to patients with tremor predominant (TD) symptoms. PIGD patients are also at high risk for falling, and some of the worst fallers seem to react impulsively to their environment. We tested the hypothesis that PIGD patients show poorer control over motor impulses compared to TD patients.

Methods—34 PD participants were divided into predominant PIGD (n=17) or TD (n=17) functional subtypes based on their presenting symptoms in their optimally treated motor state. All participants performed a speeded reaction task that quantified motor impulsivity and the proficiency of inhibiting prepotent motor impulses.

Results—The groups showed similar reaction times, but compared to TD patients, PIGD patients made significantly more impulsive motor errors. Notably, when the initial impulsive erroneous response was avoided, PIGD and TD groups were similar in their ability to suppress the incorrect motor impulse from further interfering with the selection of a correct action.

Conclusions—PD patients with PIGD predominant symptoms show greater susceptibility to acting on prepotent motor impulses compared to TD patients. This finding may have direct implications for fall risk and also points to dissociable neurocognitive pathologies in TD and PIGD subtypes. Clinically, the use of specific cognitive instruments to assess the expression and inhibition of motor impulses may help identify PD patients who have difficulty 'thinking before they leap' and are at high risk of falling.

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INTRODUCTION

In our ever-changing environments, perceptual information (eg, detecting a snake on the ground) can sometimes trigger impulsive motor reactions (eg, an impulse to jump away). Even though spontaneous reactions can be adaptive, acting on some motor impulses can have deleterious effects. For example, in a recent editorial focusing on fall risk in Parkinson's disease (PD), Ahlskog commented that 'experience in the clinic reveals that some of the worst fallers are those who impulsively jump from their chair or turn without thinking'.¹ A subset of PD patients who are at high risk for falling present with predominant postural instability and gait difficulties (PIGD).^{2,3}

We reported recently that a large sample of PD patients with mixed clinical features did not show greater difficulties with motor impulse control compared to healthy controls.⁴ Here, in order to address a different issue, we re-analysed a subset of these PD patients after classifying them into PI GD and tremor predominant (TD) subtypes. We tested the novel hypothesis that PI GD predominant patients have more problems with motor impulse control than patients who present with tremor dominant symptoms. This dissociation may provide new insights about how PD subtypes differentially impact neurocognitive processes that have been linked to frontal-basal ganglia circuitry. Participants with PI GD or TD performed a speeded reaction task that measures one's susceptibility to act impulsively as well as the proficiency of inhibiting action impulses to reduce interference with the execution of goal actions.^{5,6} We predicted that, compared to TD patients, PI GD patients would be more susceptible to acting on strong motor impulses in error.

METHODS

Participants

Thirty-four individuals diagnosed with idiopathic PD by a movement disorders neurologist were included in this study. These participants were extracted from a pool of 52 PD patients from a larger study⁴ on the basis of meeting specific criteria for PI GD and TD subtypes as established by methods published previously.⁷ Subtype classification was based on presenting symptoms in the on-medication state. Thus, the classifications represented functional subgroups with predominant symptom patterns expressed under optimal treatment conditions and in each individual's typical, everyday motor state. The excluded patients did not meet criteria for predominant PI GD or TD. Participants were recruited from a movement disorders clinic, and all were rated stage III or less using the Hoehn and Yahr scale,⁸ indicating mild to early moderate symptom profiles.

Table 1 shows group demographics. The subgroups did not differ in age, education, years since PD onset, age at PD onset, mini-mental status exam, or medication usage (all $p > 0.10$). All patients showed improved symptom control in response to dopamine medications and were tested during the optimal 'on' phase of their medication cycle. Seven patients were taking antidepressant medication, and all reported stable mood control. Patients included in the study were free of any confounding neurological, medical or psychiatric conditions, denied depression during clinical interview at the time of testing, showed intact mental and global cognitive status on the mini-mental status exam, had corrected-to-normal vision, and provided informed consent prior to participating in the study, which was fully compliant with standards of ethical conduct in human research as regulated by the human investigation committee at the University of Virginia. Additional details on patient characteristics and exclusion/inclusion criteria can be found in Wylie *et al.*⁴

Conceptual background of the Simon task

The Simon task produces one of the most sensitive measures of motor impulsivity (cf. Simon⁵ and Lu and Proctor⁹). Participants issue speeded manual reactions based on the colour of circles that appear sequentially, but randomly, to the left or right of a central fixation point on a computer screen (eg, blue circle, left-hand response; green circle, right-hand response). Competing with this deliberate, goal-driven selection process is a spontaneous impulse to respond with the hand that is in the direction corresponding to the spatial location of the circle, that is, a circle appearing to the left visual field triggers an initial impulse to respond with the left hand, irrespective of its colour. An extensive literature has revealed that when the action impulse triggered by the stimulus location corresponds to the action signalled by the stimulus colour, the dual engagement of the same action speeds reaction times (RTs) and increases accuracy rates. Conversely, RT slows and accuracy rates decrease when the action impulse triggered by the circle's location and the action signalled by its colour are non-corresponding (eg, a coloured circle signalling a left-hand response appears in the right visual field). In this case, activation of the incorrect action impulse interferes with selection of the goal-directed response and, in some instances, captures the response system sufficiently to produce a fast impulsive error. Slowing of correct responses in this conflict situation is typically attributed to the extra time required to inhibit the interfering action impulse. The detrimental influence of location-driven response activation on the mean RTs and accuracy rates of non-corresponding trials relative to the facilitative influence on corresponding trials is called the Simon effect. This effect has been used with considerable success to study individual and group differences in cognitive control (ie, inhibition) over interfering action impulses.¹⁰

A more elaborate conceptual framework for studying impulse control in the Simon task is provided by the dual-process activation suppression (DPAS) model⁶ (see van den Wildenberg *et al*¹⁰ for a detailed review). This model uses distributional analyses to dissociate two temporally distinct processes that underlie interference control. The first process reflects the degree to which an individual reacts impulsively on the basis of the location-driven response. Motor impulsivity is inferred by differences in fast errors that are revealed when accuracy rates are plotted as a function of RT (ie, a conditional accuracy function, CAF). Stronger susceptibility to motor impulsivity leads to a higher proportion of fast errors.¹¹ The second process is assumed to reflect the top-down inhibitory control that is engaged subsequently to suppress the interference induced by an incorrect action impulse. Proficient inhibitory control is assumed to be most effective at the slow end of the RT distribution because it takes time for this control to emerge after it has been triggered by an incorrect action impulse. Thus, the model predicts that plotting the magnitude of the Simon interference effect as a function of response speed (ie, a delta plot) will yield a pattern of increasing interference across fast to intermediate response latencies that is followed by a reduction in interference towards the slow end of the distribution as inhibition becomes more fully engaged. Studies of non-clinical and clinical populations demonstrate that a steeper negative-going slope in the slowest segment of the delta plot is associated with more proficient inhibitory control over incorrectly activated action impulses.¹⁰ Together, CAFs and delta plots provide insight into the dynamics of impulse activation and inhibition that are masked in mean Simon effect values.

Simon task procedures

The experimental procedures that guided implementation of the Simon task have been described in detail previously.⁴ Briefly, participants made a button press with the right or left thumb based on predetermined mappings between circle colour and response side (eg, green circle, right-thumb press; blue circle, left-thumb press), which were counterbalanced across participants. Participants first completed 100 practice trials with the circle appearing

in the same location as the fixation point. This was used to help facilitate learning of the colour–response mappings. Next, participants completed a block of 60 practice trials in which circles appeared either to the right or left of fixation as described above. Five blocks of 60 experimental trials were then performed, totalling 300 experimental trials. One to two minute rest breaks were provided between blocks, and the entire task lasted <25 min. Trials were divided into two types based on the correspondence between the spatial location of the circle and the response signalled by its colour. ‘Corresponding’ trials occurred when the circle appeared to the side of fixation that matched the side of the response signalled by the colour of the stimulus (eg, a blue circle signalling a left-hand response appeared to the left side of fixation). ‘Non-corresponding’ trials occurred when the circle was presented to the side of fixation opposite to the side of the response signalled by the circle’s colour (eg, a blue circle signalling a left-hand response appeared to the right side of fixation). Within each block of trials, corresponding and non-corresponding trial types were presented randomly and with equal probability so that participants completed 150 corresponding and 150 non-corresponding trials across the experiment.

Design and statistical techniques

Details regarding the treatment of RT and accuracy data, including distributional analytic methods, are described in extensive detail in Wylie *et al.*⁴ Mean RT and square-rooted accuracy data were analysed first using separate repeated-measures ANOVA procedures. Each analysis included a within-subjects factor of *Correspondence* (corresponding, non-corresponding) and a between-subjects factor of *Group* (PIGD, TD). Next, the susceptibility to motor impulsivity was measured by analysing group differences in accuracy rates across all bins of the CAFs as a function of correspondence, and then focusing on a group comparison involving accuracy rates from just the fastest bin of RTs where fast errors are expected to occur (see details on binning and analytic procedures in Wylie *et al.*⁴ and description from figure 2). The proficiency of suppression was measured from delta plots, which plot the Simon interference effect (ie, mean RT for the non-corresponding condition minus mean RT for the corresponding condition) as a function of the entire RT distribution (see description in figure 3). We first analysed the slopes of the segments between all RT bins of the delta plot before focusing on the slope of the slowest RT segment, which provides the most sensitive measure of the proficiency of the inhibition process.⁶¹⁰

RESULTS

Mean RT and accuracy effects

The groups showed equivalent overall mean RTs (PIGD=496 ms, TD=507 ms; *Group*: RT, $F(1,32)=0.19$, $p=0.66$), but the PIGD group made more overall errors than the TD group (accuracy rates PIGD=93.7%, TD=96.8%; *Group*: accuracy, $F(1,32)=4.50$, $p=0.04$). As illustrated in figure 1A,B, a robust Simon effect was produced in RT and accuracy rates for both groups; that is, slower RTs and reduced accuracy rates occurred for non-corresponding than for corresponding trials (*Correspondence*: RT, $F(1,32)=58.45$, $p<0.001$; accuracy, $F(1,32)=24.01$, $p<0.001$). It can also be seen in figure 1A,B that although the Simon effect on RT did not differ between groups (PIGD=34 ms; TD=35 ms; *Group* × *Correspondence*: RT, $F(1,32)<1$), the PIGD group tended to make more errors than the TD group on non-corresponding compared to corresponding trials (PIGD=4.5%; TD=1.8%) (*Group* × *Correspondence*: accuracy, $F(1,32)=3.76$, $p=0.06$).

Group effects on motor impulsivity

Figure 2 reveals a striking difference in the CAFs for corresponding and non-corresponding trials. As we have reported previously, errors on corresponding trials were uniformly low across all response speeds, whereas a pattern of fast errors was followed by a dramatic

reduction in errors at intermediate and slow speeds on non-corresponding trials. It is apparent as well that fast errors on non-corresponding trials were much higher for PIGD than for TD patients. Guided by the DPAS model, we first analysed accuracy rates for all bins of the CAFs (*Bin* factor, seven levels) as a function of correspondence, and then proceeded with a focused analysis of accuracy rates from the fastest RT bin, which is the most sensitive measure of the strength of motor impulsivity. Confirming the mean analysis, PIGD performed less accurately overall compared to the TD (*Group*, $F(1,32)=4.69$, $p=0.03$), and this group difference was greater for non-corresponding than for corresponding trials (*Correspondence*, $F(1,32)=24.72$, $p<0.001$). Importantly, accuracy rates differed across bins (*Bins*, $F(6,192)=16.78$, $p<0.001$), and a significant three-way interaction indicated that the patient subgroups differed in their patterns of accuracy rates across bins as a function of stimulus–response correspondence, (*Correspondence* $\times$ *Bins* $\times$ *Group*, $F(6,192)=3.63$, $p=0.03$). As apparent in figure 2, this group difference is clearly evident in the pattern of accuracy for the fastest bins on non-corresponding where susceptibility to strong motor impulsivity is best revealed. Focusing our analysis on this fastest bin revealed reduced accuracy (ie, more fast impulsive errors) on non-corresponding than on corresponding trials (*Correspondence*, $F(1,32)=23.18$, $p<0.001$). The groups did not differ in the overall mean accuracy for fast responses (PIGD=84.8%; TD=90.7%; *Group*, $F(1,32)=2.69$, $p=0.11$). However, the groups showed differential patterns of fast, impulsive errors as a function of correspondence (*Group* $\times$ *Correspondence*, $F(1,32)=5.01$, $p=0.03$); specifically, while the groups showed similar accuracy rates for fastest bin of corresponding trials (PIGD=96.7%, TD=95.5%), PIGD patients showed significantly poorer accuracy (ie, made more impulsive errors, 72.9%) than did TD patients (86.0%) for the fastest non-corresponding trials ($F(1,32)=0.39$, $p=0.04$). According to the DPAS model, PIGD patients experienced enhanced motor impulsivity.

Group effects on impulse inhibition

The delta plots for the PIGD and TD groups shown in figure 3 clearly illustrate the absence of uniformity in the Simon effect across the RT distribution. As predicted by the DPAS model, fast and intermediate response latencies show positive-going delta slopes consistent with increasing interference from incorrect action impulses. However, this pattern reverses across slower response latencies, revealing a reduction of interference that is consistent with the gradual build-up of inhibitory control (*Slopes*, $F(5,28)=4.29$, $p<0.01$). Importantly, there were no group differences in slopes across the delta plot (*Slopes* $\times$ *Group*, $F(5,28)=1.73$, $p=0.16$). The slope connecting the final two segments of the delta plot is most sensitive to the effectiveness of inhibitory control, and it is more steeply negative-going for groups with stronger inhibitory control.¹⁰ The slope of the final segment of the delta plot was negative-going and of similar magnitude among PIGD ($m=-0.08$) and TD ($m=-0.13$) patients ($F(1,32)=0.30$, $p=0.59$). This suggests that PIGD and TD groups did not differ in the proficiency of inhibiting the interference produced by incorrect action impulses that were not acted upon.

Ruling out potential clinical confounds

We obtained depression ratings (Center for Epidemiological Studies Depression Scale; CESD) on 13/17 patients from the tremor group and on 15/17 patients from the PIGD group. Notably, all patients taking an antidepressant were among those who completed the depression scale. The mean depression ratings were 10.4 (SEM=2.6) and 13.2 (SEM=1.9) for the TD and PIGD groups, respectively. These depression scores did not differ statistically between groups ($F(1,26)=0.80$, $p=0.38$) and represent values well below cut-offs suggestive of clinical depression. To further test the potential influence of depression, we assessed the correlation between depression score and accuracy from the fastest bin of the conditional accuracy function for the 28/34 patients who completed the depression scale; the

correlation was not statistically significant ($r=0.21$, $p=0.27$), and also was in a direction opposite to the interpretation that higher depression scores are associated with lower accuracy (ie, more fast errors). Finally, PIGD patients made more fast, impulsive errors than TD patients (PIGD=25%; TD=12%), even after excluding patients from both groups who were taking an antidepressant ($F(1,25)=2.93$, $p<0.05$; one-sided hypothesis test aligned with prediction that PIGD more impulsive than TD). This increases confidence that neither ratings of depression nor the inclusion of patients on antidepressant medication can account for the reported data patterns.

Data were also collected on additional neuropsychological measures in the majority of patients. To rule out the potential role of general cognitive differences between groups, table 1 illustrates that the groups did not differ on measures of verbal learning, semantic fluency, and putative measures of executive functioning (ie, attention span, phonemic fluency, set-shifting and motor sequencing). None of the measures correlated with the measure of response capture in the Simon task that differentiated the PIGD and TD groups, which was true for the entire sample and separately within the subgroups. These data patterns argue against the interpretation that group differences in response capture found in the Simon task can be accounted for by global group differences in general cognitive functioning or executive cognitive abilities.

DISCUSSION

We used a powerful cognitive framework to determine whether PIGD predominant patients display an increased susceptibility to acting on strong motor impulses. As reported previously, the analytic framework of the DPAS model provided novel insights into group differences in the dynamics of motor impulse control.⁴ Compared to TD patients, PIGD patients were more impulsive. That is, their reactions were more often captured by strong, incorrect motor impulses. However, when an impulsive reaction was avoided, the groups were similar in their ability to inhibit the action impulse from further interfering with the selection of a correct action.

The demonstration that PD patients with distinct symptom profiles in their optimally treated state show differential susceptibility to reacting impulsively may be important clinically. While a direct link between motor impulsivity and fall risk awaits further investigation, these findings expose a vulnerability in motor impulse control among PIGD predominant patients that may contribute to fall risk in everyday activities. Studies have linked gait dysfunction in PD to performance on neuropsychological measures that assess broader aspects of executive functioning (eg, Trail Making Test Part B, phonemic fluency).^{12,13} Studies using more specific measures of executive control suggest that reduced proficiency in walking and performing a cognitive task simultaneously (ie, dual-tasking), as well as difficulties resolving response interference produced by visual distractors may be particularly important factors in fall risk and gait dyscontrol.^{14,15} Until the current investigation, the potential role of motor impulsivity, despite its suspected ecological and clinical relevance to gait dysfunction, had not been assessed directly. The measurement of specific cognitive control deficits, including the susceptibility to impulsive motor errors, may be essential for enhancing the assessment of fall risk and tracking the emergence and progression of diminishing gait control in PD.

The present findings also add to a broader literature indicating that non-demented PIGD and TD predominant subtypes may be associated with dissociable neuropathological and cognitive effects. For example, dopaminergic neuronal loss in PIGD appears more extensive in caudate and putamen compared to TD patients, even at early stages of the disease.¹⁶ This may account for why PIGD patients are more likely than TD patients to progress to

dementia as well as why PIGD patients tend to show particular vulnerabilities in executive cognitive abilities prior to dementia onset.^{17–20} Importantly, the increased motor impulsivity demonstrated here among PIGD patients could not be explained by differences in general cognitive functioning or depression. Future studies of PD that associate changes in frontal–basal ganglia circuit function with specific cognitive control deficits could provide important clues about neuropathological differences among PIGD and TD subgroups.

Functional imaging has demonstrated that poorer motor impulse control on conflict trials in the Simon task is associated with increased activity in the pre-supplementary motor area (pre-SMA),^{21–23} a region strongly implicated in action selection.²⁴ Increased pre-SMA activity was interpreted as reflecting greater demands on action selection processes in situations of high response conflict. One possibility is that pre-SMA activity may be relatively more hypoactive in PIGD patients compared to TD patients, thus diminishing their ability to quickly engage action control processes to prevent impulsive action tendencies from capturing the response system. It is also possible that the PIGD vulnerability to response capture involves differences in the subthalamic nucleus (STN) function, a region postulated to play an important role in holding action in check in conflict situations.²⁵ STN stimulation in PD increases fast, impulsive motor errors.²⁶ Together, these findings raise the intriguing idea that circuitry involving the pre-SMA and STN may be important systems to investigate to explain the increased motor impulsivity seen among PIGD patients.

It is important to note that impulsivity is a complex construct that describes both impulsive actions (ie, spontaneous motor reactions) as well as impulsive decisions (ie, choices made with little forethought about consequences) that involve distinct time courses and neural mechanisms.^{27,28} While PIGD patients show difficulties with impulsive actions, they may also have problems with impulsive choices that fail to take into account potential risks (eg, deciding to descend a steep driveway to retrieve the mail despite the risk of falling).

A few limitations, extant issues, and future directions are important to note. We recognise that the PD subtype method used here has limitations and that PD patients can be differentiated on the basis of other meaningful clinical features. Moreover, classification into subgroups was based on motor ratings in the on-medication state. It is possible that subgroups based on off-medication ratings might have produced different subgroups. However, an advantage of rating in the on state is the classification of functional subgroups based on the typical motor symptoms experienced every day in treated PD. This provides a more practical classification for linking measures of impulse control to real life risk for falling. Future work to improve subtype classification methods, ideally through quantitative gait assessment, or that compares PD fallers and non-fallers directly, is clearly needed.

The issue of motor symptom severity will require more attention in future studies as PIGD is typically associated with advanced disease.²⁹ In fact, we demonstrated previously that motor symptom severity in PD was linked with increased motor impulsivity in the Simon task.⁴ This raises the possibility that the evolution of postural and gait dyscontrol that marks advancing PD is paralleled by declines in impulsive motor control. Motor impulsivity in early versus late onset PIGD also requires further investigation. Interestingly, healthy controls from a previous study showed impulsive response capture intermediate to the two PD subgroups reported here.⁴ This suggests the intriguing possibility that TD patients show a compensatory improvement in impulse control, whereas PIGD patients, despite their gait impairment and fall risk, continue to show typical or increased susceptibility to acting on response impulses. Longitudinal studies that track the evolution of motor impulsivity and inhibitory control across subgroups of PD patients could help clarify these patterns.

The effect of medication on these action control parameters is not addressed in this sample as patients completed the task in the on-medication state. Notably, we recently showed that agonist medication does not affect motor impulsivity (ie, fast motor errors) in the Simon task,³⁰ suggesting that medication may not be an important factor in accounting for the subgroup patterns reported here. Assessing the effects of dopamine medications on PD subgroups' performance on action control tasks requires further investigation.

In conclusion, patients with predominant PIGD are more susceptible to acting on strong motor impulses. The incorporation of cognitive measures of action control into routine clinical assessments may prove useful in identifying PD patients with increased motor impulsivity and diminished inhibitory action control that may predispose to greater fall risk. Ultimately, pharmacological (eg, cholinesterase inhibitor)³¹ and non-pharmacological (eg, cognitive training) interventions aimed at helping vulnerable patients 'think before they leap' may prove complementary in fall risk reduction.

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Figure 1.

Mean reaction times (A) and accuracy rates (B) for predominant postural instability/gait difficulty (PIGD) and tremor dominant (TD) groups as a function of Simon correspondence (corresponding (C), non-corresponding (NC)). All patients show a slowing of reaction time (RT) and reduction in accuracy for NC compared to C trials, confirming that incorrect motor impulses interfered with selection of correct responses and sometimes captured the response system sufficiently to produce errors. The groups show similar mean interference effects on reaction time, but the PIGD group tends to make more errors than the TD group on NC trials relative to C trials ($Group \times Correspondence: F(1,32)=3.76, p=0.06$). However, unlike the distributional analytical methods described in figures 2 and 3, mean effects cannot distinguish the strength of the incorrect motor impulse from the proficiency of inhibiting this impulse. Error bars reflect SE of the means.

Figure 2.

To compute the conditional accuracy function (CAF), all reaction times (RTs) for corresponding (C) and non-corresponding (NC) trial types are rank-ordered separately and then partitioned into equal-sized bins representing the fastest to the slowest reactions. For each bin, an accuracy rate is calculated and plotted against the mean reaction time for that bin, creating a CAF that spans the entire distribution of reactions. The figure depicts the CAFs for C and NC trial types in PD patients with predominant postural instability/gait difficulty (PIGD) and tremor dominant (TD) symptoms. As expected, errors were predominantly associated with the fastest reactions on NC trials, confirming that patients selected the incorrect motor response impulsively. PIKD patients made significantly more of

these fast, impulsive response errors compared to TD patients, suggesting a greater susceptibility to acting on strong motor impulses.

Figure 3.

To compute a delta plot, reaction times (RTs) for correct responses to corresponding (C) and non-corresponding (NC) trial types are rank-ordered separately and then partitioned into equal-sized bins representing the fastest to the slowest reactions. For each bin, an interference effect is computed (mean RT for NC trials minus mean RT for C trials) and plotted against the mean RT for that bin. This allows for visualisation of the magnitude of interference from incorrect motor impulses across the entire distribution of RTs. A delta plot is depicted for PD patients with postural instability/gait difficulties (PIGD) and tremor dominant (TD) symptoms. As expected, the magnitude of interference increases across fast and intermediate response latencies, but then reverses as inhibition of the interfering motor

impulse builds up. The slope between the slowest bins of RTs provides the most sensitive measure of the inhibition process (ie, a more negative-going slope indicates more proficient suppression). Both groups show similar delta plot patterns and statistically equivalent final delta slope values, suggesting that the groups did not differ in their ability to inhibit the interference from motor impulses on correct response trials.

Table 1

Demographic data for Parkinson's disease (PD) subgroups

	PIGD	TD	p Value
Sample size	17	17	
Age (years)	65.9 (7.1)	66.4 (10.3)	0.86
Education (years)	15.9 (2.2)	17.0 (1.9)	0.15
Gender (M:F)	11:6	12:5	0.71
MMSE	28.6 (1.4)	29.0 (1.3)	0.42
Years since PD onset	8.4 (5.6)	6.5 (3.9)	0.26
UPDRS—motor subscore	21.2 (7.4)	17.3 (7.6)	0.14
Age onset	57.5 (2.4)	59.9 (2.6)	0.49
Medication (n)			
Levodopa monotherapy	6	7	
Agonist monotherapy	1	0	
Levodopa + agonist	10	9	
MAO-B inhibitor only	0	1	
Antidepressant	5	2	
Hopkins verbal learning test			
Trial 1	4.1 (0.36)	4.8 (0.42)	0.21
Trial 2	7.1 (0.53)	7.0 (0.47)	0.87
Trial 3	7.9 (0.53)	8.4 (0.45)	0.45
Delayed recall	5.8 (0.85)	7.1 (0.60)	0.21
Semantic fluency (animals)	18.6 (1.5) (n=17)	17.0 (1.2) (n=14)	0.42
Letter fluency (FAS)	36.8 (2.9) (n=17)	34.4 (3.7) (n=14)	0.60
Trials A (seconds)	43.9 (2.3) (n=17)	45.7 (5.0) (n=16)	0.74
Trials B (seconds)	84.5 (7.5) (n=17)	112.0 (15.9) (n=16)	0.12
Digit span forward max	6.9 (0.34) (n=17)	6.5 (0.31) (n=15)	0.46
Digit span backward max	4.4 (0.23) (n=17)	4.3 (0.29) (n=15)	0.96

SD shown in parentheses

MMSE, Mini-Mental Status Examination; PIGD, postural instability gait disorder; TD, tremor dominant; UPDRS, Unified Parkinson's Disease Rating Scale