



## Tests of dorsolateral frontal function correlate with objective tests of postural stability in early to moderate stage Parkinson's disease<sup>☆</sup>

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### ABSTRACT

A substantial number of individuals with Parkinson's disease who display impaired postural stability experience accelerated cognitive decline and an increased prevalence of dementia. To date, studies suggest that this relationship, believed to be due to involvement of nondopaminergic circuitry, occurs later in the disease process. Research has yet to adequately investigate this cognitive-posturomotor relationship especially when examining earlier disease states. To gain greater understanding of the relationship between postural stability and cognitive function/dysfunction we evaluated a more stringent, objective measure of postural stability (center of pressure displacement), and also more specific measures of cognition in twenty-two patients with early to moderate stage Parkinson's disease. The magnitude of the center of pressure displacement in this cohort was negatively correlated with performance on tests known to activate dorsolateral frontal regions. Additionally, the postural stability item of the UPDRS exhibited poor correlation with the more objective measure of center of pressure displacement and all specific measures of cognition. These results may serve as rationale for a more thorough evaluation of postural stability and cognition especially in individuals with mild Parkinson's disease. Greater understanding of the relationship between motor and cognitive processes in Parkinson's disease will be critical for understanding the disease process and its potential therapeutic possibilities.

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### 1. Introduction

In addition to cardinal motor changes, the sequela of Parkinson's disease (PD) impairs the speed of information processing and mental flexibility [1,2]. The prevalence of this phenotype of cognitive impairment may be as high as 80 percent of all PD cases [3]. Of note, cognitive symptoms may be linked to particular subsets of PD motor manifestation [1,2]. Patients with postural instability and gait dysfunction experience accelerated cognitive decline and may be at higher risk for dementia [4]. Despite increasing awareness regarding anatomical connectivity between gait related nuclei such

as the pedunculopontine nucleus, basal ganglia, and frontal regions of the cortex [5], quantitative clinical studies formally examining motor-frontal function in subclinical PD are few.

Frontal-subcortical circuits are separated into 'motor' and 'complex' functions, with the 'complex' functions associated with more cortical functions as they arise from, among others, the dorsolateral prefrontal cortex. Although other circuits, included those arising from the anterior cingulate cortex for example, and neurotransmitters (e.g. acetylcholine) are implicated, dopaminergic modulation of the dorsolateral prefrontal cortex circuit connecting to the dorsolateral prefrontal cortex to the basal ganglia and thalamus is most often implicated in the cognitive presentation of PD. More specifically, these connections are hypothesized to be the primary contributor to the working memory deficits commonly exhibited in PD [6]. Whereas, postural stability studies often discuss changes to the basal ganglia efferents to the brainstem and midbrain structures [7]. Although there is increasing awareness of the connectivity

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between brain stem and pre-frontal regions [8], a clear understanding of the frontal-motor relationship is lacking.

Clinical measures, such as the Unified Parkinson's Disease Rating Scale (UPDRS), have been frequently used to assess postural stability, but are subjective, often unreliable, lacking in sensitivity, and fail to sufficiently capture the contributing factors to postural instability. Therefore, the quantitative analyses of postural control and postural performance to cognitive faculties are severely compromised [9,10]. Recent studies have shown that quantitative posturography is useful for understanding motor control in PD patients and the effects of anti-PD treatment on posture [11,12]. Typical objective outcome measures of postural stability include the movement of the center of pressure (COP) under each foot, the calculated net COP displacements. The COP is defined as the point of application of ground forces under the feet. During quiet standing, changes in COP reflect the nervous system's response to movement of the whole-body center of mass (COM). Keeping this in mind, the COP is therefore the output of a complex control system that integrates visual, vestibular and somatosensory responses with nervous and muscular systems. In addition to being more sensitive, the COP is more objective than the UPDRS and provides a continuous variable for psychometric analysis.

In addition to the UPDRS, the Mini-Mental State Examination (MMSE) has been utilized to assess the relationship between cognitive and motor functioning. The MMSE was first introduced as brief assessment of cognitive functioning and as a measure of changes in cognitive status [13]. However, the MMSE lacks the sensitivity to capture contributing factors to cognitive impairment in patients with PD. For example, among the key criticisms of the MMSE is that it fails to discriminate between people with mild dementia and those who are not demented [14]. As such, utilizing more specific measures of executive function/frontal systems measures may allow for differentiation of unique frontal-subcortical connections involved in the relationship between postural control and cognitive function.

Although new work is suggesting a common pathway relating increasing posturomotor impairment and cognitive decline, a more stringent evaluation of postural stability (beyond the UPDRS) is needed to improve our understanding of PD related motor-frontal pathways. Further, examining postural control to specific cognitive measures, beyond the Mini Mental State Exam (MMSE), could provide additional insight into the relationship between ambulatory dysfunction and frontal mediated cognitive processes.

We conducted this preliminary investigation to examine the hypothesis that that postural stability, as measured with COP displacement, in mild to moderate PD will uniquely relate to cognitive performance on tests shown to involve the dorsolateral frontal region. Further, because of the limitations presented by the UPDRS for quantifying postural stability we hypothesized it would not correlate with COP measurements and frontally-mediated cognitive tests.

## 2. Methods

Twenty-two individuals with early to moderate stage idiopathic PD (i.e., having a Modified Hoehn & Yahr Stage between 1 to 2.5 in the "on" medication state) participated. These patients were recruited from the University's Movement Disorders Clinic. The diagnosis of idiopathic PD was made by a neurologist with fellowship training in Movement Disorders using standard diagnostic criteria (UK Brain Bank Criteria for PD). All participants were on stable doses of dopaminergic medications and evaluations were conducted while the patients were clinically "on", and fully responding to their PD medications (1 to 1.5 h of taking their anti-parkinsons medicines). Additionally, all patients were void of overt dementia and significant anxiety or mood disorders. At the time of testing, none of the patients exhibited any dyskinesia, dystonia, or other hyperkinetic involuntary movements. On a pull test administered by a neurologist, all patients were required to either exhibit a normal postural response or recover unaided after a good tug from behind (Hoehn and Yahr rating of 2.5 or better). Informed written consent was obtained according to Institutional Review Board guidelines.

### 2.1. Postural stability evaluation

**1. Center of Pressure Displacement.** Ground reaction forces (GRF) were recorded (360 Hz) from one forceplate (Type 4060–10, Bertec Corp., Columbus, OH) embedded level with the floor. During four quiet stance trials, participants were asked to stand as still as possible for 20 s with their feet in a self-selected, comfortable stance width.

Postural control in upright stance is quantified by measuring forces exerted against the ground at the location of the center of pressure (COP). Ground reaction forces and moments were then used to calculate the location of the COP. The COP displacement is reflective of the output of the central nervous system as it attempts to manage the body position to keep the center of mass within the base of support. Traditional measures of postural stability include the excursion lengths for the COP path in the mediolateral (ML) and anteroposterior (AP) directions in centimeters (cm). Total COP displacement area was then calculated by determining the maximum range in the ML and AP directions and multiplying the each together with the resultant in cm<sup>2</sup>.

2. **UPDRS** – The total UPDRS was evaluated on all patients during the ON medication state. We used the total UPDRS motor score as well as individual items: 27 (arising from a chair), 28 (posture), 29 (gait) and 30 (postural stability).
3. **Postural instability gait difficulties (PIGD) subscale score**– were calculated utilizing the summed total of UPDRS motor items 27–30.

### 2.2. Cognitive evaluation

We specifically hypothesized a negative relationship between worsening gait scores and performance on the following neuropsychological tests associated with dorsolateral prefrontal regions:

1. **Digit Span Backward Subtest from Wechsler Memory Scale – Third Edition** [15] – requires selective attention and working memory. It has been associated with dorsolateral and ventrolateral activation on functional imaging studies [16] and been included in several screening tools for assessing early cognitive decline [17]. (DV = total backward score).
2. **Controlled Word Association Test – 'FAS' Word** [18] – is a measure that requires processing speed, selective attention, inhibitory functions, the ability to rapidly shift mental set [19,20], and associates with dorsolateral prefrontal cortex activation in older adults [21]. Participants are required to generate words to certain letters [(e.g., "F")] DV = total word output in 60 s per letter).
3. **Stroop Color Word Test** [22] – requires selective attention and cognitive control by requiring participants to suppress the automatic tendency to read aloud words rather than the color ink words appear on the page in (DV = Color-word score, total read in 45 s). The color-word interference paradigm, in particular, has been associated with activations of the dorsolateral prefrontal cortex and anterior cingulate [23].

Other cognitive tests administered:

1. **Mini-Mental State Exam** [13] – was used to characterize the general cognition in our sample and assess. It tests orientation, three word memory, mental manipulation, comprehension, repetition, and visuospatial construction. (Dependent variable (DV) = total score out of possible 30).
2. **Category (Animal) Fluency** [24] – is a verbal fluency test associated with processing speed but also semantic knowledge integrity. Participants are required to list animal names as quickly possible during a 60 s time period. (DV = total number of different animal words generated). Positron emissions tomography with this test suggest increases in regional cerebral blood flow within left temporal cortex and associations with semantic information [21]. These findings support dissociations between animal and letter fluency in patients with temporal lobe and subcortical frontal pathology, respectively [19,25].

### 2.3. Analysis

Pearson Product Moment Correlations were used to assess relationships between COP displacement and the MMSE and the four neuropsychological measures. Nonparametric (Spearman's) correlations were used to assess the relationship between the UPDRS motor score as well as the PIGD subscale total/individual score(s) and all variables of interest. Based on theories of frontal-subcortical disruption and specifically that of the dorsolateral prefrontal cortex, we specifically hypothesized negative associations between gait and the cognitive measures of the Digit Span, Controlled Word Association Test, and Stroop Color Word score.

Alpha levels were set at  $\leq 0.05$ . From the  $r$  values, we discuss effect size based on Cohen's guidelines [26] (small,  $r = 0.01$ – $0.23$ , medium,  $r = 0.24$ – $0.36$ , larger  $r = 0.37$  or larger) and calculate  $r$  square ( $r^2$ ) values to interpret percent of memory performance explained.

### 3. Results

#### 3.1. Demographics

**Table 1.** Participants scored in the non-demented range on the general cognitive screener (MMSE:  $29.66 \pm 2.21$ ) and within “normal” age range for each of the four cognitive tasks. Postural stability as scored with the UPDRS was within “normal” range (UPDRS item #30:  $0.81 \pm 0.71$ ). Average COP displacement area was  $5.05 \pm 3.76 \text{ cm}^2$ , which is three to five times greater than rates in the literature for healthy older adults [27]. No participant in our cohort reported significant gait problems or falling. We therefore consider this increased COP displacement area indicative of “subclinical” postural instability.

#### 3.2. COP displacement and UPDRS

**Table 2.** UPDRS PIGD subscale score did not correlate with COP displacement area ( $r = 0.271$ ;  $p = 0.17$ ). The score on Item 30 of the UPDRS, postural stability, did not significantly correlate with COP displacement area ( $r = -0.208$ ;  $p = 0.35$ ).

#### 3.3. COP displacement and cognitive measures

**Table 3.** There were moderate negative associations between COP displacement area and selected cognitive measures: Digit Span Backward ( $r = -0.371$ ;  $p = 0.04$ ), Stroop Color Word ( $r = -0.448$ ;  $p = 0.01$ ), and Controlled Word Association ( $r = -0.417$ ;  $p = 0.02$ ), suggesting that 13 to 20% of the variance in motor function can be explained by these test measures. By contrast, there was no statistically significant relationship between and the general measure of cognition (MMSE) ( $r = -0.288$ ;  $p = 0.89$ ) and Category Verbal Fluency ( $r = -0.237$ ;  $p = 0.14$ ) and COP displacement area or postural stability as measured by the UPDRS.

#### 3.4. UPDRS and cognitive measures

**Table 2.** The UPDRS total motor score, UPDRS PIGD scale negatively correlated with general cognitive function as measured by the MMSE ( $p = 0.04, 0.05$ , respectively). There were no significant correlations between any neuropsychological tests, UPDRS total motor score, or UPDRS PIGD subscale score, or the postural stability score (all  $p > 0.05$ ).

**Table 1**

Means and standard deviations on all demographic data and raw scores of the dependent measures of interest.

Age (yrs)	69.45 ± 7.07
Education (yrs)	15.75 ± 2.69
Disease duration (yrs)	9.70 ± 4.59
MMSE	29.66 ± 2.21
Age at onset	58.24 ± 8.79
UPDRS Motor Score	28.25 ± 4.90
PIGD Score	2.8 ± 1.76
COP Displacement ( $\text{cm}^2$ )	5.05 ± 3.76
UPDRS – Item 30	0.81 ± 0.73
Controlled Word Association	11.75 ± 4.45
Digit Span Backwards	6.31 ± 2.12
Stroop Color Word	34.81 ± 8.61
Category (Animals) Fluency	16.31 ± 5.94

Abbreviations: MMSE–Mini Mental State Exam; UPDRS–Unified Parkinson's Disease Rating Scale; PIGD–Postural Instability Gait Difficulties; COP–Center of Pressure; UPDRS – Item 30 = Postural Stability.

**Table 2**

Spearman's correlations between demographic characterizes, COP displacement, cognitive function and the UPDRS as well as the PIGD score and postural stability item of the UPDRS.

Spearman's correlation	UPDRS Motor Score		PIGD subscale Score		UPDRS – Item 30- Postural Stability	
	r	P	r	P	r	P
Age	-0.051	0.82	-0.375	0.09	-0.018	0.93
Education	-0.203	0.32	0.12	0.60	0.102	0.66
Disease duration	-0.059	0.79	-0.069	0.76	-0.248	0.29
MMSE	<b>-0.384</b>	<b>0.03</b>	<b>-0.444</b>	<b>0.04</b>	-0.096	0.33
Age at onset	-0.114	0.62	0.141	0.26	0.155	0.51
UPDRS Motor Score			<b>0.560</b>	<b>0.00</b>	0.394	0.06
PIGD Score	<b>0.560</b>	<b>0.00</b>			<b>0.635</b>	<b>0.00</b>
COP Displacement	-0.116	0.30	0.271	0.17	-0.208	0.35
Controlled Word Association	0.034	0.44	0.047	0.41	0.160	0.23
Digit Span Backward	-0.142	0.27	-0.104	0.32	0.161	0.23
Stroop Color Word	-0.224	0.15	-0.072	0.37	0.160	0.23
Category (Animal) Fluency	-0.142	0.26	0.108	0.31	0.211	0.17

Bold indicates statistical significance at  $P < 0.05$ . Abbreviations: MMSE–Mini Mental State Exam; UPDRS–Unified Parkinson's Disease Rating Scale; PIGD–Postural Instability Gait Difficulties; COP–Center of Pressure.

### 4. Discussion

Consistent with our hypotheses, this preliminary investigation demonstrated that properly selected objective measures of postural stability were correlated with cognitive performance in persons with relatively early or mild idiopathic PD. More specifically, we demonstrated that cognitive tests specific to dorsolateral frontal function correlate with greater postural instability in this cohort of PD patients. This relationship could not be substantiated utilizing the postural stability measure of the UPDRS, however. Overall, these results are in line with previous literature that has suggested that greater axial motor involvement is related to a worsening cognitive PD profile. Our results build on the literature by suggesting that as the magnitude of the postural instability increases, specific frontal executive task performance worsens. By contrast, disease duration, age, general cognition (as measured by the MMSE), and test of semantic fluency did not relate to the COP measure of postural stability or the postural stability measure provided by the UPDRS. These results suggest that 1) utilizing specific, more sensitive, evaluation paradigms may provide greater insight into the cognitive–motor relationship in PD and 2) general, more global measures, including disease duration, age as well as cognition as measured by the MMSE and postural stability as

**Table 3**

Pearson correlations between COP displacement, demographic characterizes, and cognitive function.

Pearson's correlation	COP displacement	
	r	P
Age	0.177	0.45
Education	0.114	0.62
Disease duration	-0.033	0.89
MMSE	-0.288	0.89
Age at onset	-0.109	0.31
Controlled Word Association	<b>-0.417</b>	<b>0.02</b>
Digit Span Backward	<b>-0.371</b>	<b>0.04</b>
Stroop Color Word	<b>-0.448</b>	<b>0.01</b>
Category (Animal) Fluency	-0.237	0.14

Bold indicates statistical significance at  $P < 0.05$ . Abbreviations: MMSE Mini Mental State Exam; COP–Center of Pressure.

measured by the UPDRS may not sensitive enough to identify the cognitive-motor link.

Currently, there are no clearly defined biological predictors of who will develop non-motor symptoms of PD, however risk factors have emerged in the literature. Most notably, the presence of the PIGD subtype when compared to the tremor subtype has been linked to an increased risk for the development of cognitive impairment. For example, Alves and colleagues demonstrated that at a 4-year follow-up, 97 percent of PD patients who developed frank dementia had exhibited the PIGD subtype of the disease [4]. To date, however, the cognitive-motor relationship has solely been demonstrated in patients that have clinically observable balance difficulties with cognitive impairment or even overt dementia. Although our PD participants had greater COP displacements than those of healthy older adults typically reported in the literature, all were free of “clinically significant” postural instability as measured by the UPDRS and the Hoehn and Yahr. Longitudinal studies will be needed to confirm that those with early increased postural instability will develop cognitive impairment or frank dementia.

Previously, in a broader PD cohort that included advanced stage patients, we investigated the relationship between the type of motor dysfunction as measured by the UPDRS and general cognitive performance measured by standard dementia screening tools (MMSE and DRS). [28] In that study, the PIGD items and the total UPDRS motor score were related to both measures of cognitive performance [28]. In the current study overall UPDRS motor score correlated with MMSE, however, the UPDRS motor score did not correlate to any specific tests of cognitive function suggesting that early on in the disease process the relationship may be subtle and not completely developed. Further, while the PIGD subscale scores correlated with MMSE, they were not related to any of the other tests of cognitive function. Interestingly, the postural stability item of the UPDRS did not correlate with any specific tests of cognitive function or with the MMSE.

Taken together it appears that the relationship among postural stability and cognitive performance is highly influenced by the specificity and sensitivity of the evaluation tools. Utilizing a more specific and objective measure of postural stability and cognitive functioning, we were able to demonstrate an association between postural sway and tests known to activate the dorsolateral prefrontal cortex [29]. This relationship was evident despite having a cohort with subclinical or pre-clinical cognitive and balance dysfunction. Postural instability and cognitive associations could be hypothesized to be attributed to altered communication between the pedunculopontine and other brainstem nuclei, thalamus, basal ganglia, and dorsolateral prefrontal cortex. In our sample, worsening postural stability correlated only with those tests known to activate the caudate as well as the dorsolateral prefrontal cortex (e.g., Digit Span Backward, Controlled Word Association test, Stroop Color Word test) [29]. Category (animal) Fluency, by contrast, has been shown to activate the inferior temporal cortex [30]. Therefore, the relationship between cognitive decline and postural instability appears to be specific to tests assessing dorsolateral prefrontal cortex and its unique frontal-subcortical connections. It should be noted that these participants were tested in the “on” medication state. Levodopa therapy has been shown to influence both postural stability [31] and cognitive functions [32]. Future research may benefit by examining this relationship in the “off” state to partition out the influence of drug therapy.

We acknowledge that this is a relatively small, relatively early PD group and that sample size should be improved in future studies. Additionally, an age matched non-PD control group would provide additional evidence demonstrating that the correlation between cognitive performance and subclinical postural instability is specific to PD. Future studies may need to focus more closely on

an objective measure such as the COP rather than the traditional UPDRS. Further, other deficits affecting postural stability such as visual defects and/or sensory ataxia should be examined and controlled in future studies. Despite any limitations the data from this earlier PD group are enlightening in postural instability and its relationship to frontal systems.

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