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Cognitive associations with comprehensive gait and static balance measures in Parkinson's disease

Rosie Morris[a,*], Douglas N. Martini[a], Katrijn Smulders[b], Valerie E. Kelly[c], Cyrus P. Zabetian[d,e], Kathleen Poston[f], Amie Hiller[a], Kathryn A. Chung[a], Laurice Yang[f], Shu-Ching Hu[d,e], Karen L. Edwards[g], Brenna Cholerton[h], Thomas J. Grabowski[i], Thomas J. Montine[h], Joseph F. Quinn[a,j], Fay Horak[a,j]

[a] Department of Neurology, Oregon Health and Science University, Portland, OR, USA
[b] Sint Maartenskliniek Research Department, Nijmegen, the Netherlands
[c] Department of Rehabilitation, University of Washington School of Medicine, Seattle, WA, USA
[d] Department of Neurology, University of Washington School of Medicine, Seattle, WA, USA
[e] Veterans Affairs Puget Sound Health Care System, Seattle, WA, USA
[f] Department of Neurology and Neurological Sciences, Stanford School of Medicine, Palo Alto, CA, USA
[g] Department of Epidemiology, University of California, Irvine, CA, USA
[h] Department of Pathology, Stanford University School of Medicine, Palo Alto, CA, USA
[i] Department of Radiology, University of Washington School of Medicine, Seattle, WA, USA
[j] Portland Veterans Affairs Health Care System, Portland, OR, USA

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ABSTRACT

Introduction: Gait and balance impairments are cardinal features of Parkinson's disease (PD) that require cognitive input. However, the extent to which specific gait and balance characteristics relate to cognition in PD is unclear. In addition, independent models of gait and balance have not been developed from the same cohort. We aimed to i) develop models of gait and balance in a large PD cohort and ii) determine which gait and balance characteristics best related to cognition.

Methods: One hundred and ninety-eight people with PD were recruited to the Pacific Udall Center. Using six inertial sensors (APDM, Inc.), comprehensive gait measurements were collected over a 2-min continuous walk and comprehensive static balance measures were collected during a 60-second standing task. Six domains of cognition were assessed: global cognition, attention, executive function, language, memory, and visuospatial function. Correlations and hierarchical linear regression determined independent associations.

Results: Principal components analysis identified a gait model containing four domains accounting for 80.1% of total variance: pace/turning, rhythm, variability, and trunk. The balance model contained four independent domains accounting for 84.5% of total variance: sway area/jerkiness, sway velocity, sway frequency anteroposterior, and sway frequency mediolateral. Gait domains of pace/turning and variability were strongly associated with attention and executive function. Sway area and jerkiness of balance associated with attention and visuospatial function.

Conclusions: Gait and balance characteristics were associated with specific types of cognition. The specific relationships between gait or balance with cognitive functions suggests shared cerebral cortical circuitry for mobility and cognitive functions.

1. Introduction

Balance and gait deficits are cardinal motor features of Parkinson's disease (PD), leading to increased risk of falls and reduced quality of life [1]. It is increasingly recognized that balance and gait are not pure motor tasks, but that cognition is also essential for safe mobility. In addition, not all balance and gait impairments are alleviated with levodopa, suggesting multiple underlying mechanisms of disease, in addition to dopamine loss [2]. The complex nature of gait and balance has led to the development of comprehensive gait models to map individual

* Corresponding author. Department of Neurology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR, 97239, USA.
E-mail address: horakf@ohsu.edu (F. Horak).

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measurements onto domains to eliminate redundancy and ease interpretation [3,4]. One previous model demonstrated that balance measures are independent from gait measures, suggesting they are independent features of mobility [5].

Neural control of balance and gait are distinct, complex systems with deficits that are not correlated among people with PD [5]. Cortical control of balance and gait are thought to differ, with previous imaging work suggesting static balance is controlled by posterior cortical regions and gait controlled by anterior cortical regions [6,7]. For example, gait and cognitive associations in PD demonstrate a key role of attention and executive function for pace and variability of gait [8]. However, cognitive associations with static balance in PD are less well understood. Furthermore, comprehensive static balance and gait measures have not been associated with cognition within the same cohort to allow for a valid comparison.

A further understanding of distinct neural correlates underlying balance and gait deficits is required to improve future medication and therapeutics, and to tailor medical intervention for individual patients. The aims of this study therefore were to: i) produce separate comprehensive models of gait and static balance to provide a framework for relating to cognition, and ii) explore associations between cognition and static balance and between cognition and gait in people with PD using objective static balance and gait measures from body-worn inertial sensors. We hypothesized that measures of static balance and gait in people with PD would demonstrate distinct associations with cognitive domains due to different underlying neural correlates.

2. Methods

2.1. Participants

Potential participants with PD were recruited and enrolled as part of the Pacific Udall Center Clinical Core which was comprised of three sites; 1) University of Washington and the Veterans Administration (VA) Puget Sound Health Care system in Seattle, Washington, 2) Oregon Health and Science University and the Portland VA Medical Center in Portland, Oregon and 3) Stanford University, Palo Alto, California. Participants with PD were included in the study if they: i) met the criteria for diagnosis of idiopathic PD using the United Kingdom Parkinson's Disease Society Brain Bank (UKBB) criteria [9], ii) had no history of other neurological disorders that affected cognition, e.g., large-vessel stroke or severe traumatic brain injury, and iii) were able to stand unsupported for 30 seconds. Volunteers with PD were assessed 'on' medication both for cognitive and mobility assessments.

2.2. Clinical assessment

Age, gender, height, and years of education were recorded for all participants. PD disease motor severity was assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) [10] and the modified Hoehn and Yahr (H&Y) score [11]. Medication dose was calculated for each PD patient using the levodopa equivalent daily dose (LEDD) [12]. Participants were also assigned to a cognitive diagnostic category: no cognitive impairment (NCI), mild cognitive impairment (MCI) or Parkinson's disease dementia (PDD) at a diagnostic consensus conference [13].

2.3. Mobility assessment

Participants performed instrumented gait and static balance assessments wearing six Opal inertial sensors (APDM Inc., Portland, OR.). Inertial sensors were placed bilaterally on the wrists and feet as well as on the sternum and the fifth lumbar vertebrae and were attached by elastic Velcro straps. For the *gait assessment*, participants were asked to walk at a comfortable pace back and forth on a straight 7 m walkway in a quiet hallway for two minutes, with 180° degree turns at each end of the walkway. For the *static balance assessment*, participants were asked to stand quietly focusing on an image ahead for 60 seconds. For both gait and balance assessments, a template was used prior to the start of the trial to achieve consistent foot placement across all trials and participants with 10 cm between the left and right heel and a 30-degree outward rotation of the feet. Gait metrics were analyzed using a commercial gait analysis system (APDM Mobility Lab™) [14,15] and balance measures were analyzed using a validated custom made algorithm [16].

2.4. Cognitive function

Six domains of cognition were assessed using a comprehensive battery of neuropsychological assessments. *Global cognition* was assessed using the Montreal Cognitive Assessment (MoCA), which is sensitive to cognitive impairment in people with PD [17]. *Attention* was assessed using i) Letter Number Sequencing Test (LNST), ii) Trail Making Test (TMT) part A and iii) Stroop reading score. *Executive function* was assessed using i) Semantic Fluency (Animals), ii) TMT B-A, iii) Stroop Interference score and iv) phonemic fluency (letter F). *Language* was assessed using the Boston naming test. *Memory* was assessed using the i) Hopkins Verbal Learning Test (HVLT) immediate and delayed recall and ii) Logical Memory I and II. *Visuospatial function* was assessed using the Judgement of Line Orientation (JoLO).

2.5. Data analysis

Data were initially inspected using histograms and boxplots and assessed for normality and transformed where needed (transformed variables are highlighted in the tables). Analyses were divided into two stages.

2.5.1. Principal components analysis for domains of balance and gait

In order to provide a framework upon which to base our analysis, principal components analysis (PCA) was performed to create separate models containing domains of gait and balance. First, fifteen characteristics of gait were entered into a model using an eigenvalue of greater than one and a varimax rotation was applied. Separately, 13 characteristics of static balance were entered into a PCA model constructed in the same way. A correlation value of ≥ 0.6 was used for factor loadings for both models.

2.5.2. Associations of cognition with gait and balance measures

For the statistical analysis, gait and balance domains were first calculated from the PCA. Domain scores were calculated by summing the Z score of each gait and static balance characteristic for each domain and dividing by the number of characteristics per domain. Preliminary partial correlations (controlling for age, gender, years of education, disease severity [MDS-UPDRS III], disease duration and site) between gait domains and cognitive assessments and balance domains and cognitive assessments were first assessed as a data reduction technique. Following this, to identify independent associations between gait and cognition and balance and cognition, partial correlations which reached a significance level of $p \leq .01$ were entered into a hierarchical regression model using the backward method. Demographic and clinical characteristics were entered into the first block (age, gender, years of education, disease severity [MDS-UPDRS III], disease duration and site). Separate models were used for gait and balance; all domains were entered into the second block. Cognitive assessments which reached the significance threshold from partial correlations were entered as the independent variable. A stringent p value of $\leq .01$ determined significance throughout analysis in order to reduce type I error.

Table 1
Demographic, clinical and cognitive characteristics, Mean (SD) of PD participants.

	Measure	PD (n = 198) Mean (SD)
Demographics	Age (years)	67.6 (8.2)
	Gender (M/F)	125/73
	Years of Education	16.4 (2.3)
	MDS-UPDRS III	25.0 (13.1)
	H & Y	2.1 (0.5)
	LEDD (mg/day)	654.0 (467.1)
	Disease Duration (years)	8.6 (5.4)
	Cognitive Status	NCI (74)/MCI+ (101)/PDD (23)
Global Cognition	MoCA	25.0 (4.0)
Attention	Letter Number Sequencing	9.55 (2.53)
	Trail Making A	37.0 (20.3)
	Stroop Reading	84.8 (16.3)
Executive Function	Semantic Fluency	19.0 (6.0)
	Trail Making B-A	58.1 (46.6)
	Stroop Interference	34.6 (10.1)
	Phonemic Fluency	15.0 (5.0)
Memory	HVLT-R Immediate	23.6 (6.0)
	HVLT-R Delayed	8.11 (3.14)
	Logical Memory I	12.5 (4.2)
	Logical Memory II	11.5 (4.5)
Language	Boston Naming Test	28.6 (1.7)
Visuospatial	Judgement of Line Orientation	12.0 (2.0)

[Abbreviations: MDS-UPDRS (Movement Disorders Society Unified Parkinson's disease rating scale), H & Y (Modified Hoehn & Yahr), LEDD (Levodopa Equivalent Daily Dose), NCI (no cognitive impairment), MCI (mild cognitive impairment), PDD (Parkinson's disease dementia), MoCA (Montreal Cognitive Assessment), HVLT-R (Hopkins Verbal Learning Test-Revised)].

3. Results

3.1. Participants

A total of 198 participants with idiopathic PD were recruited to the study. Table 1 shows the demographic characteristics for participants who completed clinical, mobility, and cognitive assessments. The PD group contained 125 males and 73 females with a mean age of 67.6 ± 8.2. On average, participants with PD had a disease duration of 8.6 ± 5.4 years with an average MDS-UPDRS III of 25.0 ± 13.1, H & Y of 2.1 ± 0.5 and LEDD of 654.0 ± 467.1. The average total years of education was 16.4 ± 2.3. Performance on cognitive assessments is presented in Table 1.

3.2. Independent models of balance and gait

Gait measures are presented in Table 2 for all participants. A total of 15 gait characteristics were entered into the PCA, yielding four factors (pace and turning, gait rhythm, gait variability, and trunk movement) accounting for 80.12% of total variance (Fig. 1A). Descriptive static balance data are presented in Table 2. A total of 13 static balance characteristics were entered into a separate PCA that contained four independent factors (sway area and jerkiness, sway velocity, sway frequency mediolateral, and sway frequency anteroposterior) accounting for 84.51% of total variance (Fig. 1B).

3.3. Associations between gait and cognition

Hierarchical regression models revealed a number of independent predictors between gait and cognition (Table 3). Slower pace and turning of gait was associated with poorer attention (stroop reading score, β.269, P = < .001 and LNST, β.213, P = < .003), poorer executive function (stroop interference, β.240, P = .003, phonemic fluency, β.281, P = < .001 and TMT B-A, β.-0.263, P = < .001) and poorer memory (Logical memory I, β.282, P = < .001). In contrast, increased variability of gait (i.e. reduced stability) was associated with poorer attention (Trails A, β.247, P = < .001). There were no associations for rhythm and trunk domains of gait. Associations (partial correlations) between individual gait metrics in each domain and cognition are summarized in Fig. 2 to guide interpretation.

Table 2
Gait characteristics, Mean (SD) for all participants.† Values log transformed for statistical analysis.

Gait and Balance Characteristics		PD (n = 198) Mean (SD)
Gait	**Pace and Turning**	
	Gait Speed (m/sec)	0.96 (0.20)
	Stride Length (m)	1.08 (0.20)
	Foot Strike Angle (deg)	18.82 (6.42)
	Turn Duration (sec)	2.50 (0.41)
	Turn Velocity (deg/sec)	151.73 (34.53)
	Number of steps in Turn (#)	4.14 (0.83)
	Rhythm	
	Stride Time (sec)	1.14 (0.11)
	Stance Time (sec)	69.88 (8.40)
	Swing Time (sec)	44.25 (3.94)
	Variability	
	Stride Length SD (m)	0.06 (0.02)
	Stride Time SD (sec)	0.04 (0.02)
	Foot Strike Angle SD (deg)	2.50 (0.92)
	Trunk Movement	
	ROM trunk coronal (deg)	4.81 ± 2.05
	ROM Trunk sagittal plane (deg)	4.26 ± 1.36
	ROM trunk transverse plane (deg)	8.44 ± 3.11
Balance	**Sway Area & Jerkiness**	
	Sway Area†	1.86 (7.15)
	Jerk AP†	1.55 (10.84)
	Jerk ML†	1.06 (5.93)
	RMS AP† (m/s^2)	0.11 (0.08)
	RMS ML† (m/s^2)	0.05 (0.05)
	Sway Velocity	
	Velocity AP† (m/s)	0.39 (0.35)
	Velocity ML† (m/s)	0.17 (0.16)
	Sway Frequency ML	
	Frequency ML (Hz)	0.79 (0.35)
	95 Frequency ML (Hz)	2.29 (0.54)
	Centroidal Frequency ML (Hz)	1.00 (0.29)
	Sway Frequency AP	
	Frequency AP (Hz)	0.55 (0.24)
	95 Frequency AP (Hz)	1.64 (0.46)
	Centroidal Frequency AP (Hz)	0.69 (0.20)

Abbreviations: SD = standard deviation, ROM = range of motion, AP = anteroposterior, ML-mediolateral.

3.4. Associations between balance and cognition

Hierarchical regression models revealed two independent associations between static balance and cognition (Table 3). Increased sway area and jerkiness was associated with poorer attention (trails A, β.186, P = .007) as well as poorer visuospatial function (JoLO, β-0.375, P = < .001). No other domains of static balance correlated with cognition. Associations (partial correlations) between specific balance metrics within each domain and cognition are summarized in Fig. 2 to guide interpretation.

4. Discussion

This study aimed to identify models of gait and static balance to use as a framework to determine whether cognitive associations with gait

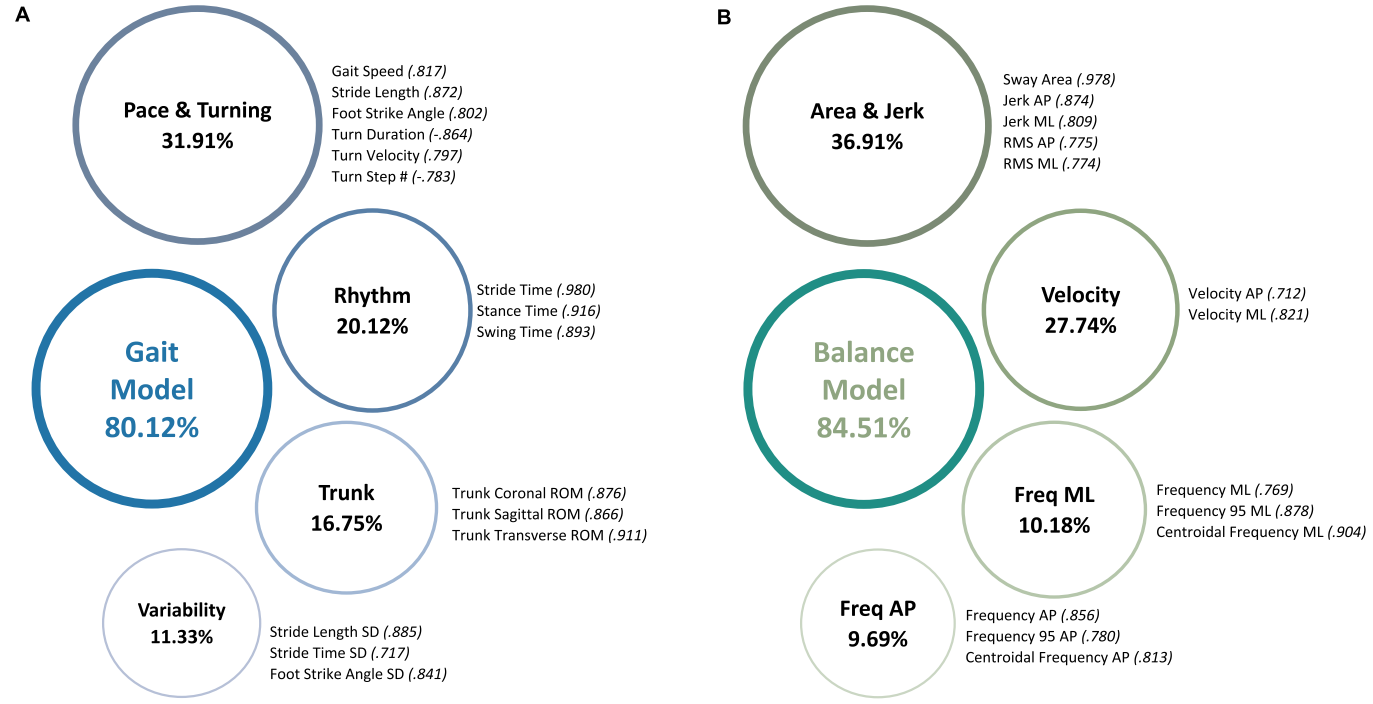

Fig. 1. Principal Component Analysis deriving A) four independent factors of gait and B) four independent factors of balance.

Table 3
Hierarchical regression models of gait and static balance associations with cognition.

Gait Domain/ Balance Domain	Cognitive Domain	Cognitive Test	β Value	P Value
Gait				
Pace and Turning	Attention	LNST	.213	**.003**
	Attention	Stroop Reading	.269	< **.001**
	Executive Function	Stroop Interference	.240	**.003**
	Executive Function	TMT B-A	-.263	< **.001**
	Executive Function	Phonemic Fluency	.281	< **.001**
	Memory	Log mem I	.282	< **.001**
Variability	Attention	Trails A	.247	< **.001**
Balance				
Sway and Jerk	Attention	Trails A	.186	< **.001**
Sway and Jerk	Visuospatial	JoLO	-.375	< **.001**

and balance domains were overlapping or specific. We identified two independent models of gait and balance in 198 people with PD, both of which described four independent domains. Several domains of gait and balance were significantly associated with performance on cognitive tests but the patterns of association were distinct between the two mobility tests. Measures of pace, including turning, and variability related to executive function, attention and memory. In contrast, measures of sway area and jerkiness of standing balance were associated with attention and visuospatial function. This confirms our hypothesis that associations with cognition differ between gait and balance, suggesting at least partially distinct involvement of underlying neural pathways.

4.1. Separate models of gait and balance have been identified

This is the first study to create independent models of gait and balance derived from the same cohort. A previous model that included both gait and static balance measures demonstrated that all gait metrics were independent domains from all balance metrics [5]. Similar to previous gait models in older adults and people with PD, we found measures of pace, rhythm and variability loaded onto separate gait domains, consistent with separate neural control mechanisms [3–5]. In contrast to previous models, however, our framework included characteristics of turning and trunk movement during gait. Indeed, turning is an essential component of gait with the majority of steps in the home and community environment occurring during turns [18]. Measures of turning loaded onto the domain that contained characteristics of pace, such as gait speed and stride length. This interdependence of pace and turning may signify the similar spatial aspects of these tasks or suggest a common neural or pathologic mechanism in PD for both pace and turning characteristics. Trunk movement during gait formed a separate domain, similar to a previous model [5]. Trunk movement represents dynamic postural stability which is particularly affected in people with PD due to rigidity and bradykinesia [19]. Our factor loading suggests these upper body measures are controlled independently from other gait variables and therefore should be assessed as part of a comprehensive gait measurement.

4.2. Cognitive associations between gait and balance differed

Associations between gait and cognition and between static balance and cognition were distinct, suggesting that the cognitive resources needed for the two tasks are different. Gait associations with cognition were primarily related to characteristics from the pace and turning domain with attention and executive function measures of cognition. These findings support previous work in PD that identified pace and variability measures of gait to be related to cognition more so than gait temporal measures, e.g., rhythm [8]. Cognitive associations of turning during gait are less well understood in PD but previous work in older adults suggests turning is highly associated with cognition [20]. The complexity of turning, a task that requires control of multiple components such as sensory integration, postural transitions and inter-limb coordination, is thought to be dependent on attention/executive function, as demonstrated in our results. Turning quality, such as slow velocity and excessive steps have been shown to be impaired very early in PD, even when gait speed is normal [21]. The close relationship

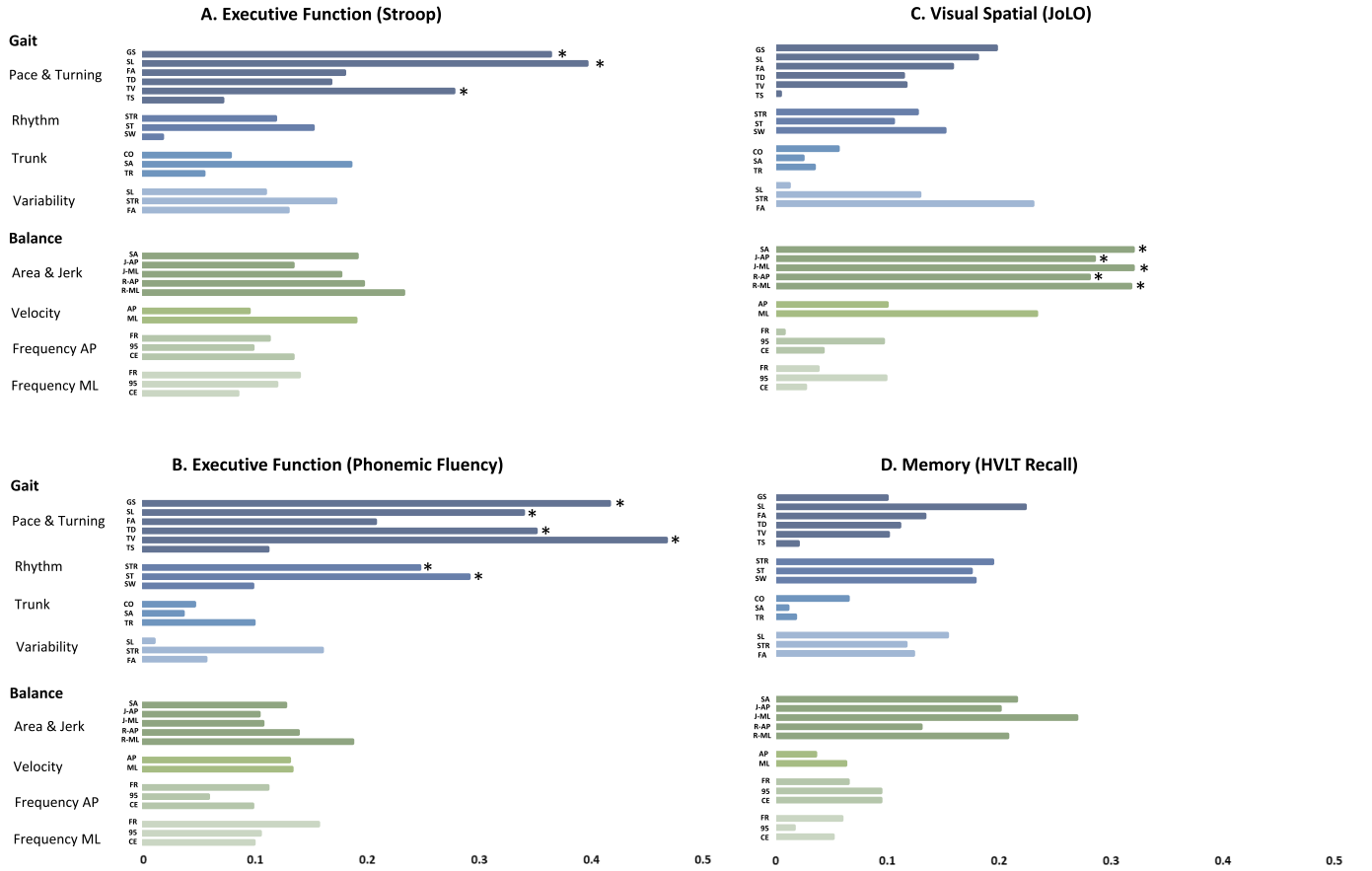

Fig. 2. Partial correlations between gait (blue) and balance (green) domains with measures of executive function; A) stroop and B) phonemic fluency, visuospatial function C) JoLO and memory D) HVLT Total Recall. Gait characteristics by domain; pace and turning; GS = gait speed, SL = stride length, FA = foot strike angle, TD = turn duration, TV = turn velocity, TS = number of steps in turn. Rhythm; STR = stride time, ST = stance time, SW = swing time. Variability as previous but SD. Trunk; CO = coronal ROM, SA = sagittal ROM, TR = transverse ROM. Balance characteristics by domain; area & jerk; SA = sway area, J-AP = jerk anteroposterior, J-ML = jerk mediolateral, R-AP = RMS Anteroposterior, R-ML = RMS mediolateral. Velocity; AP = anteroposterior, ML = mediolateral. Frequency AP; FR = frequency, 95 = 95 frequency, CE = centroidal frequency. Frequency ML as previous. * signifies statistical significance $p \leq .01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

between turning and attention/executive function is particularly important in PD due to their impact on falls risk [22] and therefore cognitive training to reduce falls may be critical for rehabilitation.

Interestingly, both attention and executive function were associated with pace and turning, but only attention associated with variability of gait. Although attention and executive function are both frontal cognitive functions, the domains are distinct and dependent on separate neurotransmitter systems; attention being dependent on the cholinergic network and executive function the dopaminergic network [23,24]. This distinction has also been recognized in functional connectivity; those with faster gait speed have stronger functional connectivity within the frontoparietal control network which is heavily involved with executive function [25]. Comparatively, those with lower gait variability have stronger functional connectivity between the dorsal attention network and default network which has been linked to sustained attention [25]. In line with our findings, characteristics of pace and variability have been found to be sensitive predictors of cognitive decline in PD [26]. Our data suggests that as well as measures of gait speed and step length, turning characteristics were also highly correlated with attention and executive function (Fig. 2). Therefore, we hypothesize that turning is also sensitive to cognitive decline and PD dementia. Thus, therapeutic targets should be tailored to gait components that are highly dependent on frontal cognitive function, including pace, turning and variability.

In contrast to gait and cognition, visuospatial function and attention were associated with measures of static balance. Consistent with our findings, previous work in a smaller cohort of people with PD demonstrated static measures of balance to be associated with visuospatial function [27]. This indicates that, unlike gait, balance measures during standing are associated with posterior rather than anterior cortical control, which is in agreement with previous imaging findings [7]. In addition, static balance may be highly dependent on vision, with visual deficits common in PD patients this further increases falls risk [28]. These findings suggest posterior cerebral cortical targets are needed to improve balance function via cortical control. Dopamine replacement therapy as well as deep brain stimulation (DBS) in the basal ganglia generally improve pace of gait but not balance, which can worsen and increase falls [29]. Studies using DBS of the pedunculopontine nucleus have aimed to improve balance impairments by increasing acetylcholine to the posterior cortex, but to date have proved difficult due to the intricate nature of the target and the multiple cell types that are positioned there [30]. A previous pharmacological study using cholinesterase inhibitors to increase acetylcholine showed improvements in static balance tasks but further work is needed to validate these findings with more comprehensive measures [31].

4.3. Clinical implications

The findings from this study have clinical implications for treatment of balance and gait in PD. Gait and balance are independent behaviors

and both are composed of multiple, independent domains that will not likely respond similarly to pharmacological, neurophysiological, or exercise/rehabilitation interventions. Recent evidence has suggested exercise therapy with a cognitive component may help improve gait and reduce falls [32]. Future studies should determine whether specific types of cognitive training can improve balance or gait and reduce falls. Our findings suggest that the type of cognitive task may enhance rehabilitation dependent on the specific mobility deficit.

4.4. Strengths and limitations

This study had a number of strengths, including a large cohort of PD subjects and comprehensive measures of gait, static balance, and cognition. The study also had limitations. First, we did not compare our findings to an age-matched control cohort. However, cognitive and mobility differences between older adults and those with PD are well established, and our main aim was to further understand differences in associations within the same cohort. Second, our neuropsychological assessment battery contained a higher number of attention and executive function tests compared with language and visuospatial assessments and therefore our results may be slightly biased towards frontal cognitive function. Third, we characterized our cognitive domains largely in line with the Movement Disorders Task Force [33], however there are discrepancies across the literature regarding classification of neuropsychological assessments and therefore interpretation may be subjective. Finally, in order to account for multiple comparisons we associated domains of gait and balance rather than individual characteristics but in turn this may reduce specificity and therefore we used a correlation figure to guide interpretation.

5. Conclusions

Our study identified separate models of gait and static balance from the same cohort of PD. Furthermore, cognitive associations with gait and balance were distinct indicating differing underlying mechanisms of disease. This may lead to different clinical targets for treatment of these two measures of mobility.

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