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Objective impairment of tandem gait in Parkinson's disease patients increases with disease severity

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ABSTRACT

Introduction: Tandem gait abnormalities have been reported to increase with advancing age, play a role in fall-prediction in Parkinson's disease, and distinguish it from atypical parkinsonism. Tandem gait has been scored based on the number of side steps off a straight line in these studies. Objective measurement of spatiotemporal tandem gait parameters in Parkinson's disease has not been previously reported.
Methods: Subjects (74 Parkinson's disease and 28 controls) were enrolled after IRB approval. Those with more than 1 fall/day or a Montreal Cognitive Assessment score < 10 were excluded. Subjects tandem walked ("heel to toe") on a 20 foot pressure-sensor mat. Data was collected and analyzed using PKMAS software (Protokinetics).
Results: Compared to controls, on tandem gait, Parkinson's subjects had increased step width, stride width and path width, with a slower stride velocity and an increased time spent in all phases of the gait cycle. Parkinson's subjects also applied greater pressure with each step and had greater step-to-step variability in tandem gait measures. While Hoehn & Yahr stage 1 subjects were not significantly different from controls, stage 2 and 2.5 + groups were different. Parkinson's subjects with freezing of gait also walked with a wider base compared to those without gait freezing. Tandem gait spatiotemporal parameters were not correlated with fall frequency.
Conclusions: Tandem gait is impaired in Parkinson's disease in a stage-dependent manner, with wider base and increased step-to-step variability, which could suggest involvement of cerebellar and mediolateral balance pathways.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting about 1% of adults over the age of 60 years [1]. Bradykinesia, tremor, rigidity, and postural instability are the four cardinal features of PD, however, gait is also very commonly impaired, especially as the disease progresses. Declining gait and balance manifests as falls, freezing of gait and development of fear of falling, all of which contribute to decreased quality of life, increased caregiver dependence and fall associated morbidity and mortality [2].

Gait imbalance or gait ataxia is often assessed on the clinical exam using tandem gait (TG). Tandem gait abnormalities have been reported to increase with aging [3,4], have been used to distinguish between idiopathic PD and atypical forms of parkinsonism (AP) [5–8], and have also been used in models of fall prediction in PD [9]. More recently, side-steps on tandem gait were reported in 63.5% of Hoehn & Yahr (H&Y) Stage 2 and 100% of H&Y Stage 2.5–3 PD patients [10]. However, while gait in PD patients is commonly tested in the clinical setting by monitoring for decreased stride length and heel strike while walking in a hallway, tandem gait has not yet been incorporated into the Unified Parkinson's Disease Rating Scale (UPDRS).

Objective quantification of steady state gait and balance in PD has been pursued using pressure sensor impregnated gait mats [11], wearable sensors [12] and motion capture systems [13]. Spatiotemporal gait assessments have also been utilized to characterize tandem gait deficits in healthy non-falling subjects [4], and subjects with essential tremor [14,15]. However, studies have limited assessment of tandem gait in PD subjects to visual inspection of the tandem walk, with impairment documented as the number of times a subject took a step off from their straight tandem path (termed side step in most studies) [5–10]. Quantifiable objective markers would help in monitoring of therapeutic interventions, such as during clinical trials, as well as more concise monitoring of disease progression. We therefore conducted this study to objectively determine whether tandem gait was affected in clinical PD and whether disease severity impacted its prevalence. Due to reported mediolateral postural impairment [16] and

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dysfunctional cerebellar connectivity in PD FOG subjects [17,18], we also wanted to determine if tandem gait could help differentiate PD subpopulations.

2. Methods

2.1. Participants

A total of 74 subjects with idiopathic PD, based upon the UK Brain Bank criteria, were recruited from the Movement Disorders Clinic at the University of Arkansas for Medical Sciences after obtaining approval from the institutional review board, and in compliance with the Declaration of Helsinki guidelines for research involving human subjects. Family members were asked to participate as healthy controls (HC) with 28 subjects participating in the study. All subjects provided written informed consent prior to any study activities being performed. Exclusion criteria included more than 1 fall/day, Montreal cognitive assessment (MoCA) score < 10, and the use of anti-dopaminergic medications in the year prior to assessment. PD subjects were also classified based on Hoehn and Yahr (H&Y) staging score [19] with 11 stage 1, 46 stage 2, and 17 stage 2.5 and higher participating. 35 PD subjects meet the criteria for probable or definite FOG by Snijders et al. [20] while the remaining 39 constituted the non-freezers (no-FOG).

2.2. Clinical assessments

All subjects received a complete Unified Parkinson's Disease Scale (UPDRS) [21] assessment (by T.V), the Giladi Freezing of Gait Questionnaire (FOG-Q) [22], and a Montreal Cognitive Assessment (MoCA) [23]. Equivalent levodopa doses were calculated based on 100% and 70% bioavailability for immediate and extended release formulations, respectively [24].

2.3. Gait protocol and analysis

All PD subjects on levodopa were assessed in the ON medication state. Subjects were instructed to walk “heel touching toe”, “similar to the drunk walk if the police pulled you over”, one length of a 20 foot long by 4 foot wide pressure sensor impregnated mat (Zeno Walkway, ProtoKinetics, Havertown, PA). The tandem walk was also demonstrated to each subject before they started. Data was collected and analyzed using proprietary software (PKMAS, Protokinetics). Footsteps were selected first using PKMAS's intrinsic algorithm for footstep detection and then each individual trial was manually corrected where needed. Side steps (when subjects stepped off the tandem path to correct for imbalance) were documented, analyzed separately but excluded in the TG spatiotemporal parameters analysis in order to study the continuous portion of tandem gait, analogous to exclusion of freezing episodes in continuous gait analysis. The majority of the spatiotemporal parameters were calculated using PKMAS's intrinsic functions, including foot area, integrated pressure, step length, stride length, stride width, stride velocity, path width, single support percentage, and double support percentage. We previously defined two additional parameters not included in PKMAS [4]; path width (the width between the center of pressure coordinates of the two most lateral footsteps over the entire 20′ tandem walk) and step width (the width between the center of pressure coordinates for each set of consecutive steps). Mean and step-to-step variability (measured as the percent coefficient of variation, %CV) was calculated for each parameter. Spatiotemporal parameters were compared between the HC and PD groups, but also within the PD group based on (1) H&Y staging and (2) presence or absence of FOG.

2.4. Statistical analysis

Statistical analysis was done using SPSS version 24. Normality of data for each parameter was determined by the Schapiro-Wilk test. For all normally distributed data, statistical comparisons between groups was determined by one-way ANOVA with post hoc Bonferroni correction for multiple comparisons where indicated. For nonparametric data, the Kruskal-Wallis test was used for all comparisons with post hoc Bonferroni correction. Pearson's correlation coefficients were calculated for fall frequency relationships to tandem gait spatiotemporal parameters.

3. Results

3.1. Parkinson's disease versus healthy control subjects

A total of 102 subjects were enrolled in the study (74 PD, 28 HC). Not unexpectedly, PD subjects had lower MOCA scores and higher UPDRS and FOG-Q scores than HC (Supplementary Table 1). Only 2 HC (7.1%) had side steps (steps taken off to the side of the expected straight path) during their tandem walk, compared to 44 PD subjects (59.5%). On spatiotemporal gait analysis, subjects with PD had a higher mean step width, stride width, path width, step time, stride time, stance and swing times, single and total double support times, integrated pressure applied per footstep, and ambulation time (Fig. 1). PD subjects also had slower stride velocity and cadence compared to HC (Fig. 1) while foot measurements were similar between groups. There was significantly higher %CV in measured spatiotemporal parameters of TG in the PD subjects except with stride width and foot measurements (Fig. 2). Stance COP distance, which is a measure of foot strike, was also more variable in PD subjects compared to controls (Fig 2P).

In PD subjects with self-reported falls in the 3 months prior to their TG assessment, there were no significant differences in TG spatiotemporal parameters, either in mean or %CV, compared to PD subjects without falls (data not shown). The presence or absence of side steps was also similar in fallers vs non-fallers ($p = 0.211$).

3.2. Disease progression analysis based on Hoehn and Yahr staging

PD subjects were also grouped according to their H&Y staging with subjects with postural instability (Stage 2.5 and higher; H&Y2.5+) combined into a single group for the purposes of this analysis (11 H&Y1, 46 H&Y2, 17 H&Y2.5+). There was a H&Y stage-dependent increase in mean MOCA scores, disease duration, and motor UPDRS scores that were not statistically significant between the PD groups (Supplementary Table 2). Total UPDRS scores and levodopa dose was significantly higher in the H&Y2 and H&Y2.5 + groups compared to the H&Y1 group (Supplementary Table 2).

While all three PD groups had significantly higher percent of subjects with side steps than HC, there were no differences within PD groups that reached statistical significance (Supplementary Table 2). On spatiotemporal analysis, there were no mean gait parameters that were significantly different between HC and H&Y 1 subjects (Fig. 2). H&Y2 and H&Y2.5 + groups, however, had a stage-dependent increase in mean step width, stride width, path width, step time, stride time, stance time, total double support times, integrated pressure applied per footstep, and ambulation time compared to controls (Fig. 3), although these parameters did not reach significance between the PD groups. There was however a stage-dependent increase in %CV in step length, step time, stance time, and integrated pressure that was significantly different between the H&Y1 and H&Y2.5 + groups (Fig. 3).

3.3. Freezing of gait group analysis

We also grouped and analyzed PD subjects according to the presence (FOG) or absence (no-FOG) of freezing of gait (39 no-FOG, 35 FOG). The FOG group had a higher total but not significantly higher motor UPDRS score, and was on a higher total daily levodopa dose than the no-FOG group (Supplementary Table 3). On TG spatiotemporal

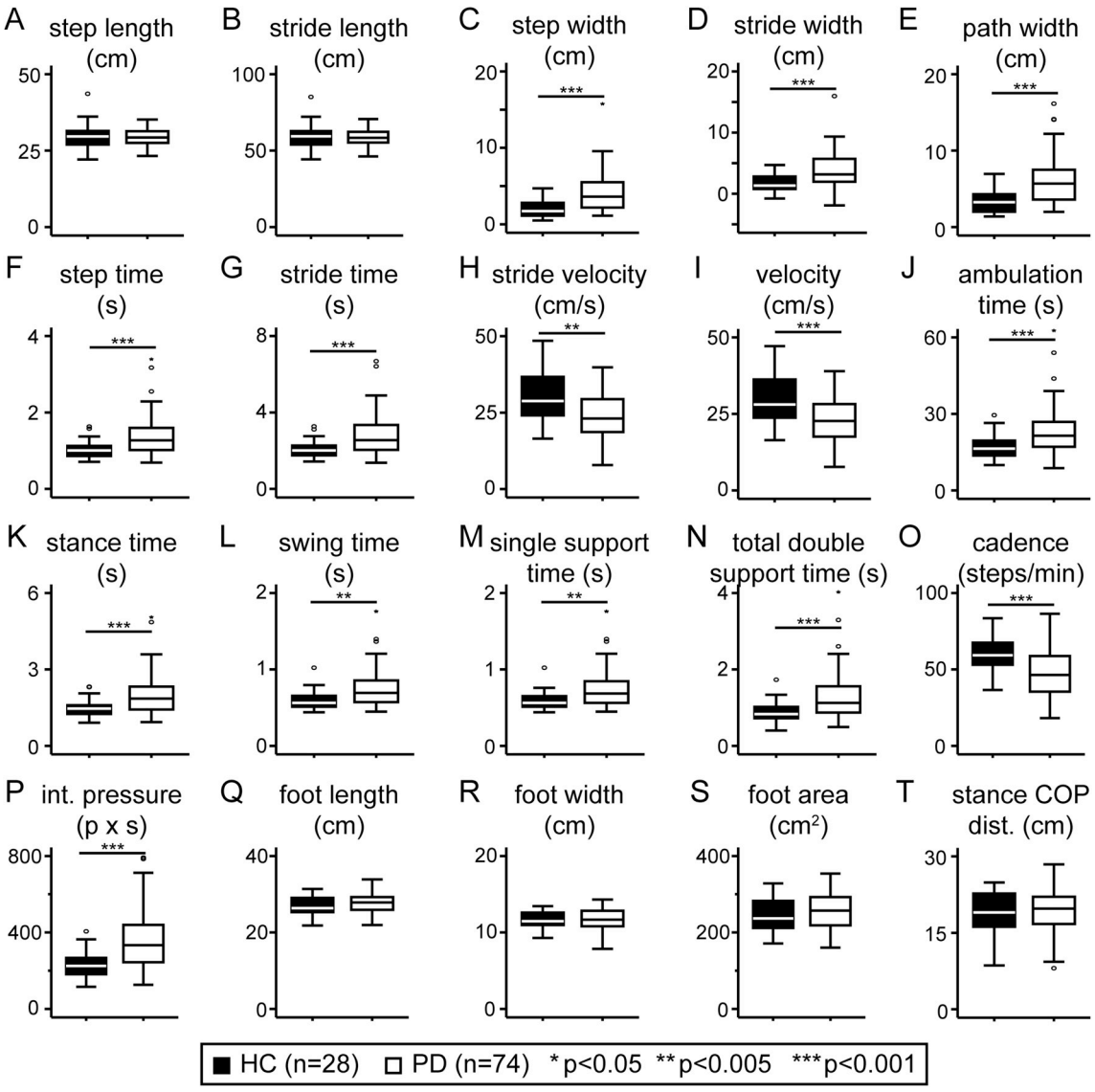

Fig. 1. Mean spatiotemporal parameters of tandem gait in healthy controls (black bars) compared to Parkinson's disease subjects (white bars).

analysis, mean step width and path width were significantly higher in FOG subjects compared to no-FOG (Fig. 4). There was also significantly higher %CV in step length and stride length in the FOG group (Fig. 4).

4. Discussion

Here we report for the first time, objective measures of TG in a cohort of 74 subjects with clinically diagnosed idiopathic PD. Compared to 28 healthy controls, PD subjects when performing the TG task took wider, but not longer steps, and had a slower stride velocity with an increased time spent in all phases of the gait cycle. PD subjects also applied greater pressure with each step (Fig. 1), and had greater step-to-step variability in TG measures (Fig. 2). These deficits were likely disease stage-dependent as H&Y stage 1 subjects were not significantly different from controls, as opposed to stage 2 and 2.5 + groups that were different (Fig. 3). Additionally, PD FOG subjects tandem walked with a wider base, as evidenced by a larger mean step width and path width, and also had increased step-to-step variability in step and stride length (Fig. 4).

The major strengths of our study are that, to our knowledge, this is the first report of a prospectively enrolled, large population of PD subjects, along with healthy control volunteers, who underwent objective TG evaluations. Previously published studies of tandem gait differences between PD and AP subjects have relied on subjective visual documentation of side steps during a 10 step tandem walk [5,7,9,25]. Combining the results from these past studies, approximately 42% of the total 265 PD subjects reported in the literature had side steps (range 8–57%), with a mean age of 64.9 years (range 57.5–67 years), and mean disease duration of 4.7 years (range 2.5–8.4 years). In our cohort, a larger percentage (almost 60%) met this definition of abnormal TG with at least one side step, with a similar age and slightly longer disease duration (Supplementary Table 1). The difference could partially be due to our longer task, with subjects walking 20 feet compared to 10 steps. However, it also suggests that lengthier evaluations may be needed to tease out the deficits in PD subjects. While we cannot rule out fatigue as an etiology for side steps, these occurred even at the beginning of TG trials, and none of the subjects reported any subjective fatigue with the single 20-foot tandem walk. Our results are more in line with a recently published study showing 63.5% of H&Y2 and 100% of H &Y2+ subjects show side steps on TG [10].

TG has previously been proposed to distinguish between patients with PD and Atypical Parkinsonism (AP) with a high sensitivity and specificity [5,7], and when combined with axial UPDRS scores, slow saccadic eye movements and dysphagia, gave an area under the curve

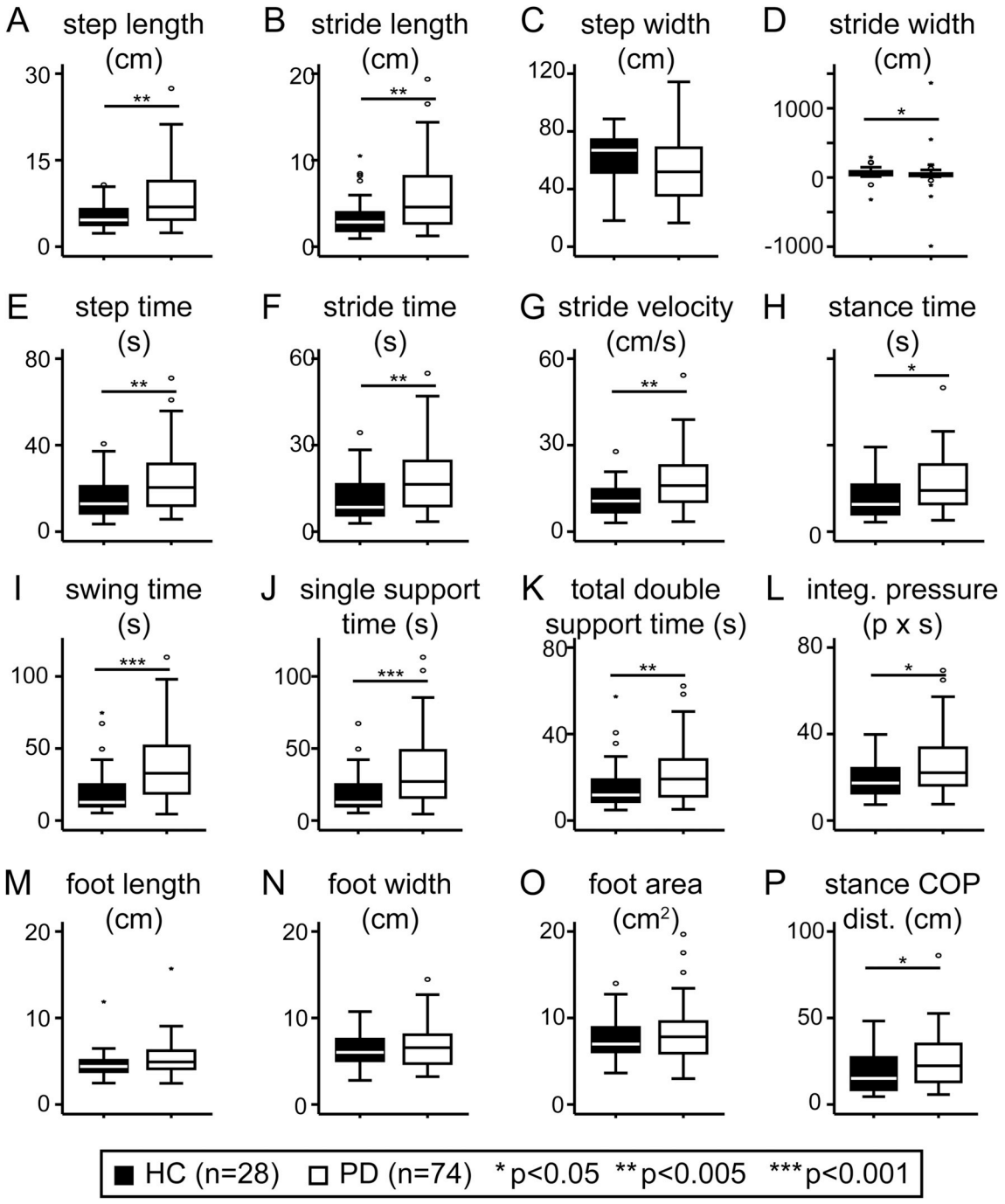

Fig. 2. Step-to-step variability (%CV) in spatiotemporal parameters of tandem gait in healthy controls (black bars) compared to Parkinson's disease subjects (white bars) showing both mean and step-to-step variability (%CV).

(AUC) of 0.93 [8]. In our study, a higher percentage of PD subjects had side steps than previously reported, albeit with a longer protocol (20 feet vs 10 steps). Our results would therefore significantly lower the sensitivity and specificity of counting side steps alone to distinguish PD from AP. We also found that, compared to HC, side steps were increased, and objective measures of TG were more significantly impacted in stage 2 and stage 2.5 + disease (Fig. 2). Even though there were no statistically significant differences between age or H&Y scores in previously published individual studies [5,7,8], they were still present, and combining the published data from these three studies, subjects had an older age (59.3 vs 66.0 years; PD vs AP; n = 152 and 175 respectively), and higher H&Y scores (2.2 vs 2.8; PD vs AP; n = 116 and 126 respectively) in the AP group. This is an important point to consider because, along with another group, we have previously shown that objective TG measures decline with age [3,4]. Additionally, our current results suggest that PD subjects with stage 2 and higher disease staging also have quantifiable and significant differences in TG compared to HC. Together these suggest that prospective studies measuring objective TG in AP patients, and comparing to age related norms as well as PD patients, would be important to further validate the use of TG to differentiate between PD and AP. If further validated, counting side steps would be more easily incorporated into a clinical movement disorders examination due to the cost and time needed to perform more objective gait analysis.

PD subjects with self-reported falls in the 3 months prior to their study visit did not have any significant differences in their mean or

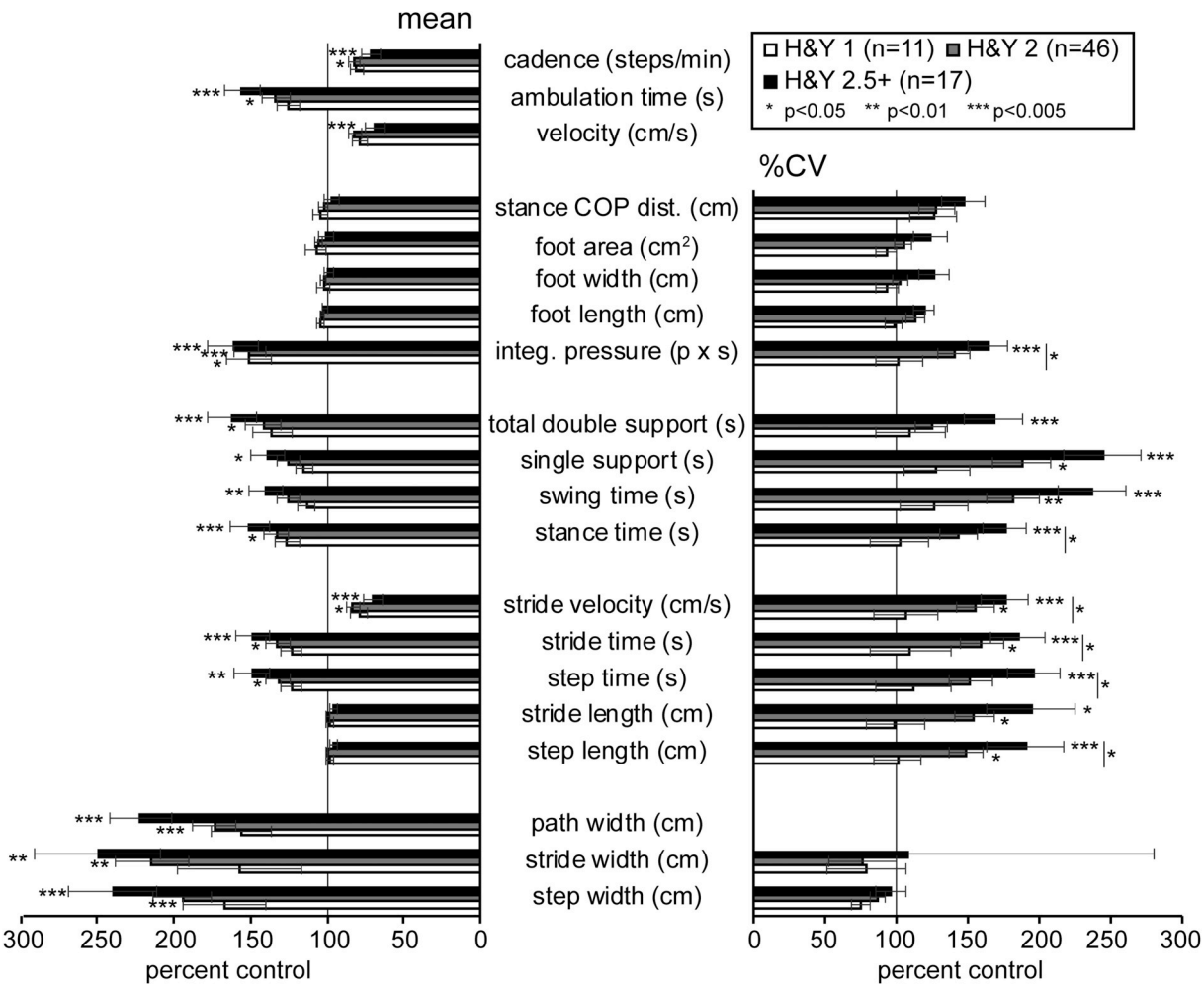

Fig. 3. Spatiotemporal parameters of tandem gait in Parkinson's disease patients as a function of Hoehn and Yahr stage, plotted as a percentage of healthy controls.

%CV TG parameters compared to non-fallers, nor did their fall frequency correlate with any TG parameters. This suggests that even though balance pathways that are involved in TG are affected in PD patients, they may not play as prominent a role in development of falls, as is the case for postural instability and FOG [2,26].

We also report for the first time that TG may be differentially affected in PD patients with FOG. In out cohort, PD FOG subjects had a wider step-to-step width and path width (width of the mat used during tandem walk) compared to no-FOG, implicating impaired mediolateral postural control. Impaired mediolateral postural control has been previously shown in PD FOG subjects, as a wider scatter in center of pressure (COP) traces along the mediolateral plane, compared to no-FOG, when performing the sit-stand-walk transition [16]; another task requiring dynamic postural control. In patients with AP, the TG impairment has also been attributed to mediolateral postural instability, and has been suggested to be due to cerebrellar involvement in patients with Multiple System Atrophy (MSA) and superior cerebellar peduncle involvement in Progressive Supranuclear Palsy (PSP) [5,6].

Dysfunction in the cerebellar circuitry has been implicated in the development of FOG. Fasano et al. [27] found that 13/14 cases of acute lesion-induced FOG in the literature, could be functionally connected to the dorsal medial cerebellum using the technique of lesion network mapping, a region that is part of the cerebellar locomotor region (CLR). Fling et al. [17] showed increased communication between the CLR (and mesencephalic locomotor region (MLR)) and the supplementary motor area (SMA) in PD FOG compared to no-FOG on fMRI, which was correlated with higher clinical ratings of FOG and higher scores on the new freezing of gait questionnaire. Bharti et al. [18] showed that functional connectivity within the CLR was higher in PD FOG compared with controls and the dentate nucleus (part of the neo-cerebellum to cerebral cortex pathway important in cognitive control of gait and posture) had decreased functional connectivity with the prefrontal and parieto-occipical cortices compared to no-FOG. Taken together, the clinically evident decreased mediolateral control in PD FOG subjects on TG, along with impaired cerebellar connectivity in both motor and cognitive pathways, suggests that dysfunctional cerebellar pathways may play a significant role in the development of freezing of gait. This may be more so in levodopa (or dopamine) resistant forms of freezing that occur in PD but also in AP, stroke and primary freezing of gait, but larger cohorts would be required to answer this question.

On TG, PD FOG also had increased step-to-step variability in step length and stride length compared to no-FOG subjects, which could be a corollary of the decreased step length seen in steady state gait [11,28]. Inclusion of tandem gait step width and step length variability in predictive models of FOG may therefore be indicated in the future.

TG dysfunction is not solely dependent on cerebellar pathways, as sensory or vestibular dysfunction can also lead to impaired TG [29]. While vestibular function is primarily impaired on an eyes-closed version of the tandem walk [30], sensory ataxia is manifested with eyes open. One limitation of our study therefore was that quantitative vibratory sensation testing was not available on all patients and therefore a component of sensory neuropathy contributing to the observed TG impairment cannot be excluded.

TG is also affected in other movement disorders and is included in

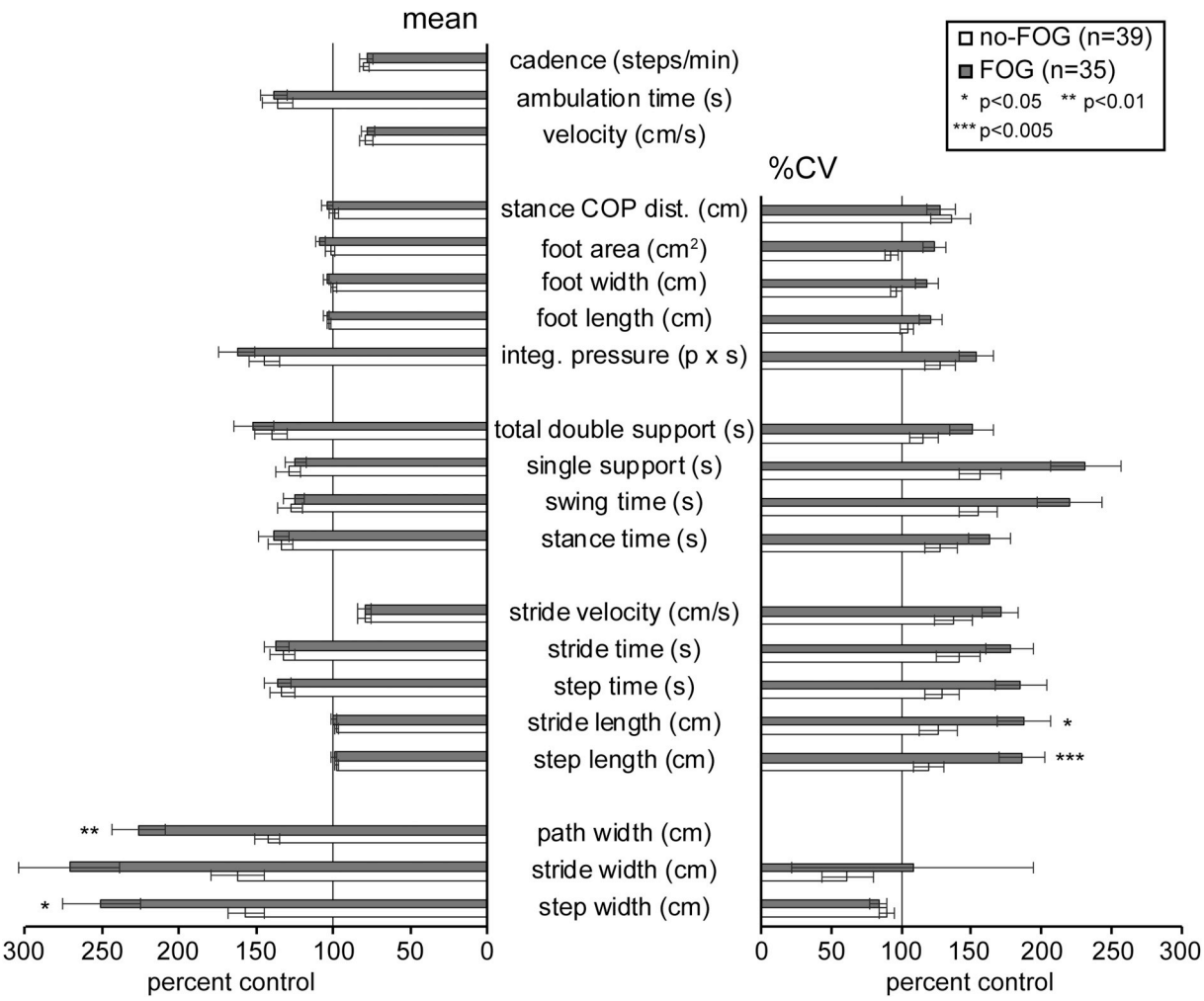

Fig. 4. Spatiotemporal parameters of tandem gait in Parkinson's disease with freezing of gait (FOG, gray bars) and without freezing of gait (no-FOG, white bars) plotted as a percentage of healthy controls.

the Scale for the Assessment and Rating of Ataxia (SARA) as well as the Unified Huntington's disease rating scale (UHDRS). Interestingly, some of our TG findings in PD patients are similar to those previously reported in Essential tremor (ET) [14,15]. In both PD (our study) and ET [15] on TG, velocity and cadence were decreased, mean step length was unchanged with an increase in stride length, step time variability, and an increased number of side steps (or mis-steps). However in PD, we found increased mean step width, stride width and path width with decreased stride width variability, although no difference in the corresponding measure of support base was reported in ET [15]. Prospective studies using objective gait measures may therefore also help differentiate complicated cases of ET and PD without the need for an expensive DAT SPECT scan.

In summary, our study has shown that objective impairment in TG is present in PD with increased impairment in an H&Y stage-dependent manner. In addition, PD FOG subjects showed selectively worsened step width, suggesting greater mediolateral impairment. These findings support a greater role of TG in the evaluation of patients with Parkinsonism and possible future inclusion into PD rating scales.

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Data statement

As this data was collected from human subjects with disease states, the IRB under which the data was collected does not allow for general sharing of raw data.

Ethics

This study was approved by the University of Arkansas' institutional review board (IRB# 203234) and complies with the guidelines in the Declaration of Helsinki for research involving human subjects.

Other

All authors have agreed to conditions noted on the Authorship and Contributorship Form. This work has not been accepted for prior publication. The authors take full responsibility for the data, the analyses and interpretation, and the conduct of the research. The corresponding author guarantees the accuracy of the references. The corresponding author had full access to all the data and has the right to publish any and all data.

Declaration of competing interest

Dr. Sharma is a neurology resident at the University of Arkansas for Medical Sciences. He received salary support from the University of

Arkansas for Medical Sciences.

Lakshmi Pillai is a research technician at the University of Arkansas for Medical Sciences and received salary support from the Clinician Scientist Training program grant to Tuhin Virmani in the preceding 12 months.

Aliyah Glover is a research technician at the University of Arkansas for Medical Sciences and received salary support from the NIGMS IDeA Program Center pilot award to Tuhin Virmani in the preceding 12 months.

Dr. Virmani is Co-Director of the Movement Disorders Program and an Assistant Professor of Neurology employed by the University of Arkansas for Medical Sciences. He received salary and grant support from the University of Arkansas for Medical Sciences Clinician Scientist program as well as grant support from the NIGMS IDeA Program Center of Excellence award P30 GM110702.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.023.

Author roles

Rohan Sharma was involved in research project execution, statistical design and execution and writing of the initial draft manuscript. Lakshmi Pillai, and Aliyah Glover were involved in research project execution and manuscript review and critique. Tuhin Virmani was involved in research project conception, organization and execution, statistical design and execution, and writing of the manuscript.

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