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Reduced after-effects following podokinetic adaptation in people with Parkinson's disease and freezing of gait

Samuel T. Nemanich^a and Gammon M. Earhart^{a,b,c,*}

Samuel T. Nemanich: nemanichs@wustl.edu; Gammon M. Earhart: earhartg@wustl.edu

^aProgram in Physical Therapy, Washington University School of Medicine in St. Louis, 4444 Forest Park Ave., Campus Box 8502, St. Louis, MO 63108

^bDepartment of Anatomy and Neurobiology, Washington University School of Medicine in St. Louis, 660 S. Euclid Ave., Campus Box 8108, St. Louis, MO 63100

^cDepartment of Neurology, Washington University School of Medicine in St. Louis, 660 S. Euclid Ave., Campus Box 8111, St. Louis, MO 63110

Abstract

Introduction—Gait dysfunction is common in people with Parkinson's disease (PD). Freezing of gait (FOG) is one such gait disturbance that significantly impacts mobility and quality of life in PD. Recent evidence suggests that cerebellar connectivity may differ in people with PD and FOG (PD+FOG) relative to those without FOG (PD–FOG). Investigation of gait adaptation, or the ability to change gait patterns in response to external perturbations, is cerebellum-dependent, is a practical means of probing cerebellar integrity and may provide additional insights regarding the FOG phenomenon.

Methods—In this study, we investigated gait adaptation in PD and FOG by measuring after-effects, namely whole-body rotation, following stepping on a rotating disc in PD+FOG compared to PD–FOG and older healthy adults. We refer to the period of stepping on the rotating disc as the podokinetic (PK) stimulation and after-effects as podokinetic after-rotation (PKAR). Our primary measure of adaptation was the magnitude and rate of decay of the after-effects.

Results—We noted that PKAR was diminished in PD+FOG compared to the other groups, indicating reduced storage of the adapted gait pattern in PD+FOG. In the PD groups, FOG explained about 20% of the variability in peak velocity. Furthermore, these differences were independent of stepping cadence or motor sign severity.

Conclusion—Our results show that gait adaptation is impaired in PD+FOG, suggesting the cerebellum may be differentially impacted in PD+FOG compared to PD–FOG. This supports

*Corresponding Author: Gammon M. Earhart, PT, PhD, Director, Program in Physical Therapy, Professor, Physical Therapy, Anatomy & Neurobiology, and Neurology, Washington University School of Medicine, Campus Box 8502, 4444 Forest Park Blvd., St. Louis, MO 63108, Phone: 314-286-1407 earhartg@wustl.edu.

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previous neuroimaging evidence of cerebellar dysfunction in PD+FOG. Overall, these data further our understanding of gait deficits in PD+FOG.

Keywords

Parkinson disease; freezing of gait; locomotor adaptation; after-effects

Introduction

Freezing of gait (FOG) is a disabling gait disturbance that affects more than half of individuals with Parkinson's disease (PD) [1]. A recent consensus paper defined FOG as a "brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" [2]. Clinically, freezers (PD+FOG) are at greater risk for falls, fear of falling, and experience poorer quality of life compared to non-freezers (PD-FOG) [3–5].

Currently, there are many hypotheses regarding the underlying mechanisms of FOG, including lack of gait automaticity, frontal-executive dysfunction and gait asymmetry (for review see [6]). A recent study by Mohammadi et al. investigated how PD+FOG, compared to PD-FOG and healthy older adults, responded to imposed asymmetry and sudden gait switches using a split-belt treadmill paradigm. They noted that PD+FOG had maladaptive stepping patterns when one belt of the treadmill was suddenly driven faster. Furthermore, they showed significant differences in rates of adaptation to split belts and re-adaptation to tied belts, such that PD+FOG were slower to adapt and re-adapt compared to PD-FOG and healthy controls [7]. Because gait adaptation is regulated by the cerebellum [8], evidence of slower adaptation in PD+FOG supports growing information about differences in the cerebellum among PD+FOG and PD-FOG [9–11]. Despite this, there are few data describing differences in cerebellar-dependent motor tasks between PD+FOG and PD-FOG.

In adaptation paradigms, the after-effect is a measure of the extent to which a newly learned motor pattern was stored in the nervous system and reflects the true recalibration achieved during adaptation [12]. Another apparatus that induces gait adaptation and after-effects is a rotating treadmill. While stepping on a rotating surface, the stance foot rotates relative to the stationary trunk, inducing a new relationship between foot and trunk position during stepping [13]. Following exposure, individuals spontaneously rotate with respect to space when stepping on a stationary surface reflecting adaptation of the foot-trunk system, termed the podokinetic (PK) system. Experimentally, after-effects, or podokinetic after-rotation (PKAR), are induced in younger adults across a range of stimulus duration and amplitudes [14]. When studying people with PD, Hong et al. found no differences in PKAR between PD and neurologically healthy older adults [15]. This null result may have been due to both small sample size, testing PD participants on dopaminergic medication, which may impact motor adaptation [16], and combining freezers and non-freezers into a single PD group. In contrast, participants with cerebellar damage exhibited reduced peak rotational velocity following PK stimulation, suggesting the cerebellum is associated with storage and expression of PKAR [17]. Based on the gait adaptation deficits during split-belt treadmill walking and differences in cerebellar connectivity in PD+FOG, we hypothesized that PD +FOG would also show reduced after-effects following PK stimulation. Therefore, the main

goal of this study was to determine whether PKAR differs in PD+FOG relative to PD–FOG following stepping on a rotating treadmill. We predicted peak velocity of PKAR would be smallest and return to baseline more slowly in PD+FOG compared to PD–FOG and controls. A secondary goal was to determine whether PKAR differs in people with PD evaluated off medication as compared to older adults, since prior work only compared people with PD on medication to older adults. We predicted that peak PKAR velocity would be smaller in the PD–FOG and PD+FOG groups off medication compared to older adults.

Materials and Methods

Participants

A convenience sample of 12 healthy older adults, 11 PD–FOG, and 9 PD+FOG took part in the study. Older adult participants were neurologically healthy and recruited from the Older Adult Volunteer database managed by the Department of Psychology at Washington University, or were spouses of PD participants. Participants with PD were recruited from the Movement Disorders Center at Washington University or from our laboratory database of those who had taken part in prior studies. All participants with PD had a diagnosis of idiopathic PD based on defined criteria [18]. FOG was classified using the New Freezing of Gait Questionnaire (NFOGQ [19]), which includes a video to illustrate the variety of ways in which freezing can occur. Each PD participant was asked if s/he had experienced freezing episodes over the past month. If the answer was yes, then we denoted her/him as a freezer (PD+FOG) and proceeded with the NFOGQ to determine a composite score assessing the duration and severity of freezing. If the answer was “no”, then we denoted her/him as a non-freezer (PD–FOG) with NFOGQ score of zero. Motor severity was assessed by a trained physical therapist using the Movement Disorder Society Unified PD Rating Scale subscale III (MDS-UPDRS III). The testing of PD participants occurred off of dopaminergic medication, defined as at least a 12-hour withdrawal from all anti-parkinsonian drugs; we excluded those who could not tolerate medication withdrawal. In addition, we excluded any individual with PD who had deep brain stimulation surgery. All participants were included if they could walk independently and stand for at least 15 minutes continuously. Further, they were excluded if they showed evidence of dementia (Mini-mental Status Exam (MMSE) <26 [20], took medications that could affect balance (e.g. benzodiazepines) or had orthostatic hypotension. All procedures described were approved by the Human Research Protection Office at Washington University. Participants provided written informed consent before beginning the study and were compensated for their time and effort.

Task

Participants stepped in place for 15 minutes on a motor-driven rotating disc (NeuroKinetics Inc., Pittsburgh, PA) embedded in the floor of the laboratory. We chose an intermittent training schedule consisting of three 5-minute bouts of stepping on the disc interleaved with 5-minute rest breaks, during which participants sat in a chair (25 minute total training session). Previous data indicate that similar after-effects appear following both intermittent and continuous training [15]. During stepping, the disc rotated clockwise or counterclockwise (randomly chosen) at 45 °/s. Participants stepped in place in the middle of the disc while maintaining a unidirectional heading. Vision and hearing were not modified

during the training session, and participants were allowed to step at a self-selected cadence. Following the final 5 minutes of stepping, participants stepped in place on the disk for ten minutes continuously with the treadmill turned off (after-effect phase). During this phase, participants wore a blindfold and earplugs to minimize sensory bias. A metronome attached to the participant at ear level and set at 120 beats/min was used to set cadence[21]. A frictionless wheel suspended from the ceiling, adjusted to each participant's height, was used for balance support and orientation while stepping during both phases.

Data acquisition and analysis

Kinematic data were collected at 100 Hz during the 10 minutes of PKAR using a high-resolution, 8-camera motion capture system (CMOS sensors, 307,200 pixels, 208 LEDs per Ringlight, Motion Analysis Inc., Santa Rosa, CA). After an initial calibration, reflective markers (19 mm diameter) were placed bilaterally on the anterior superior iliac spine to measure whole body rotation during PKAR. Additional markers were placed on the calcaneus, lateral malleolus, and first proximal phalanx of each foot to measure cadence. Raw marker data were examined for discontinuities and smoothed with a low-pass filter (Butterworth, 6 Hz cutoff). Final analysis was performed using custom Matlab (R2011b, Natick, MA) scripts. A moving average filter was applied, averaging the data over 5-second intervals. Angular position in the horizontal plane, a measurement confirmed to be reliable (accuracy = 0.98, unpublished data), was calculated using the hip markers over the total ten-minute time course. Finally, angular velocity was calculated as the derivative of angular position. A typical PKAR curve has a rising phase, normally lasting for the first two minutes, followed by a falling phase. The falling phase was identified manually by two assessors (one blinded and one unblinded) for each participant's curve and fit to a single monotonic exponential function in the form $y = A * \exp(-b * t) + C$, where b is the decay constant, C is the horizontal asymptote and $A + C$ is the maximum value of the function (when $t = 0$), and t is time. We compared these three parameters across groups (parameter estimates were similar for each assessor). To validate that individuals adhered to a cadence of 120 steps/minute during PKAR, we also calculated the average cadence during 2-minute windows of the ten-minute PKAR time-course. We used the rhythmic peaks in the vertical heel marker time series (z-direction) to determine footfall during stepping to measure cadence.

All statistical analyses were performed using SPSS (v21, IBM Corp, Chicago, IL). Appropriate parametric comparisons were made to examine differences in demographic variables (t-tests for two groups, ANOVA for more than two groups). We compared primary PKAR outcome variables peak velocity, decay rate, and asymptote using ANCOVA with group as a fixed effect and cadence as a covariate [21]. If a main group effect was present, we performed post-hoc comparisons (Tukey) between PD+FOG/PD-FOG, PD+FOG/Old, and PD-FOG/Old. We also reported effect sizes (partial η^2) for each variable. Finally, to explore the relationship between PKAR and FOG, we performed a linear regression using data from the PD groups to model peak PKAR velocity. Potential predictor variables included age, disease severity (MDS-UPDRS III), disease duration, cadence, and FOG. Age, disease severity and duration were chosen to account for general changes in somatomotor function; cadence was chosen because of its potential impact on PKAR velocity[21]; FOG

was chosen to explore its relationship to PKAR. Continuous variables (age, disease severity and duration, cadence) with significant ($p < 0.1$) bivariate linear correlation with peak velocity or categorical variables (FOG) with significant ($p < 0.1$) differences in peak velocity among the strata were included in the model. The final variables were forward-entered in separate blocks to determine the impact of each variable (change in model R^2). To assess potential collinearity among predictors, we examined the variance inflation factor, or how much an estimated coefficient is inflated based on collinearity, for all variables. For all other tests, the level of significance was set at $\alpha = 0.05$.

Results

Groups did not differ by age (one-way ANOVA: $F(28,2) = 0.62$, $p = 0.55$). Disease duration and motor sign severity were greater in the PD+FOG group compared to PD-FOG, but these differences were not statistically significant (t-tests; $p = 0.27$ for disease duration, $p = 0.08$ for MDS-UPDRS III). While we used a metronome to hold cadence fixed during PKAR, the cadence measured during PKAR differed between groups (one-way ANOVA; $F(28,2) = 3.35$, $p = 0.05$). As such, cadence was included as a covariate in our analyses. Three participants experienced FOG episodes lasting 2–13 s during PKAR, despite external cueing of cadence. These episodes all occurred after reaching peak velocity (i.e. all occurred after 5 minutes of stepping), and all time points were included in the analyses. Participant demographics are shown in Table 1.

Figure 1 shows representative PKAR velocity data and curve fits for one participant from each group. These plots illustrate the dynamics of a typical PKAR time-course: a rising phase lasting from minutes 0–2, followed by a falling phase from minutes 2–10. The equation of the exponential fit to the falling phase is shown for each curve. Peak velocity decreases by group such that Old > PD-FOG > PD+FOG. We noted a similar trend in the analysis of average group PKAR, also shown in Figure 2.

Curve fit parameters of PKAR velocity as well as post-hoc effect sizes are summarized in Table 2. Peak velocity was smallest in PD+FOG (7.17 ± 3.86 °/s) and largest in the Old group (10.66 ± 4.66 °/s). Statistical analysis showed that peak velocity was significantly different across groups ($F(28,2) = 4.78$, $p = 0.02$). Using post-hoc comparisons, we noted significant differences between PD+FOG / PD-FOG ($p = 0.03$) and PD+FOG/Old ($p = 0.03$). There were no differences in the estimates of decay rate ($F(28,2) = 0.674$, $p = 0.52$) or asymptote ($F(28,2) = 2.81$, $p = 0.08$) between the groups. Given a total sample size of 32, we had 81% power to detect a difference in peak velocity between groups.

We collapsed the two PD groups into a single group to explore the relationship between peak velocity and other demographic variables. The final regression model including age, disease severity, and FOG status (Table 3) was significant ($F(16,3) = 5.77$, $R^2 = 0.52$, $p = 0.007$). Age ($p = 0.01$) and freezing status ($p = 0.02$) were significant predictors of peak velocity in the final model (Table 3). The model's R^2 value increased by 0.19 when freezing status was added, indicating that freezing status accounted for about 20% of the overall variability in measured peak velocity after accounting for age and disease severity.

Discussion

In this study, we investigated how after-effects following stepping on a rotating treadmill were affected by PD and FOG. The main result was that individuals with PD+FOG exhibited the smallest peak velocity compared to the other groups. This result supports recent data showing locomotor adaptation is impaired in PD+FOG, and points to potential neurological mechanisms underlying this PD phenotype.

Previous work investigating locomotor adaptation in PD showed similar adaptation rate and after-effects between PD and healthy older adults. Using a split-belt treadmill paradigm, Roemmich et al. showed that people with PD adapted step length asymmetry and stored new walking patterns, as indicated by significant negative after-effects, despite increased gait asymmetry compared to controls [22]. The only study to our knowledge comparing PKAR in PD and older adults also found similar rate and magnitude of after-effects between groups [15]. In contrast, two other studies reported distinct differences in gait adaptation when separating PD+FOG and PD–FOG in comparison to healthy older adults. Nantel-Mahabier et al. noted that PD+FOG have maladaptive responses to split-belt treadmill walking such that they increase rather than decrease stride and step asymmetry over time compared to PD–FOG and older adults [23]. Furthermore, Mohammadi et al. showed a similar maladaptive response during split-belt walking, noting a significantly slower adaptation rate in PD+FOG compared to PD–FOG and controls. Interestingly, this study also observed that PD+FOG actually had larger initial after-effects but returned to baseline more slowly during re-adaptation relative to PD–FOG[7]. A larger baseline asymmetry in PD+FOG may have accounted for the initially larger after-effects. Nevertheless, there is sufficient data to indicate locomotor adaptation and retention differences exist between PD+FOG and PD–FOG.

In the current study, we observed smaller peak PKAR velocity in PD+FOG, suggesting this group was unable to store the adapted locomotor pattern induced by the rotating treadmill to the same extent as PD–FOG or older adults. These results are similar to another study of PKAR in people with cerebellar lesions, which noted lower peak velocity but similar decay rate and asymptote compared to younger adults [17]. Together with the evidence of split-belt adaptation dysfunction in PD+FOG, these data indicate the cerebellum is associated with gait adaptation and retention and may contribute to gait dysfunction observed in PD+FOG. The cerebellum has recently received more attention as a major contributor to motor dysfunction in PD[24], however, we did not observe differences in PKAR between the PD–FOG and older adults. Emerging neuroimaging data show that the cerebellar locomotor region has abnormal activity at rest [9] and during imagined gait tasks [10] in PD+FOG relative to PD–FOG. This is likely one anatomical area that is involved in the pathogenesis of PD+FOG, however its role in gait adaptation has yet to be determined.

Potential explanations for results and study limitations

Three participants experienced FOG while stepping in place. While these brief periods of festination may have caused transient declines in PKAR, the fitted parameters reflect the entire PKAR time course and not isolated segments. Furthermore, freezing episodes did not occur during the first 2–3 minutes of PKAR; as such there were no pauses during the rising

phase and FOG episodes therefore did not influence the peak velocity measure. We also tested participants with PD off dopaminergic medication, which affects not only global motor function, but motor adaptation [16] and cerebellar function.[25] However, medication may reduce after-effects following motor adaptation[16], and is associated with both increases and decreases in cerebellar connectivity[25]. Thus, the effects observed here are not likely related to freezing episodes or medication use, suggesting other factors are contributing to reduced after-effects.

One factor that has not been adequately explored in studies of PK adaptation is the influence of the vestibular and proprioceptive systems on PKAR expression. An interesting feature of PKAR is that it is not perceived by the participant. Thus, both vestibular and proprioceptive systems are remodeled during PK stimulation [14]. It is thought that during the first 1–2 minutes of PKAR, turning velocity is diminished because of vestibular suppression. While there were no differences in time to reach peak velocity across groups, some participants did peak earlier than others, perhaps indicating less or more vestibular influence on PKAR. A second possibility is that changes in proprioceptive adaptation accounted for reduced PKAR. It is well established that proprioception is impaired in PD[26, 27], and such deficient processing of proprioceptive information could similarly inhibit the PKAR response. Altogether, central processing of multiple sensory inputs PD[28] likely contributes to PKAR expression. Probing multisensory integration during and after podokinetic adaptation is an area in need of additional research.

Our results should be considered in light of the following limitations. First, categorization of PD+FOG was based on self-report and not direct observation of freezing episodes. This may have caused misclassification of some PD participants. Second, we focused on sensorimotor rather than cognitive-motor differences between groups. We did not collect specific information on cognitive function in our sample, however previous studies show deficits in several cognitive domains (for review see [29]) in PD+FOG. It is possible that unmeasured differences in cognition contributed to the differences in PKAR. Finally, we did not determine the test-retest reliability of angular rotation or marker placement in our data. However, the reliability of similar marker placement has been established [30]. While the reliability of rotational position in the transverse plane is understudied, we have no reason to expect it would be different than in other planes of movement. We based our measurements on standard biomechanical formulae and thus do not expect major changes in measurement technique or marker placement to significantly change our results.

Conclusion

Overall, our results show that after-effects following locomotor adaptation are reduced in PD+FOG and add to current knowledge of the potential mechanisms underlying FOG. Gait adaptation paradigms have implications for physical rehabilitation in people with PD with and without FOG because they explore how individuals respond in novel environments or to external perturbations, and reflect capacity to retain adapted motor patterns.

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- We compared after-effects following locomotor adaptation in Parkinson's disease
- Participants with and without freezing of gait were included
- Magnitude of after-effects were smaller in the freezer group
- After-effects were similar between controls and the non-freezer group
- People who freeze may have less storage of adapted locomotor patterns.

Figure 1.

Individual and group after-effects following stepping on the rotating treadmill. *Top:* Representative PKAR velocity time course for each group (from left to right: Old, PD-FOG, PD+FOG). Continuous line is the exponential best fit of the falling phase of the curve with corresponding equation. *Bottom:* Group average PKAR time course. Error bars are $\pm$ SEM. Old: Older adult group; PD-FOG: Non-freezer Parkinson's disease group; PD+FOG: Freezer Parkinson's disease group.

Table 1

Participant Demographics

Characteristic	Old (n = 12)	PD–FOG (n = 11)	PD+FOG (n = 9)
Age (yr)	70.51 ± 8.28	69.26 ± 4.39	67.00 ± 7.19
Males n (%)	5 (42)	7 (64)	4 (44)
Disease Duration (yr)	—	5.36 ± 2.60	6.67 ± 3.69
MDS-UPDRS Part III	—	33.91 ± 12.24	46.00 ± 10.58
NFOGQ	—	0	14.33 ± 7.51 [*]
Cadence (steps/min)	119.93 ± 4.13	125.27 ± 6.83	113.68 ± 16.67 [*]

Values represent Mean ± SD

MDS-UPDRS Part III: Movement Disorder Society Unified Parkinson Disease Rating Scale Motor Subscale (0–132); NFOGQ: New Freezing of Gait Questionnaire (0–28); Cadence measured during PKAR

^{*} Significantly different than PD–FOG (p<0.05)

Table 2

PKAR exponential fit parameters

Parameter	Old	PD-FOG	PD+FOG	η^2
Peak Velocity (°/s)	10.66 ± 1.34*	10.42 ± 0.73*	7.17 ± 1.29	0.25
Decay Rate (min)	3.92 ± 1.11	2.85 ± 0.57	2.54 ± 0.69	0.05
Asymptote (°/s)	3.97 ± 0.94	4.46 ± 0.74	2.12 ± 0.60	0.17

Values are Mean±SEM

Peak Velocity = A+C; Decay Rate = 1/b (larger is slower decay); Asymptote = C, η^2 = Partial effect size

* Significantly different than PD+FOG (p<0.05, post-hoc)

Table 3

Linear regression model of peak velocity

<u>Predictor</u>	<u>B</u>	<u>SE(B)</u>	<u>p</u>	<u>VIF</u>
<i>Step 1</i>				
Age	−0.32	0.15	0.05	1.00
<i>Step 2</i>				
Age	−0.29	0.15	0.07	1.02
MDS-UPDRS III	−0.09	0.05	0.09	1.02
<i>Step 3</i>				
Age	−0.36	0.13	0.01	1.07
MDS-UPDRS III	−0.04	0.05	0.43	1.24
FOG	−3.36	1.32	0.02	1.25

Step 1 $R^2 = 0.20$, Step 2 $R^2 = 0.13$, Step 3 $R^2 = 0.19$ Overall model fit was $R^2 = 0.52$ ($p < 0.01$). *VIF*: Variance inflation factor