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

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

1. 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 Ref. [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

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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.

2. Materials and methods

2.1. 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-h 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 min 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.

2.2. Task

Participants stepped in place for 15 min 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-min bouts of stepping on the disc interleaved with 5-min rest breaks, during which participants sat in a chair (25 min 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 min of stepping, participants stepped in place on the disk for 10 min 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.

2.3. Data acquisition and analysis

Kinematic data were collected at 100 Hz during the 10 min 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-s 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 10-min 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 2 min, 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-min windows of the 10-min 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.