Published in final edited form as:

Behav Brain Res. 2014 July 15; 268: 31–39. doi:10.1016/j.bbr.2014.03.041.

Effects of dopaminergic therapy on locomotor adaptation and adaptive learning in persons with Parkinson's disease

Ryan T. Roemmich^{1,2}, Nawaz Hack^{3,4}, Umer Akbar^{3,4}, and Chris J. Hass^{3,5}

¹Kennedy Krieger Institute, Baltimore, MD

²Department of Neuroscience, The Johns Hopkins University School of Medicine

³Center for Movement Disorders and Neurorestoration, University of Florida

⁴Department of Neurology, University of Florida

⁵Department of Applied Physiology and Kinesiology, University of Florida

Abstract

Persons with Parkinson's disease (PD) are characterized by multifactorial gait deficits, though the factors which influence the abilities of persons with PD to adapt and store new gait patterns are unclear. The purpose of this study was to investigate the effects of dopaminergic therapy on the abilities of persons with PD to adapt and store gait parameters during split-belt treadmill (SBT) walking.

Ten participants with idiopathic PD who were being treated with stable doses of orally-administered dopaminergic therapy participated. All participants performed two randomized testing sessions on separate days: once while optimally-medicated (ON meds) and once after 12-hour withdrawal from dopaminergic medication (OFF meds). During each session, locomotor adaptation was investigated as the participants walked on a SBT for ten minutes while the belts moved at a 2:1 speed ratio. We assessed locomotor adaptive learning by quantifying: 1) aftereffects during de-adaptation (once the belts returned to tied speeds immediately following SBT walking) and 2) savings during re-adaptation (as the participants repeated the same SBT walking task after washout of aftereffects following the initial SBT task).

The withholding of dopaminergic medication diminished step length aftereffects significantly during de-adaptation. However, both locomotor adaptation and savings were unaffected by levodopa. These findings suggest that dopaminergic pathways influence aftereffect storage but do not influence locomotor adaptation or savings within a single session of SBT walking. It appears important that persons with PD should be optimally-medicated if walking on the SBT as gait rehabilitation.

© 2014 Elsevier B.V. All rights reserved.

Address correspondence to: Ryan Roemmich, G-04 Kennedy Krieger Institute, 707 North Broadway Street, Baltimore, MD 21205, rroemmi1@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare that there are no relevant conflicts of interest.

Keywords

Parkinson's disease; adaptation; split-belt treadmill; dopamine; motor learning

1. Introduction

Persons with Parkinson's disease (PD) can exhibit a variety of locomotor deficits, including gait slowness [1], increased risk of falling during transitional periods [2], and the presence of gait asymmetry [3]. While some treatments induce modest gait improvement, no interventions exist which wholly restore gait performance in PD. Recent research has investigated locomotor adaptation and adaptive learning processes within the context of gait rehabilitation for populations characterized by gait asymmetry, including persons post-stroke [4,5] and with PD [6–8]. Certainly, developing a better understanding of the abilities of persons with PD to adapt and store gait patterns could have significant impact on the design of gait rehabilitation paradigms and further insight into the neural substrates facilitating these processes.

Motor adaptation and adaptive learning processes have been studied across a variety of experimental conditions, including eye movements [9], upper extremity motor tasks [10–12], and locomotion [13]. Adaptation has been defined as a short-term process of adjusting a movement to new task demands through trial-and-error practice [14]. Adaptive learning is a longer-term process representing the stored ability after practice to predict new demands and accordingly adjust movement parameters [15]. Motor adaptation is commonly studied by inducing an unfamiliar perturbation into an otherwise familiar task. The motor response (i.e., adaptation) to the perturbation is characterized by large initial errors which are eventually reduced toward a baseline asymptote given repeated exposure to the perturbation [16]. Adaptive learning is assessed during ensuing de-adaptation and re-adaptation phases. Following adaptation, deadaptation occurs when the perturbation is removed and conditions return to baseline. Large errors (commonly termed aftereffects) are initially present in the direction opposite those observed during initial adaptation and wash out over time as performance returns to baseline. Re-adaptation is studied during a second exposure to the perturbation following washout of the first. The phenomenon of savings is apparent if some memory of the first adaptation task is evident such that initial errors during re-adaptation are diminished and the rate of adaptation increases [17,18].

These phenomena have recently been investigated within locomotor paradigms using a split-belt treadmill (SBT): a treadmill consisting of one independently-controlled belt under each limb [13]. These treadmills allow for creation of walking tasks during which the limbs walk at different speeds or directions simultaneously. Previous research on SBT walking in healthy adults demonstrated that step lengths are asymmetric during initial adaptation (as the limb walking on the slow belt takes a longer step than the limb walking on the fast belt), gradually adapt toward baseline over time, and exhibit aftereffects and savings during de-adaptation and re-adaptation, respectively [13,19]. Therefore, step length is a reliable spatiotemporal measure upon which to study the response of the nervous system to errors in the gait pattern. However, during conventional gait, it has been well-established that stance

phase kinetics (specifically, ankle power production during late stance) have a profound effect on step length [20]. Kinetic changes during SBT adaptation have only recently been studied [21–23] and little is known about kinetic aftereffects and savings during locomotion. A more thorough investigation of the kinetics during late stance could indicate whether kinetic changes drive the kinematic changes occurring during adaptation and adaptive learning (as during conventional walking) or whether they are differentially controlled.

Previous work on SBT walking in PD showed that optimally medicated persons with PD adapted step lengths toward an asymmetric asymptote which paralleled their baseline asymmetry while age-matched controls adapted to a relatively symmetric state [8]. Impairments in the storage of aftereffects or savings were not observed. However, these findings were in contrast to several previous studies of upper extremity motor adaptation tasks which noted disruptions in these phenomena in PD [24–29]. A key difference is that many of these studies investigated persons with PD after levodopa withdrawal. Thus, a comparison of locomotor adaptation and adaptive learning in persons with PD on and off dopaminergic medication could provide insight into the influence of dopaminergic pathways on these processes.

The purpose of this study was to investigate the effects of dopaminergic therapy on the abilities of persons with PD to adapt and store kinetic and spatiotemporal gait parameters during SBT walking. We hypothesized that, in accordance with previous research on upper extremity motor adaptation in PD, storage of locomotor aftereffects and savings would be diminished when the participants were withdrawn from their medication, though adaptation would be unaffected. We suggest that these findings could have significant impact with regard to both gait rehabilitation in persons with PD as well as the understanding of neural and biomechanical mechanisms which contribute to locomotor adaptation and adaptive learning.

2. Methods

2.1 Participants

Ten persons with PD were recruited for the study (mean±SD: height 172.5±9.7 cm, body mass 75.8±9.1 kg; Table 1). Diagnosis of idiopathic PD was confirmed by a movement disorders specialist at the University's Center for Movement Disorders and Neurorestoration. Participants had neither walked on a SBT nor experienced any lower-extremity orthopedic injury for at least one year prior to participation. All were being treated with stable doses of orally-administered levodopa therapy. Four participants were also taking a dopamine agonist in addition to levodopa. All participants provided written informed consent before participating in the study as approved by the University Institutional Review Board.

2.2 Protocol

Participants performed the same tasks on two separate days of testing no longer than two days apart. During the first visit, the participants performed the tasks either while in their optimally-medicated state (ON meds) or after having withdrawn from taking any anti-

parkinsonian medication for at least 12 hours (OFF meds; time since last dose prior to testing (mean±standard deviation): 15±2 hours). During the subsequent visit, the participants performed the same tasks again in the opposite medicated state. The order in which the participants performed the tasks in the ON meds and OFF meds states was pseudo-randomized such that five participants were ON meds during the first visit and five participants were OFF meds. All participants took their medication one hour prior to the ON meds testing session. Prior to testing on both days, the participants performed ten overground gait trials while walking at a self-selected comfortable pace and completed the motor portion (Section III) of the Unified Parkinson's Disease Rating Scale (UPDRS) while being video-recorded (Table 1; please note that the scoring was done in accordance with the UPDRS, not MDS-UPDRS). These videos were scored by a single independent movement disorders-trained neurologist who was blinded to the medicated state of each participant.

During the locomotor testing sessions, thirty-five passive retroreflective markers were attached to the body in accordance with the Vicon Plug-in-Gait full body marker system. Kinematic data were collected using a 7-camera motion capture system (120 Hz; Vicon, Oxford, UK) while participants walked on an instrumented SBT (Bertec Corporation, Columbus, OH). Kinetic data were collected at 1200 Hz. The experimental protocol is shown in Figure 1. Participants first walked on the SBT while both belts moved together at a self-selected comfortable speed for five minutes to accommodate to walking on the treadmill. All participants wore a safety harness which provided no body weight support and held onto the handrails for the duration of all treadmill sessions. Participants were then accommodated to the slow and fast walking speeds as they first walked for two minutes with both belts moving together at .50 m/s (the “slow” speed – BASELINE), followed by two minutes with both belts moving together at 1.0 m/s (the “fast” speed), and then again for two minutes with both belts moving at the slow speed to wash out the fast period [13]. After the washout period, the treadmill was brought to a stop and then sped up such that the belt under the participant's self-reported less-affected limb moved at .50 m/s while the belt under the more-affected limb moved at 1.0 m/s (the designation of the more- and less-affected sides were later confirmed through UPDRS scores). These speeds were selected as we aimed to select speeds which could be tolerated by persons with PD while unmedicated and this specific speed combination has previously been shown to be tolerable by persons post-stroke with relatively severe gait impairment [14]. The participants walked under these conditions for ten minutes. This was considered the adaptation phase of the experiment (ADAPT). Then, the belt moving at 1.0 m/s was slowed to .50 m/s for five minutes to assess the aftereffects of the SBT gait parameters stored during de-adaptation to conventional treadmill walking (POST-TIED). Following the five-minute POST-TIED condition, the participants again walked on the SBT with the belts in the same 1.0/.50 m/s configuration as performed during ADAPT for five more minutes. This was considered the re-adaptation portion of the experiment to assess savings (RE-ADAPT). Finally, the participants were given a five-minute cool-down with both belts moving at .50 m/s for five minutes to wash out the adapted gait parameters before leaving the lab. The same protocol was performed by each participant in the opposite medicated state on the second visit.

2.3 Data analysis

Heel-strikes and toe-offs were manually labeled in Vicon software based on marker velocity profiles. Kinematic and kinetic data were filtered using 4th-order low-pass Butterworth filters with cutoff frequencies of 10 Hz and 20 Hz, respectively. Step length was defined as the distance between the ankle markers along the walking axis at heel-strike. The propulsive phase of each gait cycle was determined by the portion of the stance phase during which the anteroposterior ground reaction forces (AP-GRFs) were greater than zero. Sagittal joint angles and joint moments were calculated using the Vicon Plug-in-Gait model. Sagittal ankle power was calculated as the product of the ankle joint's sagittal angular velocity and moment. All AP-GRFs and ankle powers were normalized in magnitude to the participant's body mass as well as temporally to 100% of the gait cycle. We then calculated the AP-GRF propulsive impulses (the areas under the propulsive portions of the AP-GRF curves). An example as to how the propulsive AP-GRFs were identified is shown on Figure 2A. The A2 phase of the sagittal ankle power profile ([20]) was designated as the portion of the curves during which power moved from a negative value (i.e. power absorption) to a positive value (i.e. power generation) during late stance. An example as to how the A2 portion of the ankle power curve was defined is shown in Figure 2B. Sagittal ankle power (and specifically the A2 phase) was selected because of the remarkably strong association between A2 ankle power and step length [20]. We also calculated the work done by the ankle during A2 by integrating this area of the ankle joint power curve.

We defined symmetry in each spatiotemporal gait parameter using the following asymmetry index [30]: $\text{Asymmetry} = (\text{fast limb parameter} - \text{slow limb parameter}) / (\text{fast limb parameter} + \text{slow limb parameter})$

Spatiotemporal asymmetry data and kinetic data were averaged over the first and last five strides of ADAPT (EARLY and LATE, respectively – to assess adaptation) as well as over the first five strides of POST-TIED (to assess aftereffects during de-adaptation) and RE-ADAPT (to assess savings during re-adaptation). Baseline values were determined by averaging data across the first 30 seconds of BASELINE.

2.4 Statistical analyses

Three repeated measures MANOVAs were performed to compare the spatiotemporal and kinetic gait parameters among specific walking conditions (adaptation – BASELINE vs. EARLY vs. LATE; aftereffects – BASELINE vs. POST-TIED; savings – EARLY vs. RE-ADAPT) and between medicated states (ON meds, OFF meds) in order to assess the effects of dopaminergic therapy on adaptation, aftereffects, and savings. Paired t-tests were also performed to compare the individual step lengths of the fast and slow limbs during BASELINE and POST-TIED. Further paired t-tests were performed to compare lower extremity sagittal joint angles between limbs at heel-strikes during POST-TIED. Levels of significance for all analyses were set at $p < .05$ and Bonferroni post-hoc adjustments were applied when appropriate.

3. Results

3.1 Locomotor adaptation

A paired t-test revealed a marginally significant increase UPDRS scores when the participants were OFF meds as compared to ON meds (Table 1; $p=0.06$). All participants were able to successfully adapt to the SBT walking task in each medicated state. They were also able to maintain a 1:1 cadence between the limbs across all walking conditions (i.e., never did any participant step twice with the same limb before taking a subsequent step with the contralateral limb).

Step length adaptation—We did not observe a main effect of medication on step length asymmetry nor did we observe a significant walking condition $\times$ medication interaction during locomotor adaptation. Thus, regardless of medication state, the participants adapted step length asymmetry from EARLY to LATE in similar fashion to previous studies of persons with PD on medication [8] and healthy young and older adults [13] (Figure 3). The order in which the sessions were performed appears to have little effect on any of the conditions, with perhaps the exception of EARLY (Figure 4; statistical analyses comparing the participants tested while ON meds first to those tested while OFF meds first were not performed due to sample size limitations of $n=5$ in each subgroup).

Kinetic adaptation—We observed a significant main effect of walking condition on the fast limb propulsive impulse ($p<.05$). The fast limb propulsive impulse increased significantly during the locomotor adaptation phase, but only from BASELINE to LATE ($p<.05$, Figure 5). We did not observe a significant main effect of walking condition on the slow limb propulsive impulse.

A significant main effect of walking condition was detected for the fast limb peak A2 power, fast limb A2 work, and slow limb peak A2 power (all $p<.05$, Figure 6). We failed to detect a significant main effect of walking condition on slow limb A2 work.

The fast limb peak A2 power significantly increased from BASELINE to EARLY ($p<.05$) and remained similar in magnitude from EARLY to LATE. Similarly, A2 ankle work increased in a similar pattern from BASELINE to EARLY ($p<.05$) but not from EARLY to LATE. We did not observe any differences between BASELINE, EARLY, and LATE in slow limb peak A2 power or A2 ankle work (Figure 6).

We did not observe a main effect of medication on any kinetic gait parameters during locomotor adaptation nor did we observe a significant walking condition $\times$ medication interaction. In summary, the kinetics demonstrated during locomotor adaptation followed a similar pattern to those previously reported in healthy young adults [23]. From EARLY to LATE adaptation, the ankle mechanics drive the body forward by generating a progressively greater amount of work, resulting in a greater propulsive GRF impulse.

3.2 Locomotor adaptive learning

Step length aftereffects during de-adaptation—Step length asymmetry was significantly higher during POST-TIED than during BASELINE ($p<.05$). A significant main

effect of medication as well as a significant walking condition $\times$ medication interaction for step length asymmetry (both $p<.05$) was also observed, indicating that the change in step length asymmetry from BASELINE to POST-TIED was significantly larger in the ON meds state as compared to the OFF meds state (Figure 3).

Ensemble orientations of the limbs at heel-strike during POST-TIED are shown for both medicated states in Figure 7. During POST-TIED, the participants exhibited significantly greater hip flexion ($p<.05$) and a non-statistically significant increase ($p=.074$) in knee extension of the fast limb at heel-strike when ON meds compared to OFF meds (Figure 7). While the slow limb took a significantly shorter step during POST-TIED as compared to BASELINE in both the ON meds and OFF meds states, the fast limb only took a significantly longer step during POST-TIED as compared to BASELINE when ON meds ($p<.05$, Figure 7).

Kinetic aftereffects during de-adaptation—We hypothesized that step length aftereffects following locomotor adaptation could result from changes in the stance phase kinetics, as ankle power production during late stance profoundly influences step length [20]. That is, perhaps the diminished step length observed in the persons with PD when OFF meds resulted from diminished ankle power and GRF production during de-adaptation. However, in the present study, we observed neither significant main effects of walking condition or medication nor any significant walking condition $\times$ medication interactions for any of the AP-GRF impulse variables (Figure 5). AP-GRF impulses were not significantly different between BASELINE and POST-TIED nor did medication have any effect on AP-GRF production during these walking conditions.

Similar to the AP-GRF impulses during de-adaptation, neither significant main effects of walking condition or medication nor any significant walking condition $\times$ medication interactions for peak A2 power or A2 work production (Figure 6) were identified. Thus, sagittal ankle kinetics were not significantly different between BASELINE and POST-TIED nor did medication have any effect on the sagittal ankle kinetics during these walking conditions; it is unlikely that changes in stance phase kinetics drove the observed changes in step length aftereffects between medicated states. Group ensemble AP-GRF and sagittal ankle power profiles during BASELINE, LATE ADAPT, and POST-TIED are shown in Figure 8 to demonstrate the kinetic changes among the baseline, adaptation, and de-adaptation conditions.

Step length savings during re-adaptation—We observed the presence of savings in both medicated states such that step length asymmetry was significantly lower during RE-ADAPT than during EARLY ($p<.05$, Figure 3). However, contrary to our findings regarding the aftereffects, we did not observe a significant main effect of medication on step length asymmetry nor did we observe a significant walking condition $\times$ medication interaction.

Kinetic savings during re-adaptation—The statistical analyses failed to reveal significant main effects of walking condition or medication nor significant walking condition $\times$ medication interactions on AP-GRF impulses when comparing EARLY vs. RE-ADAPT (Figure 5). Thus, AP-GRF impulses during READAPT were not significantly

different from those observed during EARLY. Further, medication did not significantly affect AP-GRF production during RE-ADAPT.

Unsurprisingly, we also failed to detect significant main effects of walking condition or medication nor significant walking condition $\times$ medication interactions on peak A2 power or A2 work production (Figure 6). Thus, sagittal ankle kinetics during RE-ADAPT were not significantly different from those observed during EARLY. Further, medication did not significantly affect AP-GRF production during RE-ADAPT.

4. Discussion

We investigated the effects of dopaminergic therapy on the abilities of persons with PD to adapt and store kinetic and spatiotemporal gait parameters during SBT walking. Even when OFF meds, persons with PD exhibited the ability to adapt gait to SBT walking, stored aftereffects during de-adaptation, and demonstrated savings upon re-adaptation. However, we observed that the step length aftereffect during de-adaptation was diminished in magnitude when the participants were OFF meds as compared to ON meds. These changes in step length aftereffects were not accompanied by changes in kinetic aftereffects; in fact, we did not observe any aftereffects in the AP-GRFs or ankle power profiles, and thus step length aftereffects appear to be independent of kinetic adaptation. Contrary to our hypothesis, we observed no effect of levodopa on the savings of the SBT gait pattern during re-adaptation. As hypothesized, locomotor adaptation was also unaffected by levodopa.

4.1 Effects of levodopa on locomotor adaptive learning

Our findings indicating reduced step length aftereffects during de-adaptation are consistent with previous studies of persons with PD in other adaptive motor learning paradigms. For instance, Stern and colleagues observed diminished spatial aftereffects during de-adaptation (i.e., the reach of the PD participants was significantly more accurate upon removal of the prism glasses) despite unaffected adaptation patterns during a prism reaching task [31]. Similarly, Fernandez-Ruiz and colleagues utilized a prism throwing adaptation task to investigate visuomotor adaptive learning in persons with different basal ganglia disorders (PD ON meds and Huntington's disease) [25]. These investigators also observed normal visuomotor adaptation patterns and rates but a reduced aftereffect in the throwing task upon removal of the prism glasses in both basal ganglia disorder groups. Another study by Isaías and colleagues demonstrated that persons with PD exhibit reduced interlimb transfer following a visuomotor adaptation task [26]. However, these studies were all limited to examination of visuomotor adaptive learning and thus suggested that the basal ganglia seem to play an important role in the storage of visuomotor aftereffects specifically. Our locomotor findings supplement the results of these studies to suggest that dopaminergic pathways may play a role in the storage of aftereffects across various paradigms of adaptive motor learning.

While we observed significantly diminished step length asymmetry during de-adaptation when persons with PD were OFF meds, we surprisingly did not observe any effect of medication on savings of the SBT gait pattern upon re-adaptation to the task. These findings are in contrast to previous studies of various upper extremity visuomotor tasks which

demonstrated significant involvement of the basal ganglia in savings of adapted movements [24,27,32]. We suggest that these differences potentially result from the differing nature and demands of adaptive locomotor and visuomotor tasks and perhaps the varying degree of overlearning allowed. Overlearning is quantified by the amount of practice given during the initial adaptation task after performance has reached asymptote [33]. Previous research suggests that overlearning increases the amount of savings demonstrated during subsequent re-adaptation tasks of similar nature [34]. Previous studies of visuomotor adaptation in PD have either minimized overlearning [32] or truncated the adaptation task such that asymptote was not attained [24]. To our knowledge, only Leow and colleagues [27] intentionally allowed for overlearning, but even then appeared to allow for only 10–15 trials of practice once the performance asymptote was reached. Indeed, previous research has noted impairments in PD when retaining newly-learned motor tasks in the absence of sufficient practice [28]. In the present study, participants typically walked for several minutes once they had returned to the baseline level of step length symmetry. If we consider each pair of steps to be a “trial”, the PD participants in this study performed hundreds of “trials” after reaching the asymptotic state. We suggest that it may be possible that the prolonged overlearning period provided in the present study compensated for the previously-observed deficits in savings.

However, it should be considered that walking is a relatively automatic task while the visuomotor tasks likely require a greater degree of cognitive and attentional resources. Thus, it is unlikely that performance of a single pair of steps during SBT walking is directly analogous to performance of a single discretely-performed visuomotor adaptation trial. Further research across motor adaptation paradigms should expand on our notion that basal ganglia-related deficits in savings during adaptive motor learning may be overcome by allowing sufficient overlearning to occur.

4.2 Biomechanics of reduced step length aftereffects during de-adaptation

A primary finding of this study indicated that step length aftereffects were diminished during de-adaptation. How then might step length be changed from a biomechanical perspective? Our results indicate that, during the first five strides of POST-TIED, persons with PD exhibited significantly greater hip flexion and knee extension at the heel-strike of the fast limb while ON meds as compared to OFF meds. While the slow limb took a significantly shorter step during POST-TIED as compared to BASELINE in both the ON meds and OFF meds states, only while ON meds did the persons with PD take a significantly longer step with the fast limb during POST-TIED as compared to BASELINE. Thus, while OFF meds, step length asymmetry during POST-TIED was limited by decreased hip flexion and knee extension of the fast limb. That is, the fast limb foot was placed more directly under the center of mass (in the anterior-posterior direction) at heel-strike while OFF meds, which ultimately limited length of fast limb step during POST-TIED such that it was similar to BASELINE.

Perhaps due to the increased rigidity observed when persons with PD are OFF meds [35], the fast limb step length was limited during POST-TIED because the participants simply were unable to generate significantly more hip flexion and knee extension with the more-

affected (fast) limb than that which was observed during BASELINE. We also collected baseline gait data in which the participants walked with both limbs moving at the fast speed. During this fast speed baseline, the participants demonstrated the ability to generate steps which were markedly longer than those observed during de-adaptation, even with the more-affected limb and while OFF meds. The diminished aftereffect observed OFF meds appears to result from a change in kinematic motor control rather than simply cardinal parkinsonian motor features.

Our results regarding the role of the kinetics in locomotor adaptive learning also support the notion of altered kinematic control. During conventional walking, stance phase kinetics have a profound influence on step length. For instance, change in the push-off during late stance due to injury or disease affects the ability to drive the body forward [36]. Judge and colleagues provided specific insight into this process by demonstrating that ankle plantarflexor power generation during push-off (i.e., the A2 phase) is the strongest kinetic predictor of step length [20]. We observed that the fast limb generates significantly higher ankle plantarflexor work and peak power during push-off as well as greater AP-GRFs throughout the propulsive phase of stance as compared to the slow limb during SBT walking. However, these kinetic parameters returned to baseline values immediately during de-adaptation such that they were not significantly different from baseline. These findings indicate that the antero-posterior kinetics adapt reactively (similar to intralimb spatiotemporal parameters, such as stride length and stance time) during SBT walking and further suggest that dopamine influences primarily the storage of adapted kinematics.

4.3 Neural mechanisms potentially underlying diminished aftereffect storage OFF meds

Several neural mechanisms could potentially underlie the diminished storage of step length aftereffects observed in the current study when persons with PD were OFF meds. Cerebellar dysfunction restricts aftereffects during de-adaptation after SBT walking [37]; however, persons with PD do not uniformly demonstrate cerebellar hypoactivity. Rather, the cerebellum has instead been found to be hyperactive during movement in PD when OFF meds [38–40]. As reduction in cerebellar inhibition of the motor cortex is essential to the storage of SBT aftereffects [15], it is possible that the cerebellar hyperactivity observed in PD when OFF meds could diminish aftereffect storage. However, cerebellar inhibition of the motor cortex also influences the magnitude of adaptation during SBT walking [15]. As the magnitude of adaptation from EARLY to LATE was not significantly different between the ON and OFF meds states, it is difficult to conclude that cerebellar hyperactivity is likely the sole mechanism underlying the results observed in the current study.

It is also possible that the basal ganglia may play a role in the modulation of cortical activity during de-adaptation. Activity in the basal ganglia has influence over cortical activity via the thalamus through the classically-described cortico-basal-thalamic loops [41,42]. After withdrawal of dopaminergic medication, persons with PD demonstrate reduced excitability of the primary motor cortex relative to the optimally-medicated state [43]. This is important given that recent work in the upper extremity has dissociated the effects of the cerebellum on adaptation from the effects of the primary motor cortex on storage of aftereffects during de-adaptation [44]. Direct electrical stimulation of the cerebellum facilitated faster

adaptation while stimulation of the primary motor cortex facilitated larger aftereffects during de-adaptation [44]. Thus, if excitability of the primary motor cortex is essential for the storage of aftereffects during deadaptation [44], then the reduced cortical excitability observed in persons with PD when OFF meds could significantly impair the storage of aftereffects. However, we did not employ electrophysiological techniques in the current study and thus investigation of mechanisms involved in motor aftereffect storage in PD certainly warrants further research.

4.4 Clinical implications

We have previously shown that an acute bout of SBT walking can at least temporarily alter step length asymmetry in persons with PD [8]. While not all persons with PD exhibit significant gait asymmetry, those affected by asymmetric walking patterns may benefit from SBT training. We have observed that some persons with PD may demonstrate a “default” step length asymmetry; that is, they exhibit significant step length asymmetry while walking under conditions during which step length is typically symmetrical in healthy adults. This is observed even after step length asymmetry has been initially perturbed and subsequently adapted toward symmetry during SBT walking [8]. Thus, repetitive exposure to large aftereffects during deadaptation may be helpful to gradually overcome this “default” asymmetry with chronic training [5]. The findings of the present study indicate that, in order to induce maximal step length aftereffects after SBT walking, persons with PD and rehabilitation professionals should be careful to ensure that the exercise is being performed while the patient is optimally-medicated. Effects of asymmetric locomotor training on the SBT may be lesser in magnitude if performed before the dopaminergic medication has taken full effect, during wearing-off periods, or in the absence of medication entirely.

The current study is not without limitations. As we collected data in discrete 30-second intervals during the locomotor adaptation and adaptive learning tasks, measurement of adaptation, de-adaptation, and re-adaptation rates over the entire timecourse of the protocol were not possible. Further, all conditions were performed while participants walked on the treadmill. While this is common procedure [13], the assessment of aftereffects during de-adaptation has the most direct clinical relevance when these trials are performed overground. Finally, the ability to be able to walk continuously for approximately 45 minutes was necessary inclusion criteria for this study and thus the participants are all of mild-to-moderate disease severity. In many cases, this meant that the participants had relatively small global motor responses to levodopa as quantified by the UPDRS. However, the UPDRS is relatively insensitive to gait dysfunction and we did observe a significant improvement in gait (as quantified by gait speed) after levodopa intake in the cohort (Table 1).

5. Conclusion

The results of the current study indicate that persons with PD can adapt locomotion to an SBT perturbation, store aftereffects of the adapted SBT pattern during de-adaptation, and demonstrate savings of the adapted SBT pattern upon re-adaptation to a second bout of SBT walking even while OFF meds. However, though adaptation and savings were unaffected,

step length aftereffects were diminished during de-adaptation in the unmedicated state. These findings have important implications on gait rehabilitation of persons with PD and on advancement of the understanding of neural processes controlling locomotor adaptation and adaptive learning. If SBT training is to be used as therapy to address gait symmetry in persons with PD, training sessions should be performed while the patients are optimally medicated to induce maximal aftereffects. Further, dopaminergic pathways appear to play a significant role in the storage of aftereffects following motor adaptation.

Acknowledgments

This work was supported in part by NIH grants 1R21AG033284-01A2 and UF National Parkinson's Foundation Center of Excellence.

Abbreviations

PD	Parkinson's disease
SBT	split-belt treadmill
UPDRS	Unified Parkinson's Disease Rating Scale
AP-GRF	anterior-posterior ground reaction force

References

1. Knutsson E. An analysis of Parkinsonian gait. *Brain*. 1972; 95(3):475–486. [PubMed: 4655275]
2. Rahman S, Griffin HJ, Quinn NP, Jahanshahi M. On the nature of fear of falling in Parkinson's disease. *Behav Neurol*. 2011; 24(3):219–228. [PubMed: 21876261]
3. Yogeve G, Plotnik M, Peretz C, Giladi N, Hausdorff JM. Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention? *Exp Brain Res*. 2007; 177(3):336–346. [PubMed: 16972073]
4. Reisman DS, Wityk R, Silver K, Bastian AJ. Split-belt treadmill adaptation transfers to overground walking in persons poststroke. *Neurorehabil Neural Repair*. 2009; 23(7):735–744. [PubMed: 19307434]
5. Reisman DS, McLean H, Keller J, Danks KA, Bastian AJ. Repeated split-belt treadmill training improves poststroke step length asymmetry. *Neurorehabil Neural Repair*. 2013; 27(5):460–468. [PubMed: 23392918]
6. Dietz V, Zijlstra W, Prokop T, Berger W. Leg muscle activation during gait in Parkinson's disease: adaptation and interlimb coordination. *Electroencephalogr Clin Neurophysiol*. 1995; 97(6):408–415. [PubMed: 8536593]
7. Nanhoe-Mahabier W, Snijders AH, Delval A, Weerdesteijn V, Duysens J, Overeem S, Bloem BR. Split-belt locomotion in Parkinson's disease with and without freezing of gait. *Neuroscience*. 2013; 236:110–116. [PubMed: 23370318]
8. Roemmich RT, Nocera JR, Stegemöller EL, Hassan A, Okun MS, Hass CJ. Locomotor adaptation and locomotor adaptive learning in Parkinson's disease and normal aging. *Clin Neurophysiol*. 2014 Feb; 125(2):313–319. [PubMed: 23916406]
9. Kojima Y, Iwamoto Y, Yoshida K. Memory of learning facilitates saccadic adaptation in the monkey. *J Neurosci*. 2004; 24(34):7531–7539. [PubMed: 15329400]
10. Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. I Focal olivocerebellar lesions impair adaptation. *Brain*. 1996; 119(Pt 4):1183–1198. [PubMed: 8813282]
11. Krakauer JW, Ghilardi MF, Ghez C. Independent learning of internal models for kinematic and dynamic control of reaching. *Nat Neurosci*. 1999; 2(11):1026–1031. [PubMed: 10526344]

12. Shadmehr R, Mussa-Ivaldi FA. Adaptive representation of dynamics during learning of a motor task. *J Neurosci.* 1994; 14(5 Pt 2):3208–3224. [PubMed: 8182467]
13. Reisman DS, Block HJ, Bastian AJ. Interlimb coordination during locomotion: what can be adapted and stored? *J Neurophysiol.* 2005; 94(4):2403–2415. [PubMed: 15958603]
14. Reisman DS, Wityk R, Silver K, Bastian AJ. Locomotor adaptation on a split-belt treadmill can improve walking symmetry post-stroke. *Brain.* 2007; 130(Pt 7):1861–1872. [PubMed: 17405765]
15. Jayaram G, Galea JM, Bastian AJ, Celnik P. Human locomotor adaptive learning is proportional to depression of cerebellar excitability. *Cereb Cortex.* 2011; 21(8):1901–1909. [PubMed: 21239392]
16. Shadmehr R, Smith MA, Krakauer JW. Error correction, sensory prediction, and adaptation in motor control. *Annu Rev Neurosci.* 2010; 33:89–108. [PubMed: 20367317]
17. Huang VS, Haith A, Mazzoni P, Krakauer JW. Rethinking motor learning and savings in adaptation paradigms: model-free memory for successful actions combines with internal models. *Neuron.* 2011; 70(4):787–801. [PubMed: 21609832]
18. Smith MA, Ghazizadeh A, Shadmehr R. Interacting adaptive processes with different timescales underlie short-term motor learning. *PLoS Biol.* 2006; 4(6):e179. [PubMed: 16700627]
19. Malone LA, Vasudevan EV, Bastian AJ. Motor adaptation training for faster relearning. *J Neurosci.* 2011; 31(42):15136–15143. [PubMed: 22016547]
20. Judge JO, Davis RB, Ounpuu S. Step length reductions in advanced age: the role of ankle and hip kinetics. *J Gerontol A Biol Sci Med Sci.* 1996; 51(6):M303–M312. [PubMed: 8914503]
21. Mawase F, Haizler T, Bar-Haim S, Karniel A. Kinetic adaptation during locomotion on a split-belt treadmill. *J Neurophysiol.* 2013; 109(8):2216–2227. [PubMed: 23365187]
22. Ogawa T, Kawashima N, Ogata T, Nakazawa K. Limited transfer of newly acquired movement patterns across walking and running in humans. *PLoS One.* 2012; 7(9):e46349. [PubMed: 23029490]
23. Roemmich RT, Stegemöller EL, Hass CJ. Lower extremity sagittal joint moment production during split-belt treadmill walking. *J Biomech.* 2012; 45(16):2817–2821. [PubMed: 22985473]
24. Bédard P, Sanes JN. Basal ganglia-dependent processes in recalling learned visual-motor adaptations. *Exp Brain Res.* 2011; 209(3):385–393. [PubMed: 21311878]
25. Fernandez-Ruiz J, Diaz R, Hall-Haro C, Vergara P, Mischner J, Nuñez L, Drucker-Colin R, Ochoa A, Alonso ME. Normal prism adaptation but reduced after-effect in basal ganglia disorders using a throwing task. *Eur J Neurosci.* 2003; 18(3):689–694. [PubMed: 12911765]
26. Isaias IU, Moisello C, Marotta G, Schiavella M, Canesi M, Perfetti B, Cavallari P, Pezzoli G, Ghilardi MF. Dopaminergic striatal innervation predicts interlimb transfer of a visuomotor skill. *J Neurosci.* 2011; 31(41):14458–14462. [PubMed: 21994362]
27. Leow LA, Loftus AM, Hammond GR. Impaired savings despite intact initial learning of motor adaptation in Parkinson's disease. *Exp Brain Res.* 2012; 218(2):295–304. [PubMed: 22430183]
28. Mochizuki-Kawai H, Kawamura M, Hasegawa Y, Mochizuki S, Oeda R, Yamanaka K, Tagaya H. Deficits in long-term retention of learned motor skills in patients with cortical or subcortical degeneration. *Neuropsychologia.* 2004; 42(13):1858–1863. [PubMed: 15351634]
29. Smiley-Oyen AL, Lowry KA, Emerson QR. Learning and retention of movement sequences in Parkinson's disease. *Mov Disord.* 2006; 21(8):1078–1087. [PubMed: 16671075]
30. Malone LA, Bastian AJ. Thinking about walking: effects of conscious correction versus distraction on locomotor adaptation. *J Neurophysiol.* 2010; 103(4):1954–1962. [PubMed: 20147417]
31. Stern Y, Mayeux R, Hermann A, Rosen J. Prism adaptation in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1988; 51(12):1584–1587. [PubMed: 3221228]
32. Marinelli L, Crupi D, Di Rocco A, Bove M, Eidelberg D, Abbruzzese G, Ghilardi MF. Learning and consolidation of visuo-motor adaptation in Parkinson's disease. *Parkinsonism Relat Disord.* 2009; 15(1):6–11. [PubMed: 18424221]
33. Driskell JE, Willis RP, Copper C. Effect of overlearning on retention. *J Appl Psychol.* 1992; 77(5):615–622.
34. Joiner WM, Smith MA. Long-term retention explained by a model of short-term learning in the adaptive control of reaching. *J Neurophysiol.* 2008; 100(5):2948–2955. [PubMed: 18784273]

35. Hornykiewicz O. Dopamine in the basal ganglia. Its role and therapeutic implications (including the clinical use of L-DOPA). *Br Med Bull.* 1973; 29(2):172–178. [PubMed: 4356552]
36. Balasubramanian CK, Bowden MG, Neptune RR, Kautz SA. Relationship between step length asymmetry and walking performance in subjects with chronic hemiparesis. *Arch Phys Med Rehabil.* 2007; 88(1):43–49. [PubMed: 17207674]
37. Morton SM, Bastian AJ. Cerebellar contributions to locomotor adaptations during splitbelt treadmill walking. *J Neurosci.* 2006; 26(36):9107–9116. [PubMed: 16957067]
38. Cerasa A, Hagberg GE, Peppe A, Bianciardi M, Gioia MC, Costa A, Castriota-Scanderbeg A, Caltagirone C, Sabatini U. Functional changes in the activity of cerebellum and frontostriatal regions during externally and internally timed movement in Parkinson's disease. *Brain Res Bull.* 2006; 71(1–3):259–269. [PubMed: 17113955]
39. Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. *Brain.* 2005; 128(Pt 10):2250–2259. [PubMed: 15958505]
40. Yu H, Sternad D, Corcos DM, Vaillancourt DE. Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage.* 2007; 35(1):222–233. [PubMed: 17223579]
41. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci.* 1986; 9:357–381. [PubMed: 3085570]
42. DeLong MR. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* 1990; 13(7):281–285. [PubMed: 1695404]
43. Ueki Y, Mima T, Kotb MA, Sawada H, Saiki H, Ikeda A, Begum T, Reza F, Nagamine T, Fukuyama H. Altered plasticity of the human motor cortex in Parkinson's disease. *Ann Neurol.* 2006; 59(1):60–71. [PubMed: 16240372]
44. Galea JM, Vazquez A, Pasricha N, de Xivry JJ, Celnik P. Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. *Cereb Cortex.* 2011; 21(8):1761–1770. [PubMed: 21139077]
45. Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: Comparison with the unified Parkinson's disease rating scale. *Mov Disord.* 2013; 28(5):668–670. [PubMed: 23408503]

Highlights

1. Persons with Parkinson's disease walked on a split-belt treadmill.
2. Dopaminergic medication did not affect the ability to adapt locomotion.
3. Aftereffects were reduced when the participants were withdrawn from medication.
4. Savings of the adapted gait pattern were apparent in both medicated states.

Figure 1.

An outline of the protocol we employed to investigate locomotor adaptation and adaptive learning. Solid black horizontal lines indicate that the belts were moving at the same speed. The solid white lines represent the more-affected limb while the dashed white lines represent the contralateral limb.

Figure 2.

Single-subject traces of the A) AP-GRF and B) sagittal ankle power profiles during stance.

Black shaded areas indicate the A) propulsive phase of the AP-GRF and B) A2 phase of the ankle power. AP-GRF – anterior-posterior ground reaction force.

Figure 3.

Mean step length asymmetry during all walking conditions. Error bars indicate standard error. * indicates $p < .05$ between medicated states. Indications of significant effects of walking condition are omitted for clarity. ** indicates healthy older adult (HOA) data provided for reference (from [8]). This data was collected under a slightly different protocol and thus was not statistically compared to the PD data in the present study.

Figure 4.

Mean $\pm$ standard error step length asymmetry during all walking conditions with participants grouped in accordance with the order of the testing sessions (i.e., those performing the ON meds session first and those performing the OFF meds session first).

Figure 5.

Mean propulsive AP-GRF impulses during all walking conditions. No significant effects of medication were observed. Error bars indicate standard error. Indications of significant effects of walking condition are omitted for clarity.

Figure 6.

A) Mean peak A2 ankle power and B) mean A2 ankle work during all walking conditions. No significant effects of medication were observed. Error bars indicate standard error. Indications of significant effects of walking condition are omitted for clarity.

Figure 7.

Ensemble orientations of the limbs at heel-strike during POST-TIED (left), mean knee hip (white) and knee (black) angles of the fast limb at fast heel-strike during POST-TIED (top), and mean step lengths during BASELINE (white) and POST-TIED (black) of the fast and slow limbs (bottom) in both medicated states. Error bars indicate standard error, * indicates $p < .05$, and + indicates $p = .07$.

OFF Meds **Figure 8.**

Group ensemble (mean $\pm$ SD) AP-GRF and sagittal ankle power profiles (normalized to participant body mass) during BASELINE (left), LATE ADAPT (middle), and POST-TIED (right) both while the participants were OFF Meds (top) and ON Meds (bottom). Solid lines indicate the kinetics of the limb which walked on the fast belt during ADAPT (i.e. the more-affected limb) while dashed lines indicate the kinetics of the limb which walked on the slow belt during ADAPT (i.e. the less-affected limb).

Table 1

Participant characteristics and demographic information.

ID	Sex	Age (yrs)	Disease duration (yrs)	OFF meds UPDRS	ON meds UPDRS	OFF meds H&Y	ON meds H&Y	OFF meds gait speed (m/s)	ON meds gait speed (m/s)	LEDD (mg/day)	TD/PIGD
1	M	65	5	40	38	2.5	2.5	0.99	1.29	1100	PIGD
2	F	71	1	46	41	3	3	0.95	1.12	375	PIGD
3	M	69	6	39	42	2.5	2.5	0.94	1.14	825	TD
4	M	76	N/A	58	46	3	3	1.31	1.35	1250	TD
5	M	65	4	40	39	2.5	2	1.07	1.22	413	PIGD
6	M	66	5	45	39	2.5	2	0.82	1.3	750	PIGD
7	F	49	5	24	23	2	2	1.16	1.17	N/A	PIGD
8	M	72	10	41	37	2.5	2.5	1.02	1.35	642	PIGD
9	M	70	9	32	34	3	2.5	1.00	1.02	N/A	PIGD
10	M	65	4	31	28	2.5	2.5	0.98	1.03	488	PIGD
Mean		66.8	5.4	39.6	36.7	2.6	2.5	1.03	1.20	730.4	
SD		7.3	2.7	9.3	6.8	0.3	0.4	0.14	0.12	318.4	

ID – participant ID, Disease duration – time since initial diagnosis, UPDRS – Unified Parkinson’s Disease Rating Scale Motor Score (Section III), H&Y – Hoehn & Yahr stage, Gait speed – self-selected overground gait speed, LEDD – levodopa equivalent daily dose, TD/PIGD – tremor-dominant/postural instability and gait disorder subtype [45], N/A – data not available.