Age-Related Striatal Dopaminergic Denervation and Severity of a Slip Perturbation

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Background. Striatal dopamine activity declines with normal aging. Age-related striatal dopaminergic denervation (SDD) has been implicated in standing balance and unperturbed gait. The goal of this study was to analyze the association between the degree of SDD and the magnitude of an unexpected slip perturbation induced during gait.

Methods. Fifty healthy participants aged 20–86 years old underwent dopamine transporter positron emission tomography to classify SDD severity as mild, moderate, or severe. Participants also walked on a floor that was unexpectedly contaminated with a glycerol solution for gait testing. The magnitude of a slip was quantified using the peak slip velocity (PSV), measured at the slipping foot. Data were analyzed for both fast (greater than 1.2 m/s) and slow walkers as gait speed correlated with slip severity. All data analyses were age adjusted.

Results. Greater severity of dopaminergic denervation in the caudate nucleus was correlated with higher PSV ($p < .01$) but only in the fast speed walking group. The relationship between SDD in the putamen and slip severity was not statistically significant in fast and slow walkers.

Conclusions. Age-related SDD may impact the ability to recover from large perturbations during walking in individuals who typically walk fast. This effect, prominent in the caudate nucleus, may implicate a role of cognitive frontostriatal pathways in the executive control of gait when balance is challenged by large perturbations. Finally, a cautious gait behavior present in slow walkers may explain the apparent lack of involvement of striatal dopaminergic pathways in postural responses to slips.

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GERIATRIC falls often occur during gait after balance is perturbed by external environmental hazards, such as walking on a slippery surface or tripping. Specifically, base of support perturbations such as slips, trips, and stumbles initiate up to 67% of falls in healthy older adults (1–5). These types of falls are also among the leading generators of serious injuries in older adults. In particular, slips and trips account for up to 49% of falls with fractures (6), and slip-initiated falls alone account for 10%–26% of geriatric fall-related hip fractures (7,8).

Recovering from a slip is a complex balance task. First, the slip has to be detected. Research on how humans detect slipping during walking is limited; however, it is suspected that the vestibular and somatosensory systems play an important role in this process (9). Second, slip-relevant sensory information is integrated and a fast and coordinated postural response involving multiple body joints is generated to recover balance and to continue walking (10). Furthermore, it has been shown that the risk of slip initiation and the ability to prevent an imminent slip-precipitated fall depend on both pre-slip parameters related to normal gait style in noncontaminated environments (eg., cadence, step-length, foot–floor angle at heel contact, gait speed) (11) and on post-slip postural response parameters (eg, reaction onset, magnitude, and/or coordination of response) (12–15). Thus, preventing a balance loss triggered by a slip depends on many aspects of the postural control system including sensory, motor, and central integration aspects.

Neurobiological mechanisms of balance recovery from slips remain largely unknown. Previous studies have shown that slip severity is highly correlated with gait speed, indicating that selection of gait velocity–dependent motor program for gait regulation may play a role in modulating slips (16). The basal ganglia and the neurotransmitter dopamine have been key targets for research exploring the physiology underlying movements. Striatal dopamine activity declines with age even in the absence of a Parkinson’s disease diagnosis. Specifically, striatal dopaminergic transporters
decline at an average rate of about 5%–7% per decade in healthy volunteers (17–19). Although this age-related striatal dopaminergic denervation (SDD) has been shown to impact motor function (20–22), research on its implications in postural control is scarce. Our own recent findings suggest that SDD plays a role in at least two aspects of postural and gait control, namely the ability to integrate sensory information important for standing balance (23) and to control cadence during normal or unperturbed walking (24). As these aspects of postural and gait control may also play a possible role in recovery of a slip, the primary goal of this study was to analyze the association between the degree of SDD and the magnitude of an unexpected slip perturbation induced during gait.

**METHODS**

**Participants**

Fifty participants participated in a gait study involving an exposure to an unexpected slippery condition. The study sample represented volunteer community-dwelling participants across different ages. The mean (SD) age, stature, and body mass of the participants was 64.9 (14.7) years, 170.0 (10.8) cm, and 78.4 (15.7) kg, respectively. Written informed consent, approved by the Institutional Review Boards of the VA Pittsburgh Healthcare System and the University of Pittsburgh, was obtained prior to participation. Participants with clinical evidence of the following conditions that are known to impact balance or gait were excluded: orthostatic hypotension (defined as a drop in systolic blood pressure of >20 mmHg upon standing), impaired vision (<20/40 corrected OU), vertiginous disorder (defined by clinical symptoms of linear or rotational illusion of motion), myelopathy (defined by neurological examination findings of hyperreflexia, weakness, and/or sensory loss), myopathy (defined by a presence of muscle weakness and prior laboratory evidence of a myopathic process), neuropathic and radicular syndromes (defined by examination findings of decreased or absent deep tendon reflexes with segmental weakness or dermatomal or neuropathic sensory loss), cerebellar syndromes (clinical examination findings of limb or gait ataxia), Parkinson’s disease (based on clinical and positron emission tomography [PET] evidence), large-vessel stroke, Binswanger’s disease, tumor or focal intracranial lesions based on MR data, history of joint prosthetic surgery, polypharmacy (taking more than eight prescription drugs), and taking neuroleptics or taking benzodiazepines or barbiturates. Finally, patients with a history of a major depressive disorder or dementia were not eligible for the study.

**Imaging**

All participants underwent $^{[11]}$C-$\beta$-CFT dopamine transporter PET imaging. Volumes of interest (VOIs) were defined manually on the SPGR MRI for the striatum in 3D using in-house developed software (VOILand). VOIs were applied on successive dynamic PET frames to generate time radioactivity curves of the regions. Regional cerebral $[^{[1]}$C-$\beta$-CFT binding was determined for the striatum by graphical analysis of the bolus-plus-infusion transformation (BPIT) plot of bolus-only PET experiments (25). BPIT values for two striatal sites were derived: caudate nucleus (BPIT$_{Caud}$) and putamen (BPIT$_{Put}$). The continuous distribution of $^{[11]}$C-$\beta$-CFT binding potential was used to classify the degree of SDD in three groups for each of the striatal sites of interest: mild (67th–100th percentile), moderate (33th–67th percentile), or severe (0–33th percentile).

**Gait Testing and Data Processing**

**Instrumentation and experimental setup.**—Participants were instrumented with an in-house developed set of 79 reflective markers (26) to track whole-body motion and feet kinematics at 120 Hz using a Vicon 612 motion capture system (Vicon, Lake Forest, CA). Participants were asked to walk along an 8-m vinyl tile walkway instrumented with two force platforms (Bertec FP4060; Bertec Co., Columbus, OH) embedded in the floor in the middle of the walkway. These force platforms were used to collect ground reactions forces at 1080 Hz, data subsequently used to identify heel contact and toe off frames. Slips were induced at heel contact when the left leg impacted the first force platform contaminated with a glycerol–water solution (75%–25%). Coefficients of friction for the dry and slippery conditions, measured by the English XL VIT Slipmeter (ASTM F1679) at the shoe–floor interface, were .53 and .03, respectively. To prevent the participant from discerning the contaminated floor in the slippery condition, the lights were dimmed during the entire duration of testing. All participants wore the same brand and model of polyvinyl chloride sole shoes. Finally, all participants were fitted with a safety harness to prevent impact onto the floor in case of an irrecoverable balance loss.

**Gait protocol.**—Participants were asked to walk on the vinyl tile walkway at their own self-selected pace while looking at a target on the opposite wall. The starting position of the gait trial was modified to ensure a clean hit on the force platforms. Participants were allowed to practice walking. Participants were exposed to two experimental conditions: a baseline condition in which participants walked on a known dry floor and an unexpected slippery condition in which the floor was contaminated with the glycerol–water solution without the participant’s knowledge. To distract participants from the potential application of the glycerol solution prior to the slippery trial, participants listened to loud music and faced away from the walkway for about 1 minute between all trials. At the end of the waiting period,
participants were informed that the first few trials would be dry. On average, four baseline trials were first collected to capture normal gait followed by the unexpected slippery trial.

Gait data processing.—The heel marker placed on the slipping foot was used to quantify the severity of the slipping perturbation. The medial-lateral and anterior-posterior position of the heel marker’s position data were numerically differentiated to compute heel velocity components, which were then combined to compute the resultant horizontal heel velocity. Typical trajectories of the resultant horizontal heel velocity computed during normal or baseline walking (non-slip) and during slip trials are shown in Figure 1. Peak slip velocity (PSV), determined as the first local maximum horizontal heel velocity 50 ms after heel contact on the slippery surface (11), was calculated as a slip severity measure (Figure 1).

Gait speed was computed during the normal or baseline walking trial based on the anterior–posterior position data of a trunk marker, which was numerically differentiated to compute the instantaneous gait speed and then averaged across the duration of trial to yield a mean gait speed measure for each trial.

Statistical Analyses
Understanding the role of striatal dopamine deficiencies in the ability to recover from large perturbations such as slips was the focus of the analysis. However, as anticipated based on the work of Bhatt and colleagues (16), in this study, slip severity (PSV) was also found to be highly correlated with gait speed, indicating that selection of gait speed–dependent motor program for gait regulation may play a role in modulating slips. Thus, due to this strong correlation between PSV and gait speed, the statistical analyses were performed within each gait speed group (slow and fast). The sample size of the fast and slow groups was 24 and 26, respectively. No statistically significant age difference was found between the two gait speed groups (p > .1).

To comprehensively assess the association between SDD and PSV, we employed two analytic strategies. First, we used Pearson correlation coefficients (r) to quantify association between quantitative SDD scores and partial correlation coefficients to obtain a measure of the same association after controlling for age. Second, to examine the association between SDD group (mild, moderate, and severe) and PSV, we fit a series of analysis of variance type linear models with PSV as the response variable and each of the two the three-level SDD group as the primary factor of interest. Fisher’s least significant difference was used to make pairwise comparisons among the three SDD groups. The two-stage protected test approach was used to protect the Type I error rate from multiple comparisons (27,28). Briefly, this approach involves performing pairwise comparisons without a further multiplicity adjustment if the overall analysis of variance test is significant and with a conservative Bonferroni correction if the overall analysis of variance test is not significant. To obtain between-SDD group comparisons after controlling for age, age was added as an additional covariate to the models. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS
Table 1 lists the mean age, walking speed, slip severity, and regional striatal SDD distribution in the slow and fast walking speed groups based on the preferred gait velocity of 1.2 m/s reported in healthy adults, which also is near the median gait speed in our sample of participants (1.186 m/s). Fast walkers slipped more severely than slow walkers, with a mean (SD) PSV value of 1.25 (0.58) m/s and 0.70 (0.50) m/s, respectively (p < .001). There was no statistically significant age difference between the two gait speed groups (p > .1).

Also, as expected (11) age was not significantly associated with slip severity in both slow walkers (r = −.16, p = .4423) and fast walkers (r = .03, p = .8753).

Caudate nucleus SDD was significantly associated with slip severity in fast walkers (Table 2). Controlling for age, partial correlation between caudate nucleus SDD, and PSV was −0.47 (p = .0239). Adjusting for age, slip severity significantly differed among the three caudate nucleus SDD groups (p = .0037), primarily driven by the mild group. Compared with those with mild caudate nucleus SDD, significantly greater slip severity was seen in those with moderate (0.97 ± 0.29 m/s; p = .0031) and severe (1.19 ± 0.32 m/s; p = .0013) SDD. There was no significant difference in slip severity between those with moderate and severe SDD (p = .3563). There was no evidence of a significant associa-
The findings of this study indicate that in participants who walk at a self-selected faster speed, the severity of age-related SDD in the caudate nucleus may compromise the ability to recover from a slip. The statistically significant effects of caudate nucleus SDD on slip severity were not evident in the slow walking group. Previous studies have shown that slip severity is highly correlated with gait speed, indicating that selection of gait velocity–dependent motor program for gait regulation may play a role in modulating slips (16). Our findings suggest that gait speed modulates the impact of SDD on the perturbation of a slip. Slow walkers experience less severe slips than fast walkers, implying that fast and coordinated postural response may be unnecessary when walking slowly, which in turn may explain the apparent lack of involvement of striatal dopaminergic pathways in this group. It is possible that somatosensory, vestibular, or cognitive cortical compensatory mechanisms may predominate during slow or cautious gait. Although the vestibular and somatosensory systems are believed to be responsible for sensing sudden perturbations, these systems do not have a primary dopaminergic neural substrate. Thus, SDD does not appear to impact mechanisms related to the sensing of large balance perturbations such as slips and trips. However, although somatosensory or vestibular reflexes may be involved in the initiation of the postural response to a slip, the actual execution of the coordinated whole-body movements underlying a slip is likely to be regulated by the striatum, and dopamine may play a critical role. Therefore, our findings suggest an impact of SDD on motor system responses that are required to successfully recover from a slip or trip during fast gait speed conditions. These responses need to be fast and require coordinated movements involving multiple body joints. Thus, SDD may have an impact on the onset, magnitude, and/or coordination of the response required to recover from a slip or trip during fast walking.

Our findings are in line with the results of Chastan and colleagues (29), suggesting that at slower gait, “active” braking defined as the participant’s ability to brake the center of gravity fall before foot contact is not necessary. In contrast, active braking before foot contact in the gait cycle is required during fast walking speeds as festination and related fall risk may occur otherwise. Additionally, gait speed–related differences in our findings may be viewed as supportive evidence of one of Vasudevan and Bastian’s (30) conclusions, namely that neural networks that control locomotion in humans are gait speed (slow or fast) specific.

Unlike more primary motor functions related to the putamen, the caudate nucleus appears to be more involved in

Table 1. Age, Gait Speed, Slip Severity, and Degree of SDD Severity for Slow and Fast Walkers

<table>
<thead>
<tr>
<th>SDD Measure/Group</th>
<th>Unadjusted</th>
<th>Adjusted for Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[Correlation] or Mean Difference ± SE</td>
<td>p Value</td>
</tr>
<tr>
<td>Slow Walkers</td>
<td>Fast Walkers</td>
<td></td>
</tr>
<tr>
<td>Overall three-group comparison</td>
<td>—</td>
<td>0.0593</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>Mild vs moderate</td>
<td>0.25 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>Mild vs severe</td>
<td>0.31 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>Moderate vs severe</td>
<td>0.56 ± 0.23</td>
</tr>
<tr>
<td>Putamen</td>
<td>Mild vs moderate</td>
<td>0.33 ± 0.26</td>
</tr>
<tr>
<td></td>
<td>Mild vs severe</td>
<td>0.05 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>Moderate vs severe</td>
<td>−0.27 ± 0.25</td>
</tr>
<tr>
<td>Numeric BPIT value</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Overall three-group comparison</td>
<td>—</td>
<td>0.4399</td>
</tr>
</tbody>
</table>

Note: BPIT = bolus-plus-infusion transformation; SDD = striatal dopaminergic denervation.
cognitive or psychomotor function (31). In this study, we found that participants with more severe SDD of the caudate rather than the putamen slipped more severely than participants with moderate and mild SDD. These findings would indicate that the effect of SDD on the coordinated multi-joint execution of the slip response involves cognitive striatofrontal pathways (31). Striatofrontal pathways have been implicated to play a compensatory role in gait control in patients with Parkinson’s disease (32). These findings suggest that walking under fast gait speed condition require higher order cerebral control to prevent falls as the cyclical acceleration and deceleration (braking) of the center of gravity during fast walking requires increased integration of sensorimotor programs. Our findings are also in line with recent new insights in executive gait control functions (33). Gait is no longer considered as merely an automated motor activity that utilizes minimal higher-level cognitive input. Instead, the multifaceted neuropsychological, especially executive and attention, influences on walking and the interactions between the control of mobility and related behaviors are increasingly appreciated (34). For example, elderly fallers perform more poorly than controls on executive functions and are more inconsistent in their reaction times (35).

Although an average person may lose about 33% of striatal dopaminergic innervation between the ages of 25 and 75 years (36), this is not as severe as in Parkinson’s disease where losses often exceed 50%–80% (37). Unlike a posterior-to-anterior and asymmetric gradient of predominant and severe putaminal losses in Parkinson’s disease, the topographic striatal pattern of SDD is more diffuse affecting the putamen and caudate nucleus about equally and symmetrically (17). Although SDD is not a precursor of Parkinson’s disease, it may affect age-associated motor functions (20–22).

Limitations of our study are the technical inability to perform dynamic PET imaging during the actual slip events and our assessment only limited to the quantification of presynaptic nigrostriatal nerve terminals. Furthermore, we were unable to assess cortical dopaminergic functions because of low cortical binding affinity of our dopamine transporter radioligand.

In conclusion, our findings suggest that age-related SDD may be implicated in the ability to recover from large perturbations such as slips and trips and that these effects may be modulated by gait speed or more directly by the severity of the balance perturbation. The relationship of SDD with caudate nucleus, more prominent than putaminal SDD effects, may implicate a role of cognitive frontostriatal pathways in the executive control of gait when balance is perturbed under these conditions.

**Funding**

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**Conflicts of Interest**

No conflict of interest.

**References**

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