Bilateral coordination of walking and freezing of gait in Parkinson’s disease

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Keywords: bilateral coordination, gait asymmetry, human locomotion, stepping phase

Abstract

Freezing of gait (FOG) in Parkinson’s disease (PD) occurs most frequently during turns or step initiation, two tasks that likely demand a high degree of bilateral coordination between the legs. Our objective was to test the hypothesis that impairments in bilateral coordination of stepping are associated with FOG in PD. We compared locomotion features while walking on level ground between patients with PD that experience FOG (PD + FOG; n = 21) and patients with PD that do not (PD – FOG; n = 13). To study bilateral stepping coordination, we defined the stride duration of one foot as a gait cycle or 360°, determined the relative timing of contralateral heel-strikes and defined this as the phase, φ (ideally, φ = 180°). The sum of the coefficient of variation of φ and the mean absolute difference between φ and 180° was defined as the phase coordination index (PCI), representing variability and inaccuracy, respectively, in phase generation. During the ‘Off’ state (= 12 h off anti-parkinsonian medication), PCI values were higher (poorer coordination) in PD + FOG compared with PD – FOG (P < 0.024). Stride-to-stride phase adjustments, Δφ, were also studied. Both groups scaled their converging adjustments (towards 180°) to the same extent, but when generating diverging Δφ (away from 180°), PD + FOG patients exhibited larger errors compared with PD – FOG patients (P < 0.006). This study demonstrates that patients with PD who experience FOG have distinctive impairments in the bilateral coordination of locomotion. Poor bilateral coordination of walking may predispose to FOG, especially during challenging tasks that demand a high degree of left–right coordination.

Introduction

Freezing of gait (FOG) is a debilitating gait impairment in patients with Parkinson’s disease (PD), prevalent in about 50% of the patients with advanced disease (Fahn, 1995; Giladi, 2001). The origins of FOG are largely unknown (reviews: Giladi et al., 2004). Several studies that have examined the physiological mechanisms associated with FOG in PD suggested that abnormalities of the spatiotemporal characteristics (Nieuwboer et al., 2001; Iansek et al., 2006) and of the sequencing of gait (Iansek et al., 2006) may lead to the onset of freezing. Dysrhythmic (Hausdorff et al., 2003) and asymmetric (Plotnik et al., 2005) gait were also associated with FOG in PD.

We hypothesized that impaired bilateral coordination of gait may be associated with FOG. A clinical observation that leads to this hypothesis is that FOG most frequently occurs at turns or during the initiation of walking (Schaafsma et al., 2003). In contrast to forward walking where both legs basically perform similar motor patterns, during turns the pivot leg carries out a different motor pattern from the swing leg because each of the legs covers different distances and turn with different radii. At gait initiation, the difference between the motor activity of each leg is even more pronounced as one leg takes a step while the pivot leg provides support. In both conditions, due to the marked difference in the actual movement of each leg, there is a need for a high degree of coordination. Therefore, impairments in the bilateral coordination of gait, if they exist, might lead to ineffective execution of locomotion and to the appearance of FOG, particularly during those two locomotion tasks.

The mechanisms underlying the coordination of bipedal human walking are not fully understood. The studies that quantitatively investigated bilateral coordination of locomotion in humans primarily employed paradigms involving non-natural conditions, e.g. bicycle pedaling (Abe et al., 2003) or walking on a split-belt treadmill (for a review, see Dietz, 2002). An incomplete understanding is notable in patients with gait pathologies, such as those seen in PD. While studies have observed characteristics suggestive of impaired bilateral coordination of locomotion in PD (Dietz et al., 1995; Abe et al., 2003), most studies have not examined walking.

To address this issue, we recently developed a new metric that enables the quantification of the bilateral coordination of stepping during functional forward walking. Focusing on the phase of the gait cycle of one leg with respect to the other, we defined a phase coordination index (PCI). This quantifies the accuracy and consistency of the phase generation performed by one leg with respect to the other (Plotnik et al., 2007). Using this index, we found that young adults display better bilateral coordination of gait, as compared with healthy elderly subjects, and that the PCI is sensitive to ageing more than other gait features (e.g. stride length). Marked deterioration in bilateral coordination of gait was observed...
in patients with PD, as compared with healthy elderly subjects (Plotnik et al., 2007).

In the present study, we utilize this novel methodology to test the hypothesis that FOG in PD is related to impairments in bilateral coordination of gait.

Materials and methods

In this study, we apply the PCI method to data obtained from a previously described investigation (Hausdorff et al., 2003), adding data recently collected following similar procedures. More specifically, in order to assess bilateral coordination of gait, data are required from both legs. Because complete sets were not always available for the subjects who participated in the original study (28 out of 32 were available), data from an additional six patients with PD were added. The gait protocol and system that were used for the additional subjects were identical to those of the original study. The execution of the experimental protocol was supervised by the principal investigators of the original study (N.G. and J.M.H.). Thus, the gait assessment protocol (see below) was standardized across all patients.

Subjects

Subjects were recruited from the outpatient clinic of the Movement Disorders Unit at the Tel Aviv Sourasky Medical Center (TASMC). We included patients with PD, as defined by the UK Brain Bank criteria (Gelb et al., 1999), who were on levodopa treatment, experienced motor response fluctuations, and had a Hoehn and Yahr scale (Hoehn & Yahr, 1967) score less than four while in the ‘Off’ state (> 12 h without anti-parkinsonian medications). Patients were excluded if they had had brain surgery, had clinically significant co-morbidities likely to affect gait including diabetes mellitus, rheumatic or orthopedic disease, dementia (scores on the Mini Mental State Exam, MMSE < 25; Folstein et al., 1975), major depression or a history of stroke. Each patient was classified as either a PD + FOG (≥ 1 on item #3 of the FOG Questionnaire, FOG-Q #3; Giladi et al., 2000) or PD − FOG (0 or 1 on the FOG-Q #3). The experimental protocols were approved by the Human Studies Committee of the Tel Aviv Sourasky Medical Center. All subjects provided informed written consent according to the Declaration of Helsinki prior to enrolment in the study.

Clinical evaluation

Patients were first assessed in the morning during the ‘Off’ state. The assessment included: (a) gait (as described below); and (b) Part III (the motor portion) of the Unified Parkinson’s Disease Rating Scale (UPDRS; Fahn et al., 1987).

To assess asymmetry in PD motor symptoms, a factor that might explain PCI changes, we calculated the sum scores of items 20–26 in the motor part of the UPDRS for the left and right side separately. UPDRS asymmetry was defined as the ratio (Plotnik et al., 2005):

\[
\text{UPDRS asymmetry} = \frac{\text{higher sum} - \text{lower sum}}{\text{higher sum} + \text{lower sum}}.
\]

After the completion of the motor tests in the ‘Off’ state, patients took their morning dose of levodopa, and after reaching a self-declared ‘Good On’ state (approximately after 40–75 min after medication intake), the above tests were repeated.

Walking protocol

The patients were instructed to walk at their comfortable pace on level ground for a total of 80 m. Force-sensitive insoles were placed in the subjects’ shoes. The recorded output was a time series (300 Hz) of the vertical ground reaction force. Measurements from both feet were synchronized. A more complete description of the measurement system was provided earlier (Hausdorff et al., 1998, 2003).

With ambulatory gait analysis systems that do not measure spatial gait parameters such as stride or step length, one conventional way for gait speed assessment is based on measuring the time that is required to cover a certain distance within the walking path (e.g. 10 m). Based on the measured time and on the given distance covered, an averaged figure for gait speed can be calculated. Because the present study involved patients with PD with freezing, it was impractical to use this way in order to calculate gait speed. That is due to the fact that freezing episodes occurred also within the designated 10-m segment for gait speed measurement.

In the original protocol (i.e. for 28 patients out of the 34 included here, see above), in addition to the gait protocol the patients performed the Stand Walk Sit (SWS) test, which is a part of the Core Assessment Program for Intracerebral Transplantation (CAPIT; Langston et al., 1992). This is a performance test in which the time required for a subject to stand up from a chair, walk 7 m, turn and walk back to the chair and sit down is measured. Although not a perfect substitute of gait speed measurements, the measures of the SWS test could serve as an indicator for gait speed and most likely reliably rank the subjects according to their gait velocity.

Offline analysis of gait

We focused on the assessment of undisturbed continuous ‘regular’ walking. Thus, gait segments that included freezing episodes, stops and turns were excluded from the analysis (Hausdorff et al., 2003).

Assessment of left–right coordination of gait

The stride time, the time between two consecutives heel-strikes of the same leg, and the swing time, the time one foot is in the air, were determined using off-line computerized analysis of the force signal. Bilateral coordination of gait was assessed by examining the phase difference between the step timing of the left and right legs. Two primary outcome measures were defined: the phase, \(\psi\), and the PCI, as previously described (Plotnik et al., 2007). Briefly, each stride defines one gait cycle. The time between the start of a gait cycle and the time point when the other leg’s heel-strike occurs is used to determine the phase. Normalizing the step time with respect to the stride time and scaling by 360° defines the phase of the \(i\)th stride (\(\psi_i\); denoted in degrees, see more details in Fig. 1).

The PCI is a metric that combines the accuracy and consistency of stepping phases generation. The level of accuracy, i.e. how close are the series of generated phases to the value 180°, was assessed by the mean value of the series of absolute differences, \(\psi_i - 180°\), denoted as \(\psi_{\text{ABS}}\), a measure of temporal accuracy:

\[
\psi_{\text{ABS}} = |\psi_i - 180°|.
\]

The degree of consistency of the stepping phase generation is calculated by the coefficient of variation of \(\psi_i\), denoted as \(\psi_{\text{CV}}\), and given as a percentage. Therefore, \(\text{PCI} = \psi_{\text{CV}} + P_{\psi_{\text{ABS}}}\), where \(P_{\psi_{\text{ABS}}} = 100 \times \left(\psi_{\text{ABS}} / 180\right)\). Thus, PCI is the sum of two relative values, each given as a percentile. PCI was calculated for each
To study the ability of each subject to adjust the left–right stepping phase from one stride to the next stride, we calculated the values of \(\Delta \varphi\), where \(\Delta \varphi = \varphi_{i+1} - \varphi_i\). Each value of \(\Delta \varphi\) was classified either as ‘converging’ or ‘diverging’, depending on whether the shift was towards or away from the ideal value of 180°, respectively. For example, if \(\varphi_i = 193°\) and \(\varphi_{i+1} = 182°\), then \(\Delta \varphi\) would be considered as converging as the change was towards the value of 180° (regardless of the magnitude of the change). If, for example, \(\varphi_i = 181°\) and \(\varphi_{i+1} = 183°\), then \(\Delta \varphi\) would be considered as diverging as the change was away from the value of 180° (regardless of the magnitude of the change).

Two additional ratios were defined. For converging \(\Delta \varphi\), the converging ratio quantified the magnitude (absolute value) of the correction relative to the initial distance from 180°, i.e. converging ratio = \(\Delta \varphi/|\varphi_{ABS}\). The closer this converging ratio is to 1.0, the more precise is the scaling of phase adjustment, in other words the value of 1.0 indicates perfect alignment (i.e. 180°). For diverging \(\Delta \varphi\), we defined the diverging ratio = |\(\Delta \varphi\)|/\(\varphi_{ABS}\). The higher the diverging ratio is, the larger the relative drifts from 180°. For each subject, the median value of converging ratio and diverging ratio was designated as a summary measure of these measures, as the distributions of both parameters were positively skewed.

**Statistical analysis**

To evaluate the relationships between \(\varphi\), PCI and the presence of FOG, we assessed the effect of Group (PD + FOG and PD – FOG), the effect of medication intake (‘Off’ and ‘On’ states) and the Group \times Medication interaction, using mixed effect models (Proc Mixed-SAS software, SAS, Cary, NC, USA). The dependent measures were \(\varphi\) and PCI. Group and medication state were fixed factors, and ‘subject’ was a random factor. Effects on additional outcome measures \(\varphi\), \(\varphi_{CV}\) and \(\varphi_{ABS}\) were evaluated in separate mixed effect models. A P-value less than or equal to 0.05 (two-sided) was considered statistically significant.

**Results**

Data from 21 PD + FOG and 13 PD – FOG were studied. Subject characteristics of the two groups (PD + FOG vs PD – FOG) are summarized in Table 1. Mean values of Hoehn and Yahr scale, disease duration, MMSE score and scores of UPDRS items #20–#26 during the ‘Off’ and the ‘On’ states were not significantly different between PD + FOG and PD – FOG.

**The relation between left–right stepping phase coordination and FOG**

Left–right stepping coordination was impaired in PD + FOG, as compared with PD – FOG patients. Figure 2 exemplifies this point. Phase values, \(\varphi\), are plotted for one PD + FOG patient and one PD – FOG patient. During the ‘Off’ state, for the PD + FOG patient, \(\varphi\) fluctuated relatively far from the 180° ‘ideal’ line. For the PD – FOG patient, on the other hand, \(\varphi\) values were less variable, seemingly aligned with the 180° line (cf. Fig. 2).

Consistent with the example shown in Fig. 2, during the ‘Off’ state, mean values of \(\varphi_{CV}\), \(\ABS\varphi\) and PCI were significantly higher for PD + FOG.

**Table 1. Clinical characteristics of PD + FOG and PD – FOG patients**

<table>
<thead>
<tr>
<th></th>
<th>PD + FOG (N = 21)</th>
<th>PD – FOG (N = 13)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.6 ± 6.7</td>
<td>64.6 ± 6.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/6</td>
<td>7/6</td>
<td>0.20</td>
</tr>
<tr>
<td>PD duration (years)</td>
<td>10.6 ± 4.1</td>
<td>10.0 ± 4.2</td>
<td>0.50</td>
</tr>
<tr>
<td>H &amp; Y ‘Off’</td>
<td>2.9 ± 0.5</td>
<td>2.7 ± 0.4</td>
<td>0.19</td>
</tr>
<tr>
<td>H &amp; Y ‘On’</td>
<td>2.7 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>0.68</td>
</tr>
<tr>
<td>UPDRS (#20–26) ‘Off’</td>
<td>21.5 ± 11.6</td>
<td>24.2 ± 12.2</td>
<td>0.52</td>
</tr>
<tr>
<td>UPDRS (#20–26) ‘On’</td>
<td>9.7 ± 6.6</td>
<td>13.9 ± 7.2</td>
<td>0.09</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.1 ± 1.9</td>
<td>28.2 ± 1.8</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated: two-tailed t-test; \(\chi^2\) square analysis. Values are means (± SD), except for gender. FOG, freezing of gait; H & Y, Hohen and Yahr scale; MMSE, Mini Mental State Exam; PD, Parkinson’s disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

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*European Journal of Neuroscience, 27, 1999–2006*
The effects of levodopa on left–right stepping phase coordination

For both patient groups, left–right stepping phase tended to become less variable, and for the PD + FOG group more accurate (i.e. lower values of the PCI reflecting a more coordinated state in both groups) in the ‘On’ state. This effect on the PCI, however, was only marginally significant for the PD + FOG group ($P = 0.059$) and not significant for the PD – FOG group ($P > 0.9$). The group differences during the ‘On’ state and the Group × Medication interaction were not statistically significant (Table 2B). Despite the deviations, group mean values of phase ($\phi$) were close to the ‘ideal’ value of 180° both during the ‘Off’ and the ‘On’ states for both patients’ groups (Table 2B).

Ongoing adjustments of stepping phases in PD + FOG and PD – FOG patients

Values of stride-to-stride shifts in phase values ($\Delta \phi$) were studied during the ‘Off’ state ($n = 1579$ phase shifts), as this period reflects underlying pathology, independent of levodopa. The number of strides in which the phase value shifted towards 180° (i.e. converging shifts) was much higher than the number of diverging phase shifts. The proportions of converging phase shifts were 67.5.8% (SEM = 2.1%) and 69.9% (SEM = 2.8%) for the PD + FOG and the PD – FOG, respectively. The proportions of diverging shifts were 32.5% (SEM = 2.1%) and 30.1% (SEM = 2.8%) for the PD + FOG and the PD – FOG, respectively ($P < 0.005$, for within-group comparisons of % diverging vs % converging). Group differences were not statistically significant ($P > 0.49$).

The partition between diverging and converging phase shifts likely does not reflect simply random fluctuations, as demonstrated by the
following secondary analysis. The same set of $\Delta \varphi$ values was alternatively classified into two categories, ‘positive’ and ‘negative’, depending on whether $\varphi_{i+1} - \varphi_i \geq 0$ or $\varphi_{i+1} - \varphi_i \leq 0$, respectively. The proportion of ‘negative’ shifts was similar to the proportion of ‘positive’ shifts for both groups (50.4% and 49.6%, respectively, combined for both groups). In Fig. 3A, the number of negative phase shifts is plotted against the number of positive phase shifts for each subject. It can be seen that for the PD + FOG group as well as for the PD − FOG group (see key) are roughly equally distributed from both sides of the unity line. (B) The number of ‘converging’ phase shifts is plotted against the number of ‘diverging’ phase shifts, showing that most subjects aim at shifting stepping phase towards the value of 180° (see text).

**Table 2B.** Left–right stepping phase parameters during the ‘On’ state

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PD + FOG</th>
<th>PD − FOG</th>
<th>$P$-value</th>
<th>Withingroup medication effect</th>
<th>Group × Medication interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI (%)</td>
<td>9.87 ± 1.81</td>
<td>6.95 ± 0.86</td>
<td>0.401</td>
<td>$P = 0.059$</td>
<td>$P &gt; 0.9$</td>
</tr>
<tr>
<td>$\varphi_{CV}$ (%)</td>
<td>5.34 ± 1.26</td>
<td>3.42 ± 0.55</td>
<td>0.322</td>
<td>$P = 0.113$</td>
<td>$P = 0.866$</td>
</tr>
<tr>
<td>$\varphi_{\text{ABS}}$ (deg)</td>
<td>8.2 ± 1.1</td>
<td>6.3 ± 0.9</td>
<td>0.553</td>
<td>$P = 0.0311$</td>
<td>$P &gt; 0.9$</td>
</tr>
<tr>
<td>$\varphi$ (deg)</td>
<td>180.6 ± 1.4</td>
<td>178.7 ± 1.7</td>
<td>0.506</td>
<td>$P &gt; 0.9$</td>
<td>$P &gt; 0.9$</td>
</tr>
</tbody>
</table>

Data are presented as mean values (± SEM). FOG, freezing of gait; PCI, phase coordination index; PD, Parkinson’s disease.

**Fig. 3.** Classification of gait cycle into gait cycle stepping phase shifts. (A) Each data point represents the number of ‘positive’ phase shifts as a function of the number of ‘negative’ phase shifts for each subject. Data points from the Parkinson’s disease (PD) + freezing of gait (FOG) group as well as for the PD − FOG group (see key) are roughly equally distributed from both sides of the unity line. (B) The number of ‘converging’ phase shifts is plotted against the number of ‘diverging’ phase shifts, showing that most subjects aim at shifting stepping phase towards the value of 180° (see text).

**Fig. 4.** (A) Converging ratios (C-Ratio) were similar for the Parkinson’s disease (PD) + freezing of gait (FOG) and the PD − FOG patients. The mean values (± SEM) of converging ratio were 1.0 ± 0.1 and 1.2 ± 0.1 for the PD + FOG and PD − FOG groups, respectively ($P = 0.092$, Mann–Whitney test). (B) Diverging ratios (D-Ratio) were higher for the PD + FOG patients as compared with the PD − FOG patients. Mean values (± SEM) of the diverging ratio were 1.8 ± 0.3 and 0.9 ± 0.2 for the PD + FOG and PD − FOG groups, respectively ($P = 0.006$, Mann–Whitney test). Data from the ‘Off’ state.

The group mean value of the converging ratio was slightly higher for the PD − FOG as compared with the PD + FOG groups ($P = 0.092$; Fig. 4A). The group mean value of the diverging ratio was significantly higher for the PD + FOG as compared with the PD − FOG group ($P < 0.006$; Fig. 4B).
PCI and its relationship to UPDRS asymmetry, gait speed and clinical observations

To assess whether impairments in stepping phase during gait were related to asymmetry often seen in the clinical symptoms of PD, we assessed the correlation between UPDRS asymmetry and the PCI. During the ‘Off’ state, UPDRS asymmetry was slightly higher among PD – FOG patients. Mean values of UPDRS asymmetry were 0.23 ± 0.04 and 0.14 ± 0.02 for the PD – FOG and PD + FOG groups, respectively (P = 0.07, Mann–Whitney test). No correlation was found between PCI and UPDRS asymmetry in the PD + FOG group or in the PD – FOG group, both in the ‘Off’ and ‘On’ states (for all analyses: Spearman’s rho < 0.32, P > 0.37).

During the ‘Off’ state, PCI was not significantly correlated with SWS times (Spearman’s rho = 0.236, P ≥ 0.23). This was also the case when the analysis was performed separately for the PD + FOG and the PD – FOG group (Spearman’s rho ≤ 0.085; P ≥ 0.80). During the ‘On’ state, PCI values were significantly correlated with SWS values (Spearman’s rho = 0.628, P = 0.001). Significant correlations were found in separate analyses for the PD + FOG group (Spearman’s rho = 0.563, P = 0.015) and for the PD – FOG group (Spearman’s rho = 0.841, P = 0.036). The correlations between PCI and SWS values during the ‘On’ state are in agreement with earlier results showing correlations between PCI and gait speed during ‘On’ state in patients with mild PD (Plotnik et al., 2007).

During the ‘Off’ state, we found that for PD – FOG, but not for the PD + FOG patients, there was a significant inverse correlation between PCI and the UPDRS item (item #29) describing postural stability. It was inversely correlated in the PD – FOG patients (Spearman’s rho = −0.70; P = 0.018), but not in the PD + FOG patients (Spearman’s rho = 0.019; P = 0.936). No significant correlation was found between PCI and the UPDRS item (item #30) describing gait for either group (P ≥ 0.17). Among the PD + FOG patients, no correlation was found between PCI values and the score on the FOG questionnaire (P ≥ 0.5).

Discussion

The present results support the hypothesis that impairments in left–right coordination are associated with the presence of FOG in patients with PD. The key findings are as follows. (1) Stepping phases are less accurate and less consistent among PD + FOG patients as compared with PD – FOG patients (i.e. PCI is larger in PD + FOG). (2) During walking, patients with PD, both freezers and non-freezers, generally modify their stepping to maintain the phase close to the value of 180°. Both freezers and non-freezers also similarly scale their correct adjustments (towards 180°). (3) Intriguingly, however, when diverging from the ‘ideal’ 180° phase value, PD + FOG patients exhibit far less control, i.e. less attenuation of the level of the error, as compared with PD – FOG patients.

Left–right coordination of stepping in PD with FOG

Due to the erratic nature of leg movements during freezing episodes, much of the physiological research on FOG has focused on gait segments in between or just prior to the episodes. Studies have revealed that a decreasing stride length (Nieuwboer et al., 2001), an abnormal timing of leg muscle activation (Nieuwboer et al., 2004) and impairments in step amplitude scaling (Jansek et al., 2006) precede the occurrence of freezing episodes in PD. During successful walking in between freezing episodes, increased gait dysrhythmicity (Hausdorff et al., 2003) and gait asymmetry (Plotnik et al., 2005) were also observed. During normal healthy walking, variability may reflect a richness of possibilities and behaviors, for example, for transitioning from one mode of locomotion to another (e.g. walking to running; van Emmerik & Wagenaar, 1996). During steady-state walking, on the other hand, increased stride-to-stride variability represents pathological gait (Hausdorff et al., 1998). Previous findings observed that the PCI is increased in patients with PD, relative to age-matched controls, and the present findings indicate that the PCI is further increased in patients with PD with FOG, compared with those without. These results suggest that the bilateral coordination of stepping is more variable and less accurate in pathological conditions such as FOG, i.e. higher PCI values are less healthy.

How are gait asymmetry and the bilateral coordination of gait distinguished from each other? The difference between left and right swing times (i.e. gait asymmetry) reflects asymmetry in the motor function (i.e. programming and activation) related to leg propulsion. On the other hand, left–right step phase coordination (i.e. PCI) represents the degree to which the rhythmic process of stepping in one leg is coordinated with the rhythmic process of stepping of the other one. Theoretically therefore, gait asymmetry and PCI are distinct from each other (indeed these measures were not correlated in the present study — data not shown). To illustrate the unique properties of PCI and gait asymmetry, consider the hypothetical shortening or elongation of the duration of one foot’s swing times while keeping stride times constant (recall, the stance period is complementary to swing within the stride cycle). This will increase gait asymmetry, but will have no effect on phase coordination (e.g. gait patterns seen among amputees; Zmitrowicz et al., 2006). Thus, the present results emphasize the coordination deficits seen in PD + FOG patients, beyond the mere feature of an asymmetric gait.

Studies using a split-belt treadmill through which stepping propagation velocity can be induced differentially to each leg (i.e. belts are running at different speeds) have suggested that the neural networks responsible for each limb’s stepping in humans are interconnected in a flexible manner, basically producing anti-phased (~ 180°) leg activation (Prokop et al., 1995). The results of a recent study on patients with mild PD (Plotnik et al., 2007) suggest that this inter-leg coordination is impaired in PD as compared with healthy elderly subjects. Here we observed that the impairment is further aggravated in PD + FOG.

Abe and colleagues (Abe et al., 2003) studied left–right coordination of lower limb bicycle pedalling, and showed that PD + FOG patients exhibited relative phase drift monotonously from 0 to 360° or an irregularly modulated phase. In contrast, we did not observe continuous phase drifts. This difference between bicycling and walking makes sense because ongoing adjustments of left–right stepping phasing were executed by all subjects, a behavior that is required for forward walking.

Previously, adjustments of movements were not studied in PD within the context of maintaining successful rhythmic movements such as walking. Ongoing corrections of movements were investigated in PD primarily with respect to motor sequencing (Harrington & Haaland, 1991), reaching hand movements (Plotnik et al., 1998) and eye tracking (Desmurget et al., 2004). A common finding is that the basal ganglia are involved in ongoing movement adjustments. In the present study, PD + FOG had a reduced ability to bring under control diverging adjustments of left–right stepping phases (recall Fig. 4), an impairment that likely contributed to the irregular phasing seen in this group.

Insufficient capacity to automatically coordinate the steps of one leg in reference to the stepping performance of the other leg may result in difficulties during walking tasks that are inherently not symmetrical,
e.g. turning or at the start of a sequence of gait cycles. One can speculate that the motor system through, for example, the neural coordination of efferent referential copies of the planned bilaterally coordinated motor sequences (Takakusaki et al., 2003), identifies an emerging failure. In response, the effect is a motor block of gait, i.e. FOG.

**Clinical aspects**

In spite of the typical asymmetry of motor symptoms in PD, we found no correlation between PCI and the UPDRS asymmetry index. Earlier, no correlation was found between gait asymmetry and UPDRS asymmetry in patients with advanced (Plotnik et al., 2005) and mild-to-moderate PD (Yoge et al., 2007). The clinical motor symptoms of PD typically appear on one side first (Hughes et al., 2001). Severity of symptoms may remain uneven throughout the disease progression (Lee et al., 1995). It is very tempting to associate the asymmetric hypo-dopaminergic basal ganglia state with the deficits in the bilateral coordination in PD. However, the lack of correlation between reduced bilateral coordination of gait and asymmetry in motor symptoms suggests that the former is governed by structures or networks that are not only influenced by dopamine, for example, the spinal cord, brainstem (pedunculo-pontine nucleus), thalamus or premotor frontal cortex (Rivlin-Etzion et al., 2006). Nonetheless, dopamine does play a role, as demonstrated here by the improvement seen from the ‘Off’ to ‘On’ state. It cannot be ruled out that levodopa facilitates bilateral coordination of gait by direct action on spinal central pattern generators (Guertin, 2004).

We found a significant inverse correlation among PD – FOG patients between PCI and the UPDRS postural stability score (item #29), suggesting that the less coordinated the gait of these patients the lower is their postural stability. However, the relatively low number of patients in that group (n = 13) suggests that further investigation is needed regarding this point.

The correlation analysis between SWS and PCI suggests that during the ‘Off’ state, the medication period in which patients are more prone to freezing, PCI values are not related to gait velocity, further pointing to a distinct coordination malfunction associated with FOG. Despite the fact that gait speed was not measured in the present study (see Materials and methods), we assume that impaired PCI is not a strong reflection of reduced gait speed in PD + FOG, as compared with PD – FOG. This assumption is supported by the findings of Willems et al., who reported that spatio-temporal gait parameters, including gait speed, did not differ between freezers and non-freezers during walking segments free from FOG episodes (Willems et al., 2006). In addition, in healthy subjects, left–right stepping phase maintained the anti-phase pattern (180°) during the transition between walking and running (Diedrich & Warren., 1995), and anti-phase coordination was maintained for alternating leg movements in different movement frequencies (Kelso & Jeka, 1992). At the same time, it is important to note that our earlier results (table 3 of Plotnik et al., 2007) suggest that among patients with PD, while ‘On’ their medication, but not in healthy subjects, PCI values are inversely related to gait speed, in agreement with the significant correlation between PCI values and SWS values during the ‘On’ state reported here.

The results described in the present work together with findings reported by others (e.g. Abe et al., 2003) suggest that an alternative perspective of FOG in PD is worthy of consideration. Although FOG is an episodic event, it is apparently also related to ongoing gait impairments. Asymmetry (Plotnik et al., 2005) and poor coordination are associated with PD + FOG gait. We suggest the possibility that when gait asymmetry and/or reduced bilateral coordination of gait increase to exceed a certain threshold, gait becomes arrested. We speculate that those patients with PD with inherently lower capacity to coordinate their left–right stepping pattern are those patients who are more susceptible to freezing. Perhaps impairments in bilateral coordination of gait combine with certain external or internal triggers to cause FOG. For example, cognitive loading has been shown to increase bilateral dyscoordination of gait (Plotnik et al., 2006), and stress has been associated with FOG (Giladi & Hausdorff, 2006). Future studies in patients with FOG should explore the possibility that cognitive loading exacerbates the alterations in these aspects of gait and also triggers FOG.

**Limitations and future directions**

Cause-and-effect evidence showing that transient deterioration in bilateral coordination actually leads to freezing episode is lacking as we studied gait segments where walking was ‘regular’. Therefore, we can infer an association between PCI changes and FOG, but can only speculate about causality. Additional, controlled experiments are needed to address this point more directly. For example, in order to strengthen the observed association between FOG episodes and PCI, it may be helpful to quantify the number and the duration of the FOG episodes seen in a given gait task, and to study the relationship between these quantities and the PCI value calculated for this particular gait task.

Another methodological limitation is the lack of spatial parameters, in particular kinematics of leg joints or step length. Recently, Nieuwboer and colleagues observed decreased movement ranges around the ankle and hip joints in the sagittal plane a few strides prior to the occurrence of freezing episodes (Nieuwboer et al., 2007). They also found that intra-limb temporal coordination was not affected in those strides, but did not address inter-limb coordination. Impairments in the regulation of bilateral coordination of gait during ‘regular’ walking, on which we report here, are not mutually exclusive with step length reduction (Nieuwboer et al., 2001; Iansek et al., 2006) or decreased joint movement range (Nieuwboer et al., 2007) just prior to freezing. It is possible that they are each manifestations of the underlying trigger of FOG. Thus, the present observations of the PCI and stepping phase adjustments provide a more complete understanding of the processes involved in this debilitating phenomenon. Along with studies that are designed to understand the mechanisms in the causal pathway of a particular FOG episode, it may also be important to study, in a prospective manner, the factors that transform a PD patient into a PD + FOG patient. Perhaps such studies will demonstrate that alterations in gait quality including bilateral coordination, cognitive and/or motor decline may contribute to this unfortunate transformation.

**Acknowledgements**

We thank the patients for their participation, time and effort. We thank Ms Talia Herman and Ms Galit Yoge for invaluable assistance. This work was supported in part by the Inheritance Fund of the Israeli Ministry of Health, NIH grants AG-14100, RR-13622, HD-39938 and AG-08812, by the US-Israel Bi-National Science Foundation, by the Parkinson’s Disease Foundation (PDF), New York, USA, and the National Parkinson Foundation (NFP), Miami, USA, and by the European Commission in the context of the FP6 projects DAPHNet, FET-018474-2, and SENSATION-AAL, INFOSO-IST-045622.

**Abbreviations**

CV, coefficient of variation; FOG, freezing of gait; MMSE, Mini Mental State Exam; PCI, phase coordination index; PD, Parkinson’s disease; SWS, Stand Walk Sit; TASCe, Tel Aviv Sourasky Medical Center; UPDRS, Unified Parkinson’s Disease Rating Scale.

References


