WALKING PATTERNS IN PARKINSON’S DISEASE WITH AND WITHOUT FREEZING OF GAIT

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Abstract—The pathophysiology underlying freezing of gait (FOG) in Parkinson’s disease remains incompletely understood. Patients with FOG ("freezers") have a higher temporal variability and asymmetry of strides compared to patients without FOG ("non-freezers"). We aimed to extend this view, by assessing spatial variability and asymmetry of steps and interlimb coordination between the upper and lower limbs during gait. Twelve freezers, 15 non-freezers, and 15 age-matched controls were instructed to walk overground and on a treadmill. Kinematic data were recorded with a motion analysis system. Both freezers and non-freezers showed an increased spatial variability of leg movements compared to controls. In addition, both patient groups had a deficit in interlimb coordination, not only between ipsilateral arms and legs, but also between diagonally positioned limbs. The only difference between freezers and non-freezers was a decreased step length during treadmill walking. We conclude that parkinsonian gait—regardless of FOG—is irregular, not only in the legs, but also with respect to interlimb coordination between the arms and legs. FOG is reflected by abnormal treadmill walking, presumably because this provides a greater challenge to the defective supraspinal control than overground walking, hampering the ability of freezers to increase their stride length when necessary. © 2011 Published by Elsevier Ltd on behalf of IBRO.

Key words: central pattern generator, freezing of gait, gait disorders, interlimb coordination, Parkinson’s disease.

Gait disturbances are among the most disabling features of Parkinson’s disease (PD) (Morris et al., 2001). Approximately 30%–60% of PD patients suffer from freezing of gait (FOG), an episodic gait disorder during which patients suddenly become unable to start walking or to continue moving forward (Schaafsma et al., 2003). FOG impairs quality of life, mobility and independence, and can lead to falls (Moore et al., 2007).

Several studies that investigated the pathophysiology of FOG focused on the coordination of leg movements. The results showed differences in temporal stride regulation between PD patients with FOG ("freezers") and patients without FOG ("non-freezers"). Even outside actual FOG episodes, freezers showed a markedly increased stride-to-stride variability (Hausdorff et al., 2003) and a higher asymmetry of gait, defined as larger differences between left and right swing times (Plotnik et al., 2005, 2008). Additionally, it has been shown that freezing like episodes, so-called motor blocks, can occur in the upper limbs during voluntary hand movements, such as tapping (Ziv et al., 1999) or a bimanual rhythmic task (Nieuwboer et al., 2009).

Arm swing is integrated into locomotion via tight coordination between the upper and lower limbs (interlimb coordination) by specialized neural circuits in the spinal cord that can produce self-sustained patterns of behavior (central pattern generators, CPGs) (Dietz et al., 2001; Dietz, 2002; Zehr and Duysens, 2004). In PD, the adaptive coordination of interlimb movements during walking appears defective, both when walking speed is varied (Dietz et al., 1995; Winogrodzka et al., 2005) or kept constant (Carpinella et al., 2007; Crenna et al., 2008). During gait there is a basic difference between arm and leg movements, as leg movements involve load regulation, that is input from load receptors provide afferent input to the leg muscles for appropriate activation (Dietz, 2003). A decreased load sensitivity has been suggested as a cause for gait disorders in PD: a deficit in the processing of load related input may lead to reduced leg extensor activation during the stance phase of gait (Dietz and Duysens, 2000). Several etiologies have been suggested for FOG (Okuma, 2006). In this experiment, we will focus on two of these explanations: defects in coordination of leg movements and an altered load regulation. If FOG is mainly a disorder of load regulation, then no major interlimb coordination difference is expected between freezers and non-freezers. Conversely, if FOG is actually the ultimate manifestation of a severe segmental coordination problem, then interlimb coordination deficits should be amplified in freezers. To address this question, we studied leg movements (spatial and temporal parameters) and interlimb coordination between the upper and lower limbs during gait in PD patients with and without FOG, and in healthy controls. We
examined overground walking and also treadmill walking, as this requires a more complex supraspinal control (Regnaux et al., 2006).

### EXPERIMENTAL PROCEDURES

#### Subjects

We recruited 27 PD patients, diagnosed according to the UK Brain Bank criteria (Hughes et al., 1992), and 15 age-matched controls (Table 1). All participants were free from other neurological, visual, vestibular or muscular limb deficits that would influence their gait. Other exclusion criteria were cognitive disturbances (Mini Mental State Examination<25 or Frontal Assessment Battery<12), psychiatric pathology or severe co-morbidity. All subjects gave written informed consent according to the Declaration of Helsinki prior to participation. The study was approved by the local ethics committee. Patients were recorded in an OFF-state, after at least 12 h withdrawal of dopaminergic medication.

#### Assessment of FOG

All patients completed a FOG provocation trajectory in off medication state (Snijders et al., 2008), which involved rising from a chair, gait initiation, 360° and 540° turns to both sides, passing between narrowly placed barriers, and gait termination. This was done thrice: at preferred speed, as rapidly as possible, and in combination with a cognitive dual task (counting back from 100 with steps of seven). If any FOG episode was observed during this gait trajectory, the patient was defined as a freezer. However, since FOG is difficult to elicit in a research setting (Snijders et al., 2008), all patients additionally completed the new FOG questionnaire (NFOG-Q) (Nieuwboer et al., 2009a). As a part of this questionnaire a video with examples of typical FOG episodes was shown, to ensure that patients understood what was meant by a FOG episode. Subsequently, if they answered “yes” to the first question of the NFOG-Q (“Have you experienced FOG episodes during the past month?”), they were also defined as a freezer. Twelve patients were thus defined as having “off” period FOG (all with subjective FOG according to the NFOG-Q, and seven (58.3%) with additional FOG episodes during the gait trajectory).

There were no differences in age, gender, and cognitive scores between the three groups (Table 1). In addition, Hoehn & Yahr (H&Y) stage, Unified Parkinson’s Disease Rating Scale (UPDRS) score and disease duration were not significantly different between freezers and non-freezers (Table 1). None of the PD patients showed any freezing episodes during the formal experiment (consisting only of straight walking).

#### Gait analysis

To analyze overground gait, participants walked across an 8-meter walkway. Six trials while walking at preferred speed were recorded. Spatiotemporal data were collected for each trial, using a 6-camera VICON® motion analysis system (Oxford Metrics, UK) with reflective markers placed according to the standard VICON® Plug-in-Gait marker set.

Subsequently, subjects were instructed to walk on a treadmill at their preferred speed. Treadmill speed was increased or decreased until a comfortable walking speed, indicated by the subject, was reached. After that, treadmill speed remained constant during the experiment. Before recording, subjects were familiarized with treadmill walking for approximately 10 min. Then, spatiotemporal data were collected during one min of walking, in the same way as described above. We always performed the overground protocol first to avoid possible short-term treadmill training effects. We did not inform the subjects about the aims of the study and we instructed them to walk as naturally as possible, without any “tricks” they could have learned from their physiotherapist to improve gait or arm swing. During the experiment we did not observe any remarkable gait patterns.

#### Outcome measures

We measured gait variables during the two conditions. Outcome measures were amplitude, variation, and asymmetry of step length (spatial) and step time (temporal). Step length was defined as the distance traversed between heel strike of one foot and the consecutive heel strike of the contralateral foot. Step time was calculated as the time elapsed between sequential left and right heel strikes. Spatial variation was calculated as the coefficient of variation (CV) of all step lengths in one trial, while temporal variation was the CV of all step times. These outcome measures were determined for the most affected side in patients (highest UPDRS score) and for the non-dominant side in controls. Spatial asymmetry between left and right step length was calculated using the following formula: \( \frac{\text{max amplitude} - \text{min amplitude}}{\text{max amplitude}}\times 100\% \), where “max amplitude” represents the largest step length among mean left and right step lengths, and “min amplitude” represents the smallest step length. Temporal asymmetry was calculated in the same way for step time. Additionally, we calculated the phase coordination index as the duration of one step divided by the duration of one stride, a measure of bilateral coordination in producing left–right stepping phases (Plotnik et al., 2007).

### Table 1. Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Freezers</th>
<th>Non-freezers</th>
<th>Controls</th>
<th>Group* differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>15</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>60.5±7.9</td>
<td>60.2±9.2</td>
<td>57.9±7.3</td>
<td>NS</td>
</tr>
<tr>
<td>Female (%)</td>
<td>29%</td>
<td>30%</td>
<td>40%</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE</td>
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<td>29.1±1.2</td>
<td>29.4±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>FAB</td>
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<td>15.7±2.1</td>
<td>17.3±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration</td>
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<td>7.7±4.5</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>H&amp;Y*</td>
<td>2.4±0.3</td>
<td>2.1±0.3</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>UPDRS (Part III)*</td>
<td>35.4±8.9</td>
<td>30.6±7.0</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>NFOG-Q score (max. 24)</td>
<td>11.8±5.3</td>
<td>0.0±0.0</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data reflect means ± SE. N, number of subjects; NS, not significant; MMSE, Mini Mental State Exam; FAB, Frontal Assessment Battery; UPDRS, Unified Parkinson’s Disease Rating Scale; H&Y, Hoehn & Yahr; NFOG-Q, New Freezing Of Gait Questionnaire.

* UPDRS and H&Y score were determined in off medication state.
Interlimb coordination between the upper and lower limbs was determined as the synchronization between arm swing and steps. “Ipsilateral synchronization” was defined as the delay in time between heel strike of the foot and the maximal backward arm swing of the ipsilateral arm (Fig. 1A). This was calculated for both sides of the body: most affected leg vs. most affected arm (MA leg vs. MA arm) and less affected leg vs. less affected arm (LA leg vs. LA arm). “Contralateral synchronization” was defined as the delay in time between heel strike of the foot and the maximal forward arm swing of the contralateral arm (Fig. 1B). Two comparisons were made: most affected leg vs. less affected arm (MA leg vs. LA arm) and less affected leg vs. most affected arm (LA leg vs. MA arm). While ipsilateral synchronization requires adequate coupling of upper and lower limbs, contralateral synchronization is even more complex, requiring additional interlimb coupling between both legs or both arms. Synchronization was expressed as a percentage of the gait cycle time.

Data analysis

Outcome measures were calculated using MatLab (version 7.1). Statistical analysis was performed using SPSS for Windows (version 17.0). All data were normalized using log-transformation. Group comparisons across different conditions were performed using univariate ANCOVA with the outcome measure as dependent factor, “group” as independent factor, and “velocity” as a covariate to correct for gait speed. This was done separately for the treadmill and overground experiment. We examined differences between controls, freezers and non-freezers using a Tukey’s post-hoc test for multiple comparisons. Additionally, we assessed the influence of disease severity on the different outcome measures by means of a one-tailed Spearman’s correlation test. Level of significance (\( \alpha \)) was set at \( P=0.01 \).

RESULTS

Gait velocity

Mean gait velocity differed between groups and walking conditions; there was a significant main effect of group for both treadmill (\( P=0.003 \)) and overground (\( P<0.001 \)) walking. Mean gait velocity of the three subject groups during the different conditions is shown in Fig. 2.

All groups had a higher preferred speed during overground walking compared to treadmill walking (\( P<0.001 \) for controls and non-freezers; \( P=0.006 \) for freezers). Furthermore, controls had a higher gait speed than freezers during treadmill walking (\( P=0.002 \)) and overground walking (\( P<0.001 \)). Gait velocity of patients did not differ significantly between freezers and non-freezers.

Spatial step regulation

Outcome measures for spatial step regulation are shown in the upper panel in Fig. 3. Step length was larger in controls compared to freezers (Fig. 3A, treadmill: \( P<0.001 \); overground: \( P=0.005 \)), but did not differ between controls and non-freezers. Moreover, step length of non-freezers was

![Fig. 1. Calculation of synchronization between arm and leg movements; example of two strides in one PD patient. (A) Ipsilateral synchronization. Synchronization is calculated as the delay in time between maximal arm swing backward (dark vertical lines) and ipsilateral heel strike (dotted vertical lines). (B) Contralateral synchronization. Synchronization is calculated as the delay in time between maximal arm swing forward (vertical dark lines) and contralateral heel strike (vertical dotted lines). MA, most affected; LA, less affected.](image-url)
larger compared to freezers during treadmill walking (Fig. 3A, $P < 0.004$), but not during overground walking.

For step variation there was a significant main effect of group during treadmill walking ($P = 0.003$). Step variation of both freezers ($P < 0.001$) and non-freezers ($P = 0.007$) was higher compared to controls during treadmill walking (Fig. 3B). There were no differences between freezers and non-freezers in step variation. Furthermore, there were no differences in step asymmetry among the three groups (Fig. 3C).

**Temporal step regulation**

Outcome measures for temporal step regulation are shown in the lower panel of Fig. 3. There were no differences in step time between controls, non-freezers, and freezers (Fig. 3D). Step time variation was larger in freezers compared to controls during treadmill walking (Fig. 3E, $P < 0.001$). Furthermore, step time asymmetry was larger in non-freezers compared to controls during treadmill walking (Fig. 3F, $P = 0.008$). There were no differences in step time variation and asymmetry between freezers and non-freezers.

The phase coordination index was higher in freezers (182.3 $\pm$ 0.9; $P = 0.005$) and non-freezers (182.9 $\pm$ 1.5; $P = 0.03$) compared to controls (179.1 $\pm$ 2.0), only during treadmill walking. There were no differences in phase coordination index between the three groups during overground walking: 180.3 $\pm$ 1.8, 181.1 $\pm$ 3.8, and 180.5 $\pm$ 3.1 for controls, non-freezers, and freezers respectively.

**Interlimb coordination**

**Ipsilateral synchronization.** Although arm swing was very small in some patients, we measured a sinus-like movement in the arms of all patients of sufficient ampli-
Interlimb coordination

Fig. 4. Interlimb coordination in control subjects, non-freezers, and freezers while walking on a treadmill and during overground walking. (A) Ipsilateral synchronization of most affected leg and most affected arm; (B) Ipsilateral synchronization of less affected leg and less affected arm; (C) Contralateral synchronization of most affected leg and less affected arm; (D) Contralateral synchronization of less affected leg and most affected arm. Figures represent mean ± 95% CI; * significant (P < 0.01); ** significant (P < 0.001). MA, most affected; LA, less affected.

Tude to determine arm swing parameters for the calculation of interlimb coordination measures. Ipsilateral synchronization is shown in Fig. 4A, B. Synchronization delay of MA leg vs. MA arm (Fig. 4A) was larger in non-freezers and freezers (P < 0.001) compared to controls during treadmill walking. Furthermore, LA leg vs. LA arm synchronization delay (Fig. 4B) was larger in freezers (P = 0.009) compared to controls during treadmill walking, and tended to be larger in non-freezers compared to controls (P = 0.029). There were no differences between groups during overground walking. Furthermore, there were no differences between freezers and non-freezers. For ipsilateral synchronization at the affected side there was a significant group × condition interaction effect (P = 0.001).

Contralateral synchronization. Measures for contralateral synchronization between the upper and lower limbs are shown in Fig. 4C, D. Delay of contralateral synchronization of MA leg vs. LA arm (Fig. 4C) was larger in freezers compared to controls (treadmill: P = 0.009; overground: P = 0.010) and tended to be larger in non-freezers compared to controls (treadmill: P = 0.017; overground: P = 0.019). Delay of LA leg vs. MA arm (Fig. 4D) was larger in freezers (P = 0.006) compared to controls during treadmill walking, and tended to be larger in non-freezers compared to controls (P = 0.022). There were no differences between freezers and non-freezers.

Disease severity

UPDRS score was significantly associated with gait velocity (r = −0.34, P = 0.006), step length (r = −0.49, P < 0.001), spatial step asymmetry (r = −0.29, P = 0.018), spatial step variation (r = 0.44, P < 0.001), temporal step variation...
We included patients with a relatively low disease severity between freezers and non-freezers, by means of individual matching from our large patient database. More-relevant interlimb coordination differences between upper and lower limbs were larger in freezers and non-freezers compared to controls during treadmill walking. These findings suggest that parkinsonian gait is irregular, not only in the legs, but also in interlimb coordination between arms and legs.

**Step regulation**

During treadmill walking we observed a smaller step length in freezers compared to non-freezers. However, this difference was not present during overground walking. This could be caused by differences between overground and treadmill walking in behavioral context, such as anxiety and caution, leading to a more protective gait pattern on the treadmill (Stolze et al., 1997). Additionally, it has been suggested that PD patients are "hyper-reactive" to visual information (Almeida and Lebold, 2010). During overground walking patients receive a lot of optic flow information which can act as a cue to continue walking. Although the treadmill itself may also act as a cue (Frenkel-Toledo et al., 2005), the lack of the cue of optic flow during treadmill walking may complicate gait in freezers (Prokop et al., 1997). Moreover, it has been shown that treadmill walking is not an entirely automatic task, but requires additional attentional resources (Regnaux et al., 2006). Therefore, the differences found during treadmill walking may be attributed to the greater attentional demand and more consistent supraspinal control that are needed during treadmill walking. Supraspinal control may be more elaborately affected in freezers than non-freezers, resulting in an inability to increase stride length when necessary. Similar findings of decreasing stride length were seen in the steps just prior to a FOG episode (Nieuwboer et al., 2001). Moreover, a recent study showed that reducing preferred step length in freezers caused an increase in the amount of FOG episodes (Chee et al., 2009). Taken together, these previous results and our present findings add to the idea that FOG is caused by inability to generate and maintain an adequate stride length.

There were no differences in temporal and spatial variation or asymmetry of steps between freezers and non-freezers. However, we showed that there was a significant relationship between UPDRS score and step asymmetry, as well as between UPDRS score and temporal and spatial step variation. Hence, it is important to match freezers and non-freezers for disease severity, when examining gait parameters. We achieved comparable disease severity between freezers and non-freezers, by means of individual matching from our large patient database. Moreover, we included patients with a relatively low disease severity and short disease duration in order to maintain this good matching between freezers and non-freezers.

Previous studies found a higher stride time variability (Hausdorff et al., 2003) and a higher stride time asymmetry (Plotnik et al., 2005) in freezers compared to non-freezers in more severely affected patients. However, disease duration was not well-matched between the two patients groups. Therefore, it is possible that the differences between freezers and non-freezers become more obvious in advanced PD. Another explanation could be that these gait deficits are not a problem of FOG itself, but rather of advancing disease. To examine if freezers with a higher disease severity indeed present more problems in lower limb regulation, future studies should include patients with more advanced PD, yet with matched disease severity.

**Interlimb coordination**

Interlimb coordination between the upper and lower limbs during human gait is thought to be mediated by the coordinated activity of CPGs, that can independently produce self-sustained patterns of behavior (Wannier et al., 2001; Zehr and Duysens, 2004; Grillner et al., 2008). Input to the CPGs is delivered partly by supraspinal structures, in particular the tegmentum, cerebellum and basal ganglia. In PD—and maybe even more so in FOG—deficits in the basal ganglia could result in an impaired supraspinal control of the spinal interneuronal circuits involved in movement-related feedback.

We did not find differences in interlimb coordination between freezers and non-freezers. This finding would favor other pathophysiological explanations for FOG, for example that FOG is a disorder of load regulation, rather than a coordination problem (Dietz and Duysens, 2000). However, interlimb coordination was impaired in PD during treadmill walking, even in the moderately affected patients that were included in this study. Impaired coordination may be a generic manifestation of PD. In more advanced PD, interlimb coordination between the arms and legs is impaired during treadmill and overground walking (Carpinella et al., 2007; Crenna et al., 2008). In addition, more advanced PD patients have a reduced flexibility in the adaptive coordination of interlimb movements in relation to walking speed (Dietz et al., 1995; Winogrodzka et al., 2005). Our findings suggest that the impairment in interlimb coordination—probably caused by a failure in adequate supraspinal control—is already present in less advanced PD, but does not yet manifest itself during normal overground walking. Furthermore, our findings extend the previous finding of deficient ipsilateral interlimb coordination (Carpinella et al., 2007; Crenna et al., 2008), now showing that the deficit in synchronization between the upper and lower limbs also includes diagonal coordination.

**Limitations**

Not all patients in our freezers-group showed objective FOG; five freezers only indicated to suffer from FOG on history, but did not show actual FOG episodes during examination. We re-analyzed our data with the seven patients with FOG on history and upon examination ("definite" freezers). Between
non-freezers and definite freezers the same results were found, for example a difference in step length during treadmill walking ($P=0.002$, data not shown) and comparable interlimb coordination ($P>0.1$, data not shown). However, UPDRS and H&Y scores were not matched between definite freezers and non-freezers. As FOG is notoriously difficult to elicit in an experimental setting (Snijders et al., 2008) and our experiment that examined patients in the off medication state allowed only inclusion of less severely affected patients, we chose to show the results of the matched groups of non-freezers and the whole freezer-group. These freezers indicated clearly to suffer from FOG on history. We interviewed the subjects on the presence of FOG in detail, in a personal interview with an experienced clinician, as well as using the N-FOGQ and its video, which is a reliable measure of FOG (Nieuwboer et al., 2009a). As a result, we only included patients with consistent and highly characteristic descriptions of FOG episodes. Thus, we feel that this approach is a reliable measure to select patients with FOG, even when they do not show the phenomenon in the laboratory.

The aim of the study was to examine differences in gait between freezers and non-freezers outside the actual FOG episodes. Therefore, we purposely did not study FOG episodes themselves. Although no FOG episodes occurred, stride length was still shorter in freezers during normal treadmill gait. One possible explanation could be that there is no relationship between FOG episodes and changes in stride length. However, it has been shown that reduced stride length may eventually lead to FOG episodes (Chee et al., 2009). Possibly, in this study, the treadmill itself acted as a cue, preventing real FOG episodes to occur (Frenkel-Toledo et al., 2005; Snijders et al., 2010). The absence of FOG episodes during overground walking can be attributed to the location of the walkway in an open space, with no stimuli to provoke FOG.

**CONCLUSION**

We did not find differences in spatial variation or asymmetry of steps between freezers and non-freezers, but we did observe that step amplitude was smaller in freezers compared to non-freezers during treadmill walking. Treadmill walking requires a more consistent supraspinal control. Therefore, supraspinal control may be more elaborately affected in freezers than in non-freezers, resulting in an inability to increase stride length when necessary. Moreover, we found that interlimb coordination and spatial variation in steps were worse in both freezers and non-freezers compared to controls during treadmill walking. Apparently, the irregularity of parkinsonian gait is not only seen in the legs, but also in the coordination between upper and lower limbs. In agreement with previous work we found that PD patients have a deficit in ipsilateral interlimb coordination between the arms and the legs during gait. In addition, it was found that this abnormality extends to diagonal interlimb coordination as well.

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