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Abnormalities of the first three steps of gait initiation in patients with Parkinson’s disease with freezing of gait
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Acknowledgement
すくみ足は歩行開始時や歩行時、方向転換時などに足が前方に進まなくなる歩行障害であり、パーキンソン病患者にとって重要な問題である。すくみ足を呈する患者の歩行開始動作や定常歩行の異常に関する報告は多数あるが、歩行開始後定常歩行に至るまでの過渡期の異常に関する先行研究はない。過渡期は歩行開始後、歩行が安定する定常歩行に至るまでの重要な時期である。健常人では歩行開始後定常歩行に至るまで3歩必要であると報告されている。本研究の目的はすくみ足のあるパーキンソン病患者(PD+FOG)における歩行開始後3歩の異常について検証することとした。

第一研究ではPD+FOGの歩行開始後3歩の異常について検証するため、10名のPD+FOGと10名の年齢を一致させた健常者を比較検討した。対象者は自己ペースにて歩行開始した。振り出し開始側は指定せず、どちらかの歩行開始側が10回に達するまで実施した。振り出し開始側の一致率は各群において全試行の振り出し開始側が一致している人数の割合を算出した。Force platformにより歩行開始後3歩のCOP、Heel contact position、時空間指標を計測した。振り出し開始側は健常者では試行間の一致率が高かったが、PD+FOGでは一致率が低かった。PD+FOGは健常者と比較して、1-3歩目の歩幅、歩行速度が低下し、1歩目のステップ時間が延長していた。また、PD+FOGは歩行開始後2歩の両脚支持期が有意に延長していた。歩行開始時のpostural phaseにおいてCOPは後方かつ振り出し開始側に移動するが、PD+FOGのCOP後方移動距離は有意に低下していた。PD+FOGのCOPおよびHeel contact positionは、歩行開始後1歩目において振り出し開始側に偏位した。PD+FOGのCOPは健常者と比較して、歩行開始後2歩において、Heel contact positionの内側を通じた。歩行開始時のすくみ足の重症度は、歩行開始後3歩の步幅、歩行速度、両脚支持期、COPが1歩目のHeel contact positionの内側を通過する程度と有意な相関を示した。
第2研究ではすくみ足に特に関連する歩行開始後3歩の異常について検証するため、7名のすくみ足の無いパーキンソン病患者（PD-FOG）と7名の健常者の歩行開始後3歩について検証し、PD-FOGの異常と第1研究におけるPD+FOGの異常を比較検討した。さらに、歩行開始後3歩の異常に対する外的Cueの効果を検証するため、自己ペースと外的Cueによる歩行開始後3歩の異常を比較検討した。自己ペース条件では、対象者は自身のペースで歩行開始し、外的Cue条件では1回のビープ音に合わせて歩行開始した。解析は第1研究と同一の項目とした。PD+FOGのデータは第一研究から引用した。PD-FOGにおいて、1-3歩目の歩幅、歩行速度の低下、1歩目のステップ時間の延長、2歩目の両脚支持期の延長、postural phaseのCOP後方移動距離の低下、1歩目のCOP、Heel contact positionの振り出し開始側への偏位、1歩目におけるCOP軌跡のheel contact positionの内側通過などの異常を呈した。外的Cue条件では自己ペース条件と比較して、Postural phaseのCOP後方移動距離、postural phaseの期間を含むステップ時間、1歩目のステップ速度などのpostural phaseに関連する項目だけでなく、1歩目におけるCOP軌跡のheel contact positionの内側通過や2歩目の両脚支持期などのpostural phase後の項目の異常も正常化された。振り出し開始側は健常者とPD-FOGでは試行間の一致率が高かったが、PD+FOGにおいて試行間の一致率が顕著に低かった。1歩目の両脚支持期は、PD-FOGでは健常群と有意差がないがPD+FOGにおいて有意に延長し、歩行開始時のすくみ足の重症度と相関する唯一の指標であった。

これらの知見より、歩行開始時の振り出し開始側の変動性増加と1歩目の両脚支持期の延長がパーキンソン病患者のすくみ足に特に関連する異常であると考えられた。

キーワード：パーキンソン病；歩行開始；すくみ足；足圧中心
Keywords: Parkinson’s disease; gait initiation; freezing of gait; center of pressure
Introduction

Freezing of gait (FOG) is an episodic gait disorders during which patients with Parkinson's disease (PD) suddenly become unable to start walking or to continue moving forward. PD patients frequently experience FOG during gait initiation. Many studies have reported that abnormality in PD patients is particularly prominent during the postural phase, defined as the period between the onset of the weight shifting to the initial swing side and the onset of the heel off in the initial swing limb. The findings concerning abnormalities during the postural phase are derived from the whole population of PD patients, including both PD patients with FOG (PD+FOG) and PD patients without FOG (PD-FOG). There has been no study comparing abnormalities of gait initiation between PD+FOG and PD-FOG. Therefore, abnormalities of gait initiation specifically related to FOG have been unknown.

FOG occurs not only during gait initiation but also during steady-state gait in PD patients. Steady-state gait is abnormal in PD patients, and FOG affects the steady-state gait pattern. Accordingly, we hypothesized that the transition between gait initiation and steady-state gait is also abnormal in PD+FOG. However, there have been no studies about the abnormalities in the transition phase between gait initiation and steady-state gait in PD+FOG. Two or three steps are necessary in the transition between gait initiation and steady-state gait in healthy humans. Accordingly, we investigated the abnormalities of the first three steps of gait initiation in PD+FOG and PD-FOG in the present study.

External cues improve the abnormalities during the postural phase of gait initiation in PD patients. However, the effects of external cues on the abnormalities of the transition phase between gait initiation and
steady-state gait have not been investigated. Therefore, we investigated the effects of external cues on the abnormalities of the first three steps of gait initiation in PD patients.

This article consists of two chapters. In the first chapter, the abnormalities of the first three steps of gait initiation in PD+FOG are investigated by comparing between PD+FOG and age-matched healthy controls. In the second chapter, the abnormalities of the first three steps of gait initiation in PD-FOG are investigated by using a procedure similar to that of the first chapter, and the abnormalities in PD-FOG are compared with those in PD+FOG to identify the abnormalities specifically related to FOG. Additionally, we compare the abnormalities during self-generated gait initiation and cue-triggered gait initiation to investigate the effects of external cues on the abnormalities of the first three steps of gait initiation.
Chapter 1: Abnormalities of the first three steps of gait initiation in patients with Parkinson’s disease with freezing of gait

I. Introduction

Disturbance of gait initiation is common in patients with Parkinson’s disease (PD). In particular, the postural phase, defined as the phase between the onset of weight shifting to the initial swing side and the onset of the heel off in the initial swing limb, is abnormal in PD patients. Duration of the postural phase is prolonged. The displacement of the center of pressure (COP) and motoneuron pool excitability of the soleus muscle are abnormal in this phase. Furthermore, electromyographic activities in the tibialis anterior muscle, vastus lateralis muscle, and gastrocnemius muscle are decreased in this phase. The decreased step length during gait initiation may reflect some of these abnormalities in the postural phase.

Gait abnormalities in PD patients were reported not only during gait initiation, but also during steady-state gait. Step length and step velocity are reduced, double limb support duration is prolonged, and stride-to-stride variability of gait cycle timing is increased. Furthermore, movement amplitude of the legs and pelvis and the push-off peak of the vertical ground reaction force are reduced.

Given the existing findings about gait abnormality in PD patients, we hypothesized that the transition phase between gait initiation and steady-state gait may also be abnormal in PD patients. This transition phase was investigated in a previous study; however, the study was descriptive rather than a quantitative investigation. In the present study, we made a quantitative investigation of the transition phase between gait.
initiation and steady-state gait in PD patients. Two or three steps are necessary in the transition between gait initiation and steady-state gait in healthy humans. Therefore, we measured kinesiological parameters of the first three steps of gait initiation in the present study.

Freezing of gait (FOG) is a symptom in which patients suddenly become unable to start walking or to continue moving forward, and sometimes it appears during gait initiation. Start hesitation, which is a common form of FOG, occurs in 4% of PD patients during the “ON” state and in 23% of PD patients during the “OFF” state. FOG affects steady-state gait patterns. For example, stride time variability and stride time asymmetry in PD patients with FOG (PD+FOG) is higher than those in PD patients without FOG (PD-FOG), and the step length in PD+FOG is shorter than that in PD-FOG during treadmill walking. Before the occurrence of freezing during steady-state gait, reduced step length and sequence effect, increased cadence, and premature timing of tibialis anterior muscle and gastrocnemius muscle are observed. According to these findings, abnormality of gait pattern in the transition phase between gait initiation and steady-state gait may be prominent in PD+FOG. Therefore, the present study was conducted to investigate abnormality of the first three steps of gait initiation in PD+FOG.
II. Methods

1. Subjects

Ten PD patients, aged 63–78 years, and 10 age-matched healthy controls, aged 65–76 years, participated in this study. The PD patients were able to walk independently at least 10 m without assistive devices. The 6 male and 4 female subjects ranged in height from 1.42 m to 1.73 m. The healthy controls, 4 males and 6 females, ranged in height from 1.50 m to 1.69 m. There was no significant difference in age (P = 0.16) or height (P = 0.58) between the groups by unpaired t-test. Before beginning the experiment, the severity of FOG was assessed by a freezing of gait questionnaire (FOGQ). PD patients with FOGQ item 3 score > 0 were included in the experiment, because a recent study reported that this criterion is a valid indicator to distinguish between PD+FOG and PD-FOG.

Patient characteristics are shown in Table 1.1. All of the PD patients were being treated with stable doses of antiparkinsonian medications. The FOGQ total score ranged from 3 to 22. The score for FOGQ

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age (years)</th>
<th>Sex</th>
<th>H &amp; Y stage</th>
<th>UPDRS -motor</th>
<th>LED (mg/day)</th>
<th>FOGQ -total</th>
<th>FOGQ -item 3</th>
<th>FOGQ -item 5</th>
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<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>2</td>
<td>13</td>
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<td>1</td>
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<tr>
<td>2</td>
<td>65</td>
<td>F</td>
<td>3</td>
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<td>350</td>
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<td>M</td>
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<td>14</td>
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<tr>
<td>4</td>
<td>68</td>
<td>M</td>
<td>3</td>
<td>8</td>
<td>500</td>
<td>7</td>
<td>1</td>
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<tr>
<td>5</td>
<td>88</td>
<td>M</td>
<td>4</td>
<td>21</td>
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<tr>
<td>6</td>
<td>65</td>
<td>F</td>
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<tr>
<td>7</td>
<td>73</td>
<td>M</td>
<td>3</td>
<td>19</td>
<td>150</td>
<td>9</td>
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<td>1</td>
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<tr>
<td>8</td>
<td>85</td>
<td>F</td>
<td>4</td>
<td>14</td>
<td>300</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>F</td>
<td>3</td>
<td>14</td>
<td>450</td>
<td>20</td>
<td>3</td>
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</tr>
<tr>
<td>10</td>
<td>68</td>
<td>M</td>
<td>3</td>
<td>8</td>
<td>500</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
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M: male, F: female
LED: levodopa equivalent dose
FOGQ: freezing of gait questionnaire
item 3, which asks about the unique experience of the feet getting glued to the ground in different situations\textsuperscript{22}, ranged from 1 to 3, and the score for FOGQ item 5, which asks about the duration of start hesitation, ranged from 0 to 3. All the subjects gave written informed consent for study participation in accordance with the Helsinki Declaration. The experiment was approved by the ethical committee of Osaka Prefecture University.

2. Apparatus

Gait initiation was performed on a force platform (The FDM-System 2, Zebris Medical GmbH, Isny, Germany) placed on the first 2.18 m of a 9-m-long walkway. The length was expected to be sufficient to record three steps of gait initiation. The width of the platform was 0.6 m. This platform recorded vertical pressure on the surface of the force platform each 0.75 cm\textsuperscript{2} at a sampling rate of 100 Hz. The COP, heel contact positions, and spatiotemporal parameters were estimated from the vertical pressures.

3. Experimental protocol

All the experiments were conducted while the patients were in an “ON” state. The subjects stood barefoot on the force platform for a few seconds and initiated gait at their own pace. They continued to walk in the center of the walkway until the end of the walkway. They gazed at a target point 4 m beyond the end of the walkway. The target point indicated the approximate center of the walkway. One or two practice trials were performed before the experimental trials. The experimental trials were repeated until the subject successfully initiated gait by swinging the leg on either side 10 times. Only these 10 trials were included for data analysis.

4. COP displacement

The COP trajectory between the onset of displacement of COP from
quiet standing and the fourth toe off (the second toe off of the initial stance leg) was analyzed. The beginning of the COP trajectory was defined as zero along the anteroposterior and mediolateral axes. A positive COP value indicates the position anterior to zero along the anteroposterior axis and the deviation to the initial stance side in reference to zero along the mediolateral axis. The duration between the onset of COP displacement and the fourth toe off was defined as 100%. The COP trajectories were normalized according to this time scale, and the normalized COP trajectories were divided into the applicable 5% bins of the normalized time scale. Then, the COP was averaged for each 5% bin of the normalized time scale. In this way, we were able to estimate the average of twenty data points on the COP trajectory.

The 1st COP peak displacement was defined as the COP most deviated to the initial swing side before the first heel off (Figure 1.1). The 2nd COP peak displacement was defined as the COP most deviated to the initial stance side. The 3rd COP peak displacement was defined as the COP most deviated to the initial swing side after the 1st heel contact. The 4th COP peak displacement was defined as the COP most deviated to the initial stance side after the 2nd heel contact.

5. Heel contact position

The heel contact position along the anteroposterior axis was defined as the rear end of the heel. The heel contact position along the mediolateral axis was defined as the heel centerline. The amount of medial deviation of the COP from the heel contact position was also estimated. A positive value denoted medial deviation of the COP from the heel contact position, while a negative value denoted lateral deviation of the COP from the heel contact position.
6. Spatiotemporal parameters

The 1st step time was defined as the period between the onset of COP displacement and heel contact of the 1st step. The 2nd and 3rd step times were defined as the periods between heel contact in one foot and the next heel contact in the other foot. The single limb support (SLS) duration of each step was defined as the period between toe off and the next heel contact. The double limb support (DLS) duration was the period between the end of the SLS and the beginning of the next SLS. The DLS/Cycle ratio was defined as the DLS duration divided by the sum of the SLS duration and the DLS duration (gait cycle duration). The step length was defined as the distance between the rear end of the right and left heels along the anteroposterior axis. The step width was defined as the distance between the rear end of the right and left heel centerlines along the mediolateral axis. The step velocity was expressed as the step length divided by the step time.

![Diagram showing spatiotemporal parameters](image-url)

*Figure 1.1 Spatiotemporal and kinesiological parameters.*
7. Statistical analysis

Statistical tests were performed using SPSS 14.0 for Windows, SPSS Japan, Inc. Unpaired t-tests were conducted to examine the difference in each variable between the PD+FOG and healthy groups. Spearman’s rank correlation coefficient was estimated between the FOGQ item 5 score, which reflects the severity of FOG during gait initiation, and gait parameters. The alpha level was 0.05. Data were presented as the mean values and standard error of the mean [Mean (SEM)].
### III. Results

1. General features

All subjects were able to initiate gait without assistance. The first three steps were completely within the force platform in all trials of all subjects. The initial swing side was consistent throughout the trials in 9 out of 10 healthy controls. In contrast, the initial swing side was not consistent between the trials in PD+FOG; only 3 patients initiated gait with the same leg in all trials.

2. Spatiotemporal parameters

As shown in Table 1.2, step velocity and step length of the first three steps in PD+FOG were significantly smaller than those in healthy controls ($P<0.05$). The step width was not significantly different between the groups. The 1st step time in PD+FOG was significantly longer than that in healthy controls ($P<0.05$). However, the 2nd and 3rd step times were not significantly different between the groups. The 1st and 2nd DLS/Cycle ratios in PD+FOG were significantly larger than those in healthy controls ($P<0.05$).

3. COP displacement

The COP trajectory in PD+FOG tended to deviate to the posterior side and to the initial swing side as compared to that in healthy controls (Figure 1.2). The 1st COP peak displacement along the anteroposterior axis in PD+FOG was significantly smaller than that in healthy controls ($P<0.05$). The 2nd to 4th COP peak displacements along the anteroposterior axis in PD+FOG were significantly posterior to those in healthy controls ($P<0.05$). The 2nd to 4th COP peaks along the mediolateral axis in PD+FOG tended to deviate to the initial swing side as compared to those in healthy controls. We noted in particular that the deviation of the 3rd COP peak displacement along
the mediolateral axis was significantly different between the groups, as shown in Figure 1.3 (P<0.05).

4. **Heel contact position**

The heel contact positions of the first three steps in PD+FOG tended to deviate to the posterior side and to the initial swing side in comparison with those in healthy controls (Figure 1.2). The 1st to 3rd heel contact positions along the anteroposterior axis in PD+FOG were significantly posterior compared to those in healthy controls (P<0.05). As shown in Figure 1.4, the 1st and 3rd heel contact positions along the mediolateral axis in PD+FOG significantly deviated to the initial swing side, as compared to those in healthy controls (P<0.05). The 2nd heel contact position tended to deviate toward the initial swing side in PD+FOG as compared to healthy controls, although the deviation was not significant between the groups.

5. **Medial deviation of the COP from the heel contact position**

The COP trajectory in PD+FOG passed medial to each heel contact position during the first three steps, as compared to healthy controls (Figure 2). As shown in Figure 1.5, the amount of medial deviation of the COP from the 1st heel contact position and that from the 2nd heel contact position in PD+FOG were significantly larger than those in healthy controls (P<0.05).

6. **Correlation between the FOGQ item 5 score and gait parameters**

Step length and step velocity had a negative and significant correlation with the FOGQ item 5 score during the first three steps of gait initiation in PD+FOG (P<0.05), and the DLS/Cycle ratio had a positive and significant correlation with the FOGQ item 5 score during the first three steps of gait initiation in PD+FOG (P<0.05). The amount of medial deviation of the COP from the 1st heel contact position had positive and significant
correlation with the FOGQ item 5 score (P<0.05). In contrast, step width, step time, and COP peak displacements along the mediolateral axis did not have significant correlation with the FOGQ item 5 score.

Table 1.2 Spatiotemporal parameters

<table>
<thead>
<tr>
<th></th>
<th>PD+FOG</th>
<th>Healthy</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step length (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>38.0 (3.8)</td>
<td>53.8 (1.5)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>2nd</td>
<td>40.1 (3.6)</td>
<td>56.1 (1.1)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>3rd</td>
<td>44.9 (3.9)</td>
<td>58.7 (1.0)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td><strong>Step width (cm)</strong></td>
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<td></td>
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</tr>
<tr>
<td>1st</td>
<td>8.5 (0.9)</td>
<td>7.2 (1.0)</td>
<td>0.35</td>
</tr>
<tr>
<td>2nd</td>
<td>7.8 (1.4)</td>
<td>7.7 (0.9)</td>
<td>0.94</td>
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<tr>
<td>3rd</td>
<td>7.8 (1.3)</td>
<td>7.3 (0.9)</td>
<td>0.76</td>
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<tr>
<td><strong>Step time (s)</strong></td>
<td></td>
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<tr>
<td>1st</td>
<td>1.14 (0.06)</td>
<td>0.98 (0.02)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>2nd</td>
<td>0.63 (0.03)</td>
<td>0.61 (0.01)</td>
<td>0.62</td>
</tr>
<tr>
<td>3rd</td>
<td>0.54 (0.02)</td>
<td>0.53 (0.01)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Step velocity (m/min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>22.0 (2.4)</td>
<td>32.6 (0.7)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>2nd</td>
<td>39.4 (3.8)</td>
<td>54.3 (1.7)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>3rd</td>
<td>50.3 (4.1)</td>
<td>66.0 (1.8)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td><strong>DLS/Cycle ratio</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1st</td>
<td>0.38 (0.03)</td>
<td>0.32 (0.01)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>2nd</td>
<td>0.31 (0.02)</td>
<td>0.27 (0.01)</td>
<td>*&lt;0.05</td>
</tr>
<tr>
<td>3rd</td>
<td>0.30 (0.03)</td>
<td>0.26 (0.01)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Mean (SEM)

Asterisks indicate significant difference between the groups.
Figure 1.2
Averaged COP trajectory and heel contact position between the onset of COP displacement and the 4th toe off. Circles indicate the average of the normalized COPs.

Figure 1.3
Mediolateral displacement of COP peaks. Data columns indicate the mean, and error bars indicate standard errors of the mean. An asterisk indicates a significant difference between the groups (P<0.05).
Figure 1.4
Mediolateral heel contact positions. Data columns indicate the mean, and error bars indicate standard errors of the mean. Asterisks indicate a significant difference between the groups (P<0.05).

Figure 1.5
Medial deviation of the COP from the heel contact position. Data columns indicate the mean, and error bars indicate standard errors of the mean. Asterisks indicate a significant difference between the groups (P<0.05).
IV. Discussion

1. Trial-to-trial variability of the initial swing side

The initial swing side of gait initiation was consistent throughout the trials in healthy controls, but it was not consistent between trials in PD+FOG. Such variability has also been reported during reaching-with-trunk movement. Trial-to-trial variability of the timing of arm-trunk coordination during reaching movements in PD patients is larger than that in healthy controls. Furthermore, stride-to-stride variabilities of stride time, step time, swing time, and the duration of double limb support in PD patients are larger than those in healthy controls. Accordingly, trial-to-trial variability of the initial swing side of gait initiation may reflect the variable motor pattern in PD patients.

2. COP peak displacement and heel contact position

The 1st COP peak along the anteroposterior axis, reflecting backward deviation of the COP before the initial heel off of gait initiation, was found to be decreased, which was consistent with previous studies. This finding should reflect abnormalities of the postural phase in PD patients. The COP shifts backward and toward the swing limb during the postural phase. Furthermore, the 1st step time, which involves duration of postural phase, was prolonged in PD+FOG, which was also consistent with previous findings. Abnormality of the postural phase should be mostly derived from impairment of the anticipatory postural adjustment (APA). The APA is impaired during gait initiation, before protective steps induced by a forward loss of balance, or during voluntary steps in PD patients, indicating that the APA occurs during the postural phase. Therefore, the prolongation of the 1st step time and the decreased 1st COP peak along the anteroposterior axis observed in the present study should be related to impairment of the APA during gait initiation.
The 3rd COP peak displacement along the mediolateral axis in PD +FOG was significantly larger than that in healthy controls. This finding was associated with the significant deviation of the 1st heel contact position to the initial swing side in PD+FOG, compared to that in healthy controls. Such displacement should not be due to beginning to move in the wrong direction, because the subjects were instructed to walk toward a target point indicating the center of the walkway. Step width was not the cause of the displacement, because no significant difference in the step width was found between the groups throughout all the phases.

Insufficient weight shifting to the initial stance side immediately after the initial toe off may be related to the displacement. That is, a small weight shift to the initial stance side followed by normal weight shifting to the initial swing side resulted in abnormally large shifting of the COP to the initial swing side with reference to the zero position of the COP. A smaller tendency of the 2nd COP peak displacement to the initial stance side in PD+FOG supports this assumption. Another possible explanation is impaired braking of weight shifting to the initial swing side. Active braking of the center of gravity immediately before the first foot-contact of the initial swing limb during gait initiation is impaired in PD patients. This impairment may have resulted in excessive weight shifting to the initial swing side without sufficient braking against the weight shift immediately before the first heel contact.

Not only the 1st heel contact position but also the 3rd heel contact position significantly deviated to the initial swing side. This finding indicates that the deviation of the COP to the initial swing side affected subsequent heel contact positions. It is not certain that this effect continues after the transition phase between gait initiation and
steady-state gait, but it is certain that this deviation originates with the first step of gait initiation. Therefore, an increase in the 3rd COP peak displacement along the mediolateral axis should represent the abnormality specific to the transition phase between gait initiation and steady-state gait in PD+FOG.

3. Medial deviation of the COP from the heel contact position

The COP trajectory in PD+FOG was significantly medial against the heel contact positions during the first two steps compared to that in healthy controls. This may be explained by the prolonged duration of double limb support in these patients. The DLS/Cycle ratio was significantly larger in PD+FOG during the first two steps of gait initiation. This finding indicates that the tracing leg tends to remain on the ground even after the heel of the leading leg contacts the ground, which means that even when the heel contacts the ground, a certain amount of weight is still on the other limb. This finding indicates that a certain amount of weight remains on the tracing stance leg contralateral to the heel contact side. This delayed heel off in the tracing leg, and resulted in prolonged double limb support duration. Medial deviation of the COP from the 1st and 2nd heel contact position appears to specifically represent abnormality of the transition phase between gait initiation and steady-state gait in PD+FOG, because this abnormality was no longer present after the 2nd step of heel contact.

4. Correlation between the FOGQ item 5 score and gait parameters

Step length, step velocity, and duration of double limb support had significant correlations with the FOGQ item 5 score in PD+FOG. The negative correlation of step length with FOG severity was consistent with a previous finding that step length in PD+FOG was shorter than that in PD-FOG during treadmill steady-state walking\textsuperscript{19}. Generally, step velocity depends on step
length, indicating that the dependency of step velocity on FOG severity largely reflects the dependency of step length on FOG severity. The positive correlation between duration of double limb support and FOG severity was a novel finding. However, these significant correlations between spatiotemporal parameters and the FOGQ item 5 score were present throughout the first three steps of gait initiation. Accordingly, these dependencies may continue even after the transition phase between gait initiation and steady-state gait. Therefore, these dependencies may not represent dependencies specific to the transition phase between gait initiation and steady-state gait.

Medial deviation of the COP from the first heel contact position during the first step of gait initiation was significantly correlated with the FOGQ item 5 score, but the correlation was not significant during the 2nd and 3rd steps. These findings indicate that the medial deviation of the COP from the first heel contact position depends on the FOG severity, but this dependency is not sustained after the first step. Therefore, medial deviation of the COP from the first heel contact position should reflect the FOG severity specifically during gait initiation.

5. Spatiotemporal parameters

Step length and step velocity were decreased during the first three steps of gait initiation in PD+FOG. The decrease in step length should be the cause of the decreased COP displacement along the anteroposterior axis. Decreased step length and step velocity during the first step of gait initiation in these patients have been reported\textsuperscript{4,7-9}, as has a decrease in the step length of the second step\textsuperscript{6}. These decreases are present not only during gait initiation but also during steady-state gait\textsuperscript{12-15}. Accordingly, the decrease in step length and that in step velocity are probably not specific characteristics of the transition phase of gait initiation, but
general characteristics of all the phases of gait, manifested as a shuffling gait.

6. Suggestions for future studies

In this study we investigated the first three steps of gait initiation, but we did not experimentally confirm whether abnormalities were specifically present during gait initiation. Further studies investigating whether such abnormality is not present during steady-state gait are indispensable for testing whether the abnormalities are specifically present during gait initiation. On the other hand, PD+FOG are likely to show more advanced symptoms of their disease as comparing with PD-FOG. The present study included only PD+FOG. Accordingly, the present findings may be related to higher disease severity instead of the presence of FOG. Therefore, further studies in PD-FOG are needed to examine whether the findings of this study are specific to PD+FOG or applicable to PD patients in general.
V. Summary

The first three steps of gait initiation were found to be abnormal in PD+FOG. Major abnormalities include the deviation of the 3rd COP peak and the first heel contact position toward the initial swing side, indicating excessive weight shifting toward the initial swing side during the first step of gait initiation. Trial-to-trial variability of the initial swing side of gait initiation may reflect the variable motor pattern of gait initiation in PD patients. Our findings indicate that medial deviation of the COP from the first heel contact position reflects FOG severity specifically during gait initiation.
Chapter 2: Variable initial swing side and prolonged double limb support represent abnormalities of the first three steps of gait initiation in patients with Parkinson’s disease with freezing of gait.

I. Introduction

The transition phase between gait initiation and steady-state gait is abnormal in PD patients with freezing of gait (PD+FOG). In the first study, the first three steps of gait initiation were investigated because two or three steps are necessary for the transition from gait initiation to steady-state gait in healthy humans\textsuperscript{23}. Trial-to-trial variability of the initial swing side of gait initiation was observed, indicating a variable motor pattern during gait initiation. The COP peak displacement and the heel contact position deviated toward the initial swing side during the first step of gait initiation, indicating excessive weight shifting toward the initial swing side in this phase. Medial deviation of the COP from the heel contact position was observed during the first two steps of gait initiation, indicating that a certain amount of weight remains on the tracing leg contralateral to the heel contact side.

Such abnormalities of gait initiation may be specifically related to FOG, during which patients suddenly become unable to start walking or to continue moving forward. PD patients experience FOG during gait initiation with a prevalence of 58\% of PD patients in the “OFF” state and 5\% of those in the “ON” state\textsuperscript{2}. Abnormalities have been found in PD+FOG during steady-state gait or during treadmill walking\textsuperscript{17-22,30,31}. Stride time variability in PD+FOG is higher than that in PD patients without FOG (PD-FOG) during steady-state gait\textsuperscript{17}. Step length in PD+FOG is shorter than that in PD-FOG during treadmill walking\textsuperscript{19} and during steady-state gait\textsuperscript{22}. Step velocity in PD+FOG is less than that in PD-FOG during steady-state gait.
gait\textsuperscript{22}. Asymmetry and bilateral incoordination during steady-state gait are present in PD+FOG\textsuperscript{18,30}. Step length progressively decreases as the number of steps increases during steady-state gait in PD+FOG\textsuperscript{22,31}. Before the occurrence of freezing during steady-state gait, stride length and gait velocity decrease, the double limb support phase and cadence increase\textsuperscript{30}, and premature onset of tibialis anterior and gastrocnemius muscle activities occurs\textsuperscript{21}.

However, the findings concerning abnormalities during the postural phase are derived from the whole population of PD patients including both PD+FOG and PD FOG\textsuperscript{3-11}. All of the previous studies investigating abnormalities between PD+FOG and PD-FOG are derived from steady-state gait or treadmill walking\textsuperscript{17-19,22,30}. Previous findings concerning abnormalities of the first three steps of gait initiation in the first study are derived only from PF+FOG. Accordingly, there has been no study comparing abnormalities of gait initiation between PD+FOG and PD-FOG. FOG most frequently occurs at turns or during gait initiation\textsuperscript{2}, indicating that FOG may be more prominent during gait initiation than during steady-state gait. Therefore, the present study investigated the abnormalities of the first three steps of gait initiation in PD-FOG and healthy controls, and compared the abnormalities in PD-FOG with those in PD+FOG reported in the first study.

Medial deviation of the COP from the first heel contact position during gait initiation was found to be abnormal in PD+FOG, and was dependent on FOG severity, implying that medial deviation of the COP from the first heel contact position may be specifically related to FOG. However, it is impossible to rule out the possibility that FOG severity-dependent medial deviation of the COP from the first heel contact position may have originated due to the severity of the disease, because FOG severity
partially depends on disease severity. PD+FOG have significantly severe Unified Parkinson's Disease Rating Scale (UPDRS) motor scores, severe Hoehn & Yahr (H-Y) stages, and longer disease duration as compared to PD-FOG\textsuperscript{22}. FOG is correlated with UPDRS motor score\textsuperscript{24,25} and duration of the disease\textsuperscript{32}. Therefore, comparing abnormalities in gait initiation between PD+FOG and PD-FOG groups with equal disease severity is needed to investigate which abnormalities of gait initiation are specifically related to FOG. In the present study, the difference in disease severity between PD+FOG and PD-FOG was statistically tested to confirm whether the PD patients included in the present study satisfied the condition of equal disease severity.

External cues function to improve abnormalities in the postural phase of gait initiation in PD patients by reducing the duration of the postural phase\textsuperscript{5}, increasing force production\textsuperscript{5}, increasing COP displacement during the postural phase\textsuperscript{8}, and decreasing double limb support\textsuperscript{8}. Furthermore, the tibialis anterior muscle burst and soleus H-reflex depression during the postural phase of cue-triggered gait initiation were larger than those during the postural phase of self-generated gait initiation\textsuperscript{11}. However, it is not fully understood whether external cues bring about improvements in the abnormalities that occur during the transition phase between gait initiation and steady-state gait in PD patients. Therefore, abnormalities in the first three steps of gait initiation were compared between self-generated and cue-triggered gait initiation.
II. Methods

1. Subjects

Seven PD-FOG (6 males and 1 female), aged from 58 to 78 years, and 7 age-matched healthy controls (5 males and 2 females), aged from 61 to 73 years, participated (Table 2.1). An unpaired t-test revealed no significant difference in age between the groups. PD-FOG subjects were able to walk independently at least 10 m without assistive devices. PD patients with a freezing of gait questionnaire (FOGQ) item 3 score = 0, which meant that they had not experienced the feeling of their feet getting glued to the ground in any situation, were included in the experiment. FOGQ item 3 score = 0 indicated that all the PD patients included in the present study did not suffer FOG according to the criteria previously defined. The FOGQ total score ranged from 0 to 12. The scores on FOGQ item 5, which asks about the duration of start hesitation, ranged from 0 to 2. All the PD-FOG patients were being treated with stable doses of antiparkinsonian medications. The total daily levodopa equivalent dose (LED) ranged from 300 to 600 mg/day. All the experiments were conducted while PD-FOG subjects were in the “ON” state. All the subjects gave written informed consent for study participation in accordance with the Helsinki Declaration. The experiment was approved by the ethical committee of Osaka Prefecture University.

Additionally, the findings regarding self-generated gait initiation in PD+FOG were cited from the first study, in which a similar procedure was used, for comparing abnormalities of gait initiation between PD+FOG and PD-FOG. Ten PD patients (6 males and 4 females), aged from 63 to 88 years, were included in the first study. H-Y stage ranged from 2 to 4, and UPDRS motor score ranged from 5 to 24. A Mann-Whitney test revealed no significant differences in age, H-Y stage, and UPDRS motor score between the PD+FOG and PD-FOG. Total FOGQ scores ranged from 3 to 22, and the scores
on FOGQ item 5 ranged from 0 to 3. The FOGQ item 3 scores ranged from 1 to 3, indicating that PD patients in the first study can be categorized as PD+FOG according to the cut-off criteria\textsuperscript{25}. LED ranged from 150 to 500 mg/day. An unpaired t-test revealed that LED in PD-FOG was significantly higher than that in PD+FOG (P<0.05).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>H &amp; Y stage</th>
<th>UPDRS-motor</th>
<th>LED (mg/day)</th>
<th>FOGQ total</th>
<th>FOGQ-item3</th>
<th>FOGQ-item5</th>
</tr>
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<td>M</td>
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<td>400</td>
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<td>0</td>
</tr>
</tbody>
</table>

M: male, F: female
LED: levodopa equivalent dose
FOGQ: freezing of gait questionnaire

2. \textit{Apparatus}

Gait initiation was performed on a force platform (The FDM-System 2, Zebris Medical GmbH, Isny, Germany) placed on the first 2.18 m of a 9-m-long walkway. The length of the platform was expected to be sufficient to record three steps of gait initiation. The width of the platform was 0.6 m. This platform recorded the vertical pressure on the surface of the force platform each 0.75 cm\textsuperscript{2} at a sampling rate of 100 Hz. COP, heel contact positions, and spatiotemporal parameters were estimated from the vertical pressures.

3. \textit{Experimental protocol}

First, the subjects stood at the beginning of the walkway. The
subjects gazed at a target point located at the approximate center of the walkway but 4 m beyond the end of the walkway. In self-generated gait initiation, the subjects initiated walking at their own pace, while in cue-triggered gait initiation, subjects initiated walking with an auditory start cue generated from a speaker. Several practice trials were performed before the experimental trials were begun. The two types of gait initiation were performed in a random order. The experimental trials were repeated until the subjects successfully initiated walking 7 times for each type of gait initiation.

4. COP displacement

The COP trajectory between the onset of the displacement of the COP beginning from quiet standing and the fourth toe off was analyzed (Figure 2.1). The beginning of the COP trajectory was defined as zero along the anteroposterior and mediolateral axes. A positive COP value indicates anterior displacement along the anteroposterior axis and deviation to the initial stance side in reference to zero along the mediolateral axis. The duration between the onset of COP displacement and the fourth toe off was defined as 100%. Then, the COP was averaged for each 5% bin of the duration. That is, 20 mean COP data points were plotted between the onset of COP displacement and the fourth toe off.

The first COP peak displacement was defined as the COP most deviated to the initial swing side before the first heel off. The first COP peak displacement was identical to the end of the S1 period, which began with the start command and ended with the COP located in its most posterior and lateral position toward the initial swing side\textsuperscript{33}. The second COP peak displacement was defined as the first peak of the COP to the initial stance side after the first COP peak displacement. The third COP peak displacement was defined as the first peak of the COP to the initial swing side after
the second COP peak displacement. The fourth COP peak displacement was defined as the first peak of the COP to the initial stance side after the third COP peak displacement.

5. Heel contact position

The heel contact position along the anteroposterior axis was estimated from the position of the rear end of the heel. The heel contact position along the mediolateral axis was estimated from the position of the centerline of the heel. The amount of medial deviation of the COP from the heel contact position was also estimated. A positive value denoted medial deviation of the COP from the heel contact position, while a negative value denoted lateral deviation of the COP from the heel contact position.

6. Spatiotemporal parameters

The first step time was defined as the period between the onset of
COP displacement and the first heel contact. The second step time was defined as the period between the first heel contact and the second heel contact, and the third step time was defined as the period between the second heel contact and the third heel contact. The single limb support (SLS) duration of each step was defined as the period between toe off and the next heel contact. The double limb support (DLS) duration was the period between the end of the SLS and the beginning of the next SLS. The DLS/Cycle ratio was defined as the DLS duration divided by the cycle comprising sum of the SLS and DLS durations. The step length was defined as the distance between the heel contact positions along the anteroposterior axis. The step width was defined as the distance between the heel contact positions along the mediolateral axis. The step velocity was expressed as the step length divided by the step time.

7. Statistical analysis

Data were presented as the mean values and standard error of the mean. Subjects who initiated walking with the same leg in all of the trials were considered to be subjects who initiated walking with a consistent initial swing side. The number of subjects who initiated walking with the same leg in all the trials was divided by the total number of subjects to estimate the proportion of total subjects who initiated walking with a consistent initial swing side. The difference in the two proportions was statistically tested. Unpaired t-tests or a Mann-Whitney test were conducted to examine the difference in the means between the groups. The alpha level was 0.05. Effect size\textsuperscript{34}, the difference in means between the groups divided by the standard deviation of the control group, was used to estimate the magnitude of the difference in means between PD+FOG and PD-FOG. The statistical significance levels of the Spearman's rank correlation coefficients for the parameters in PD+FOG were cited from the first study.
III. Results

1. General features

All the subjects were able to initiate walking without assistance. The first three steps were performed completely within the force platform in all trials by all subjects. The initial swing side was consistent throughout the trials in all subjects, except in one healthy control during self-generated gait initiation (6/7=0.86 during self-generated gait initiation and 7/7=1.00 during cue-triggered gait initiation) and in one PD-FOG during self-generated and cue-triggered gait initiation (6/7=0.86). There was no statistical difference in the proportion of the total number of subjects who initiated walking with the same leg in all trials between the groups during both self-generated and cue-triggered gait initiation.

2. Spatiotemporal parameters

The first step time in PD-FOG was significantly longer than that in healthy controls during self-generated gait initiation (P<0.05), but it was not significantly different between the groups during cue-triggered gait initiation. The second and third step times were not significantly different between the groups during either self-generated or cue-triggered gait initiation (Table 2.2). Step length and step velocity in PD-FOG were significantly less than those in healthy controls during both self-generated and cue-triggered gait initiation (P<0.05), except for the first step velocity during cue-triggered gait initiation. The step width was not significantly different between the groups during either self-generated or cue-triggered gait initiation. The DLS/Cycle ratios were not significantly different between the groups during either self-generated or cue-triggered gait initiation, except for the second DLS/Cycle ratio, which was significantly larger in PD-FOG as compared with healthy controls during self-generated gait initiation (P<0.05).
Table 2.2: Spatiotemporal parameters

<table>
<thead>
<tr>
<th></th>
<th>Cae-triggered Healthy</th>
<th>Cae-triggered PD-FOG</th>
<th>Self-generated Healthy</th>
<th>Self-generated PD-FOG</th>
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<td>6/7</td>
<td>3/10</td>
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<td>0.32 (0.01)</td>
<td>0.34 (0.01)</td>
<td>0.38 (0.03) †</td>
<td>1.91</td>
</tr>
<tr>
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<td>0.25 (0.01)</td>
<td>0.28 (0.02)</td>
<td>0.25 (0.01)</td>
<td>0.29 (0.01) *</td>
<td>0.31 (0.02) †</td>
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<tr>
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<td>0.27 (0.02)</td>
<td>0.25 (0.00)</td>
<td>0.27 (0.02)</td>
<td>0.30 (0.03) †</td>
<td>0.74</td>
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</table>

Mean (standard error of mean)

Asterisks indicate significant difference between PD patients and Healthy controls.

Daggers indicate significant correlation between the parameter in PD+FOG and FOGQ item 5.

The data in PD+FOG were cited from the first chapter.
3. **COP displacement**

The first COP peak displacement along the anteroposterior axis in PD-FOG was significantly smaller than that in healthy controls during self-generated gait initiation (P<0.05), although it was not significantly different between the groups during cue-triggered gait initiation (Figure 2.2, Table 2.3). The second COP peak displacement along the anteroposterior axis in PD-FOG was not significantly different between the groups during both self-generated and cue-triggered gait initiation (Figure 2.3, Table 2.3). The third and fourth COP peak displacements along the anteroposterior axis in PD-FOG were significantly posterior as compared to those in healthy controls during both self-generated and cue-triggered gait initiation (P<0.05). The third COP peak displacement to the initial swing side along the mediolateral axis in PD-FOG was significantly larger than that in healthy controls during both self-generated and cue-triggered gait initiation (P<0.05). However, no significant difference was observed in the first, second, and fourth COP peak displacements during either self-generated or cue-triggered gait initiation.

4. **Heel contact position**

The first and third heel contact positions significantly deviated to the initial swing side as compared to those in healthy subjects during both self-generated and cue-triggered gait initiation (P<0.05) (Figure 2.3, Table 2.3). The second heel contact position in PD-FOG significantly deviated to the initial swing side in PD-FOG as compared with that in healthy controls during cue-triggered gait initiation (P<0.05), but this position was not significantly different during self-generated gait initiation.

5. **Medial deviation of the COP from the heel contact position**

The COP trajectory in PD-FOG passed medial to each heel contact position during the first step in comparison with healthy controls during
both self-generated and cue-triggered gait initiation (Figure 2.3). The medial deviation of the COP from the first heel contact position was significantly larger than that in healthy controls during self-generated gait initiation (P<0.05) (Table 2.3). The medial deviations of the COP from the second or third heel contact position were not significantly different between the groups during self-generated gait initiation. The medial deviations of the COP from the heel contact position were not significantly different between groups during cue-triggered gait initiation.

6. Comparison between PD+FOG and PD-FOG

The means and standard errors of the gait parameters during self-generated gait initiation in PD+FOG are cited from the first study and the effect sizes between PD+FOG and PD-FOG are shown in Tables 2.2 and 2.3. The initial swing side was consistent in all of the healthy controls (10/10=1.00), but was consistent only in 3 out of 10 PD+FOG subjects (3/10=0.30). A comparison of the proportions of all subjects in each group who initiated walking with a consistent side revealed significantly different proportions between the groups (P<0.05). The first DLS/Cycle ratio, second COP peak displacement in the anteroposterior axis, and medial deviation of the COP from the second heel contact position were the parameters which showed significant differences between healthy controls and PD+FOG subjects (P<0.05) and no significant differences between healthy controls and PD-FOG subjects. Effect sizes ranged from 1.70 to 2.02 in these parameters. For these parameters, the first DLS/Cycle ratio significantly correlated with FOGQ item 5 (P<0.05).
Figure 2.2 First COP peak displacement during self-generated and cue-triggered gait initiation. Data points indicate the averages of the first COP peak displacements. Filled data points are from healthy controls, and open data points are from PD-FOG subjects. Circles indicate the data points during self-generated gait initiation, and triangles indicate the data points during cue-triggered gait initiation. An asterisk indicates a significant difference in COP peak displacement along the anteroposterior axis between the groups (p<0.05).

Figure 2.3 Overall average of COP and heel contact position. The data points indicate the overall average of the COPs for each 5% bin of the total duration. The COP trajectories are depicted by lines connecting the nearest two COP data points.
Table 2.3 COPs and heel contact positions

<table>
<thead>
<tr>
<th></th>
<th>Cue-triggered</th>
<th>Self-generated</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy  PD-FOG</td>
<td>Healthy PD-FOG PD+FOG</td>
<td></td>
</tr>
<tr>
<td>Anteroposterior COP peak displacement</td>
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<tr>
<td>Peak1</td>
<td>-2.7(0.4) -2.1(0.2)</td>
<td>-1.8(0.1) -1.1(0.2)*</td>
<td>-1.1(0.2)*</td>
</tr>
<tr>
<td>Peak2</td>
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<td>-2.5(0.4) -2.7(0.8)</td>
<td>1.4(0.7)*</td>
</tr>
<tr>
<td>Peak3</td>
<td>56.7(1.2) 48.1(3.2)*</td>
<td>57.2(0.8) 48.1(3.2)*</td>
<td>39.9(3.8)*</td>
</tr>
<tr>
<td>Peak4</td>
<td>111.5(1.8) 95.8(4.8)*</td>
<td>112.7(1.8) 94.3(5.5)*</td>
<td>80.1(7.1)*</td>
</tr>
<tr>
<td>Mediolateral COP peak displacement</td>
<td></td>
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</tr>
<tr>
<td>Peak1</td>
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<td>-1.31(0.22) -1.27(0.24)</td>
<td>-1.14(0.23)</td>
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<tr>
<td>Peak2</td>
<td>6.63(0.76) 6.52(0.64)</td>
<td>6.72(0.63) 6.51(0.71)</td>
<td>6.93(0.45)</td>
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<td>Peak3</td>
<td>4.47(0.74) 9.99(0.94)*</td>
<td>-6.81(0.71) -9.67(1.06)*</td>
<td>-8.35(0.43)*</td>
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<tr>
<td>Peak4</td>
<td>9.78(1.19) 6.83(1.10)</td>
<td>8.25(0.62) 6.83(0.94)</td>
<td>5.88(0.66)</td>
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<td>Mediolateral heel contact position</td>
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<tr>
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<td>-2.99(0.62) -5.11(0.42)*</td>
<td>-4.91(0.65)*</td>
</tr>
<tr>
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<td>4.16(0.74) 2.09(0.80)</td>
<td>2.90(0.89)</td>
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<tr>
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<td>-1.84(0.92) -5.45(0.85)*</td>
<td>-5.28(0.79)*</td>
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<tr>
<td>Medial deviation of COP from heel contact position</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>0.34 (0.19) 1.15(0.51)</td>
<td>0.23 (0.20) 1.40 (0.39)*</td>
<td>1.03 (0.57)*</td>
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<td>0.12 (0.25) 0.43(0.30)</td>
<td>1.77 (0.58)*</td>
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<td>-0.12(0.20) 0.67 (0.33)</td>
<td>1.04 (0.48)</td>
</tr>
</tbody>
</table>

Mean (standard error of mean)

Astetisks indicate significant difference between PD patients and Healthy controls.

Daggers indicate significant correlation between the parameter in PD+FOG and FOGQ Item 5.

The data in PD+FOG were cited from the first chapter.
IV. Discussion

1. Trial-to-trial variability of the initial swing side

The initial swing side of gait initiation was consistent throughout the trials in most healthy controls and in most PD-FOG subjects. The finding in healthy controls was consistent with the finding in the first study, but the finding in PD-FOG was inconsistent with the finding in PD+FOG in the first study; the initial swing side was consistent in only 3 out of 10 PD+FOG subjects. Accordingly, trial-to-trial variability of the initial swing side during gait initiation may be an abnormality specifically related to FOG. The variability of the motor pattern during steady-state gait in PD+FOG was found to be larger than that in PD-FOG\(^1\), indicating that a variable motor pattern may result in the variable initial swing side of gait initiation. One possible reason for this finding is the disease severity associated with FOG severity. It has been reported that FOG severity partially depends on disease severity\(^22, 24, 25, 32\). However, the disease severity was not statistically different between PD+FOG in the first study and PD-FOG in the present study, indicating that the variable initial swing side of gait initiation specifically present in PD+FOG is not related to the severity of the disease.

2. Abnormalities of the postural phase

The first COP peak displacement along the anteroposterior axis, which reflects backward deviation of the COP during the postural phase, was found to be decreased during self-generated gait initiation in PD-FOG, which is consistent with the finding in previous studies that the posterior deviation of the COP during the postural phase is decreased in PD patients\(^7-10\). Furthermore, this finding was consistent with the finding in PD+FOG. Therefore, the decreased first COP peak displacement along the anteroposterior axis in PD+FOG likely reflects the abnormality of the
postural phase of self-generated gait initiation in PD patients in general, but is not specifically related to FOG.

3. Abnormalities of the other parameters

The first step time was prolonged in PD-FOG. The first step time was prolonged in PD+FOG as well. Therefore, a prolonged first step time is a parameter that is observable in the whole population of PD patients. The first step time defined in the present study involves not only the postural phase but also the first swing phase\(^9\). The postural phase\(^4,6,7\) and the first swing phase\(^9\) are prolonged in PD patients, suggesting that the prolonged first step time in the present study reflects prolongation of the postural and first swing phases.

Step length and step velocity were decreased during self-generated gait initiation in PD-FOG. This finding was consistent with the previous findings that step length and step velocity are decreased during the first step of gait initiation in PD patients\(^4,7,8\). Step length and step velocity have been reportedly abnormal during the first three steps of gait initiation in PD+FOG, indicating that abnormalities of step length and step velocity are not specifically related to FOG. The finding concerning step length conflicts with the previous finding that the step length during treadmill walking or steady-state gait is abnormal in PD+FOG, but is not abnormal in PD-FOG\(^{19,22}\). It has been reported that PD+FOG decreases step length as the number of steps increases\(^{22,31}\). Gait initiation begins from standing, indicating that the number of steps executed before the beginning of gait initiation is zero. In contrast, steady-state gait begins after at least 3 steps of gait initiation\(^{23}\). Thus, the number of steps executed before gait initiation is theoretically less than that before steady-state gait is achieved. Accordingly, the conflicting abnormalities of step length between gait initiation and steady-state gait may reflect a different
sequential effect of the steps on FOG.

The third COP peak displacement and the first heel contact position significantly deviated to the initial swing side in PD-FOG. This finding is consistent with that in PD+FOG, indicating that this abnormality is not specifically related to FOG. It has been hypothesized that a small weight shift to the initial stance side followed by normal weight shifting to the initial swing side may be the cause of the excessive shifting of the COP to the initial swing side, leading to an increase in the third COP peak displacement in PD+FOG. However, the second COP peak displacement along the mediolateral axis was not prominently decreased in the present study. Therefore, the small weight shift toward the initial stance side should not be considered the cause of the excessive deviation of the COP toward the initial swing side in PD patients.

The medial deviation of the COP from the first heel contact position was increased in PD-FOG. This finding is consistent with the finding in PD+FOG, indicating that this parameter is not specifically related to FOG. It has been hypothesized that the increase in the medial deviation of the COP from the first heel contact position may be explained by the possibility that a certain amount of weight remains on the tracing leg contralateral to the heel contact side. If this is true, medial deviation of the COP from the heel contact position should have been associated with delayed heel off leading to prolonged double limb support. However, the first DLS ratio was not prolonged in PD-FOG, indicating that prolonged double limb support is likely not the major cause of the increase in the medial deviation of the COP from the first heel contact position in PD patients.

4. Abnormalities during cue-triggered gait initiation

An auditory external cue is considered to be effective if some
parameters are abnormal during self-generated gait initiation but are not abnormal during cue-triggered gait initiation. The first step time, first step velocity, first COP peak displacement along the anteroposterior axis, second DLS ratio, and medial deviation of the COP from the first heel contact position were abnormal during self-generated gait initiation, but not during cue-triggered gait initiation. The first step time and first step velocity involve the postural phase and the first COP peak displacement occurs exactly during the postural phase. In contrast, the second DLS/Cycle ratio and medial deviation of the COP from the first heel contact position occur after the postural phase. Accordingly, the auditory external cue is effective for normalizing gait initiation not only during the postural phase but also after the postural phase of gait initiation in PD-FOG.

5. Abnormalities of gait initiation specific to PD+FOG

The present study compared the abnormalities during self-generated gait initiation in PD-FOG with those in PD+FOG cited from the first study by three procedures. First, the statistical significances of the abnormalities were compared between PD+FOG and PD-FOG. Second, the effect sizes between the means in PD+FOG and those in PD-FOG were calculated in order to estimate the magnitude of the difference in means between the groups. Third, the statistical significances of the correlation coefficients between the parameters of gait initiation and FOG severity were cited from the first study. We considered that the parameters showing statistically significant correlations with FOG severity in PD+FOG, significant abnormality in PD+FOG, no significant abnormality in PD-FOG, and a large effect size between the groups were specifically related to FOG.

Medial deviation of the COP from the first heel contact position has been believed to be abnormal during gait initiation specifically in
PD+FOG. However, the present study found that the medial deviation of the COP from the first heel contact position was abnormal in PD-FOG, indicating that abnormality of the medial deviation of the COP from the first heel contact position is not specifically related to FOG. The medial deviation of the COP from the second heel contact position was abnormal in PD+FOG, but not in those without FOG. However, the medial deviation of the COP from the second heel contact position was not significantly correlated with FOGQ item 5. Accordingly, it is not sufficient to consider medial deviation of the COP from the second heel contact position to be a parameter specifically related to FOG.

The DLS/Cycle ratio was not significantly prolonged during the first step of gait initiation in PD-FOG, but was significantly prolonged in PD+FOG. The effect size in the first DLS/Cycle ratio between PD+FOG and PD-FOG was considered to be large according to classical classification\textsuperscript{35}. Additionally, the first DLS/Cycle ratio was correlated with FOGQ item 5. Therefore, the duration of double limb support during first step of gait initiation is considered to be a parameter specifically related to FOG.

A previous finding concerning steady-state gait in PD+FOG gives us some suggestions why the first DLS/Cycle ratio is specifically related to FOG. Before freezing, the double limb support phase is larger than that before stopping during walking in PD patients in an “OFF” state\textsuperscript{20}. These previous researchers hypothesized that the increase in double limb support is caused by postural instability, leading to compensation for the increase of the time during which both feet are in contact with the ground or an inability to adequately transfer weight as a preparation for stepping. The prolonged double limb support during gait initiation found as a parameter specifically related to FOG in the present study may reflect such impairments. However, this previous finding does not explain why the first
double limb support is related to FOG. Further studies are needed to elucidate the mechanisms underlying this finding.

6. Limitations

We cannot rule out the effect of antiparkinsonian medications on abnormalities of gait initiation specifically present in PD+FOG. LED in PD-FOG was significantly higher than that in PD+FOG. Levodopa improves FOG. In the present study involving PD-FOG subjects and in the first study involving PD+FOG subjects, the experiment was conducted when PD patients were in an “ON” state. Therefore, it is possible that the fact that some gait parameters which did not reveal statistically significant abnormalities in PD-FOG but did reveal significant abnormalities in PD+FOG may be partially related to the effect of antiparkinsonian medications.
V. Summary

The first three steps of gait initiation are abnormal in PD-FOG. An external cue normalizes some abnormalities not only during the postural phase but also after the postural phase of gait initiation. Prolonged double limb support during the first step and the trial-to-trial variability of the initial swing side are likely to be abnormalities specifically related to FOG.
References


Acknowledgement

I would like to thank professor Hiraoka for sincere instructions on the study.