RESEARCH ARTICLE

Freezing in Parkinson's Disease: A Spatiotemporal Motor Disorder Beyond Gait

Sarah Vercruysse, MSc,[1]* Joke Spildooren, MSc,[1] Elke Heremans, MSc,[2] Jochen Vandenbossche, MSc,[3,4] Oron Levin, PhD,[2] Nicole Wenderoth, PhD,[2] Stephan P. Swinnen, PhD,[2] Luc Janssens, MSc,[5] Wim Vandenberghe, MD, PhD,[6] and Alice Nieuwboer, PhD[1]

[1]*Department of Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium*
[2]*Department of Biomedical Kinesiology, Katholieke Universiteit Leuven, Leuven, Belgium*
[3]*Department of Neurological Rehabilitation, Vrije Universiteit Brussel, Brussels, Belgium*
[4]*Department of Cognitive Psychology, Vrije Universiteit Brussel, Brussels, Belgium*
[5]*Groep T-International University College Leuven, Leuven, Belgium*
[6]*Department of Neurology, University Hospitals Leuven, Leuven, Belgium*

ABSTRACT: Freezing of gait (FOG) is an incapacitating problem in Parkinson's disease that is difficult to manage therapeutically. We tested the hypothesis that impaired rhythm and amplitude control is a common mechanism of freezing which is also present during other rhythmic tasks. Therefore, we compared the occurrence and spatiotemporal profiles of freezing episodes during upper limb motion, lower limb motion, and FOG. Eleven freezers, 12 non-freezers, and 11 controls performed a rhythmic bilateral finger movement task. The triggering effect of movement speed, amplitude, and coordination pattern was evaluated. Regression slopes and spectral analysis addressed the spatial and temporal kinematic changes inherent to freezing episodes. The FOG Questionnaire score significantly predicted severity of upper limb freezing, present in 9 freezers, and of foot freezing, present in 8 freezers. Similar to gait, small-amplitude movements tended to trigger upper limb freezing, which was preceded by hastened movement and a strong amplitude breakdown. Upper limb freezing power spectra were broadband, including increased energy in the "freeze band" (3–8 Hz). Contrary to FOG, unilateral upper limb freezing was common and occurred mainly on the disease-dominant side. The findings emphasize that a core motor problem underlies freezing which can affect various movement effectors. This deficit may originate on the disease-dominant body side and interfere with amplitude and timing regulation during repetitive limb movements. These results may shift current thinking on the origins of freezing as being not exclusively a gait failure.

Key Words: freezing of gait; upper limb motion; upper limb freezing; Parkinson's disease; spectral analysis

Freezing of gait (FOG) is experienced by approximately 50% of patients with advanced Parkinson's disease (PD)[1] and is defined as a transient inability to generate effective stepping.[2] As a significant predictor of falling, FOG is a major debilitating problem in PD.[3] FOG is partly responsive to dopaminergic medication[4] and subthalamic nucleus (STN) stimulation[5,6] but remains a challenging treatment target. The current understanding of its underlying mechanisms is dominated by diverging motor and non-motor hypotheses, based on specific factors known to elicit freezing; eg, turns,[4,7] postural perturbations,[8] dual tasking,[7,9] narrow spaces,[10,11] set-shifting deficits,[12,13] and stress.[14]

Additional Supporting Information may be found in the online version of this article.

***Correspondence to:** Ms. Sarah Vercruysse, K.U.Leuven, Faculty of Kinesiology and Rehabilitation Sciences, Department of Rehabilitation Sciences, Tervuursevest 101, 3001 Leuven, Belgium; sarah.vercruysse@faber.kuleuven.be

Funding agencies: This study was supported by a grant from the Research Council of Katholieke Universiteit Leuven, Belgium (contract OT / 07 / 074) and the Flanders Fund for Scientific Research (project G0691.08).
Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 31 March 2011; **Revised:** 22 September 2011; **Accepted:** 30 September 2011
Published online 21 October 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.24015

This work focuses on core aspects of motor control related to FOG. Irrespective of the trigger, FOG is mostly characterized by (1) a decrease in stride length; (2) an increase in stepping frequency preceding the episode; and (3) the presence of a highly abnormal frequency of leg movements during the episodes.[15–20] This faulty scaling-timing interaction is crucial in the development of periodic freezing events, but is also implied in a more continuously disturbed gait pattern in patients with FOG (freezers)[20–23] compared to those without (non-freezers).

There is mounting evidence of freezing-like motor blocks in various rhythmic tasks such as speech,[24] hand movements including writing and manual tapping, and other anti–phase coordination tasks[24–28] such as those used as part of the new Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[29] Although a previous study reported a correlation between freezing in different effectors,[28] it is presently unclear whether movement breakdown during gait and other rhythmic movement reflect a generic deficit in automatic motor control. Therefore, the aim of this study was to investigate timing and scaling abnormalities of freezing episodes beyond the gait network. Following the hypothesis of an effector-independent spatiotemporal deficit leading up to motor blocks, we expected to observe specific similarities between FOG and upper limb freezing, namely that: (1) small-amplitude conditions would provoke freezing episodes during upper limb motion, as they do in FOG[19]; (2) the severity of FOG and freezing during finger movements would be highly correlated; (3) a gradual decrease in movement amplitude and increase in frequency would be precursors of freezing during upper limb motion (FO-UL); and (4) similar timing abnormalities would exist during FO-UL and FOG.

Materials and Methods

Participants

Twenty-three PD patients were recruited from the University Hospital Leuven. A score ≥ 1 on the revised FOG Questionnaire (FOGQ[30]) classified a patient as a freezer ($n = 11$). Freezers and non-freezers ($n = 12$) were matched for age, sex, and disease severity (Hoehn and Yahr[31] stage II or III). Eleven age-matched controls also participated but these results are not reported in this work. Exclusion criteria were as follows: (1) neurological disease other than PD; (2) having a deep brain stimulator; (3) suffering from significant upper limb tremor interfering with movement; and (4) Mini Mental State Examination (MMSE) <24/30. Ethics approval was received by the Commissie Medische Ethiek K.U. Leuven.

Design and Procedure

Clinical screening took place while patients were *on* medication and included the Unified Parkinson's Disease Rating Scale (UPDRS[32]), FOGQ, MMSE, Hoehn and Yahr staging, and the cognitive section of the Scales for Outcomes in PD (SCOPA-COG[33]). Testing occurred while *off* medication; ie, after withholding anti-parkinsonian medications for at least 12 hours. On this day, UPDRS motor examination was repeated (UPDRS-*off*). Subjects performed 2 tasks entailing repetitive movement of the upper limbs (Task 1) and lower limbs (Task 2). Our main focus was on Task 1: a bimanual task of rhythmic flexion and extension movement of the index fingers in a $2 \times 2 \times 2$ factorial design with manipulations in coordination pattern, amplitude, and frequency. Subjects performed simultaneous or alternating movements, requiring in- or anti-phase coordination. Before testing, a single anti-phase trial served to compute subject-specific comfortable amplitude and frequency. During testing, large-amplitude (comfortable = 100%) or small-amplitude movements (66%) were required. Movement frequency was normal (comfortable = 100%) or fast (133%). Task order was randomized. Auditory pacing guided the first 6 movement cycles to enable correct frequency manipulations, after which the rhythm was to be maintained for 25 seconds. A square box covering both hands prevented visual feedback. Angular finger displacements were registered by a Micro 1401 acquisition unit (Cambridge Electronic Design Limited [CED], Cambridge, UK) through analog encoders placed on the rotation axis of the fingers. Temporal and spatial resolutions were 2000 Hz and 0.0001 degrees. Subjects were given sufficient time to familiarize themselves with task requirements and achieve automaticity of movement. Task 2 was an exploratory study of alternating foot movements. Participants performed 3 trials of foot movements at a comfortable frequency and amplitude while lying supine. Each trial lasted 30 seconds. Foot movements were not registered but clinically screened for the occurrence of freezing episodes (see Data Processing).

Data Processing

Regarding Task 1, we defined FO-UL episodes as "a period of involuntary stop or clear absence of effective cyclic movements."[2] Thus, both periods with a complete halt as well as severely disrupted motion with a nearly complete loss of movement were classified as freezing episodes. We visually determined the beginning of an FO-UL episode as the onset of abnormally small motion cycles (<50% of initial amplitude) accompanied by an irregular cycle frequency,[15] as illustrated in Figure 1. The end of the freezing episode was defined by the moment when at least 2 movement cycles with regular amplitude and rhythm were resumed or by the finish of the trial when regular movement was not regained. The minimal duration of a freezing episode was set at 75% of normal cycle duration to avoid misclassification of disruptions due to

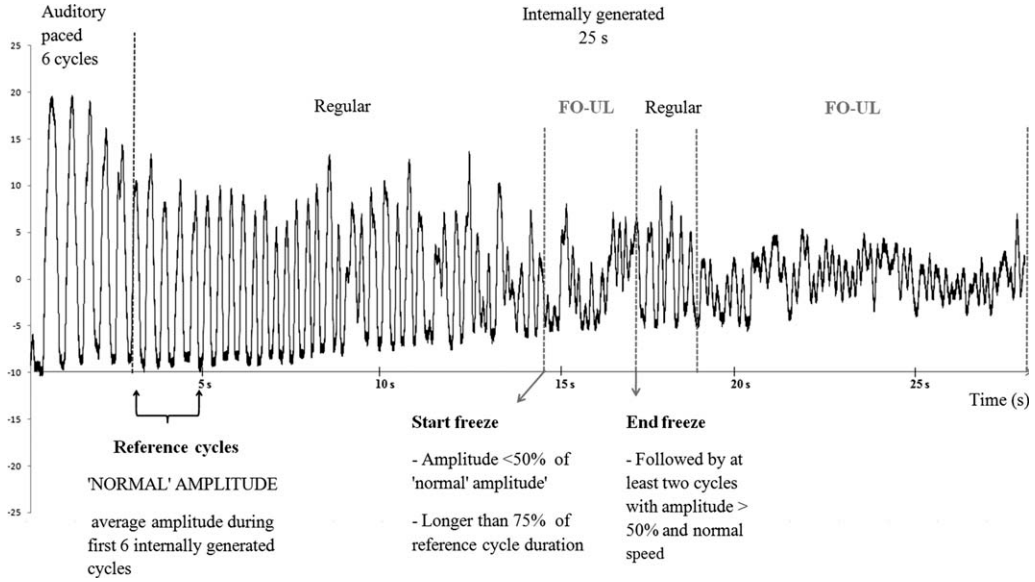

FIG. 1. Definition of upper limb freezing. Example of an upper-limb freezing episode FO-UL with a nearly complete loss of movement. Data of the right finger is shown and retrieved from a trial in which alternating movements with a comfortable amplitude and fast frequency were requested. Data of the left finger is not shown to increase visibility of the freezing episode and detection method. Based on spatial and temporal criteria, the time series is divided into regular motion and freezing episodes. **A**: The first 6 cycles after auditory pacing was removed, which served as reference cycles for the computation of the normal (ie, average) amplitude and normal (ie, average) cycle duration for the given trial. **B**: The onset of the freezing episode was set when a reduction of amplitude above 50% of the normal amplitude lasted longer than 75% of the normal cycle duration. **C**: The freezing episode was considered as ended when at least 2 normal cycles were performed. These 2 normal cycles were included in the regular motion following the freezing episode.

pattern switches. Two independent observers demarcated the FO-UL episodes on the basis of visual analysis of the movement signal using Spike 2 software (CED, Cambridge, UK) in which the exact cycle amplitude and cycle duration could be obtained using a cursor. Each trial was also classified a ''freezing trial'' or a ''no-freezing trial.'' Reproducibility of this detection method was established by a reliability study (intraclass correlation coefficient [ICC] (2,4) = 0.99).

Movement amplitude and cycling frequency were determined for each movement cycle using the difference in angular values of local maxima and minima (amplitude) and by taking the inverse of the time that elapses between successive peak positions (frequency). Linear regression coefficients (slopes, β) were computed to describe their change with time. In freezing trials, β calculation included at least 6 movement cycles preceding the FO-UL-episode or the tremor.[19] For each trial, scatter plots were used to check the distribution of amplitude and frequency data points of the left and right finger separately. Outlying data points that would distort the β calculation were removed from the data set (eg, an unusually large amplitude at the beginning of the trial). Spectral analyses were performed on movement data lasting ≥1 seconds (2000 data points). A freezing index (FI) was defined as the power in the freeze band (3–8 Hz) divided by the power in the normal motion band (0.5–3 Hz)[18] (see Supplement 1A for details).

We also performed spectral analyses of knee displacements during normal gait and FOG episodes in 1 freezer. This patient was tested while *off* medication 3 months later as part of another study[7] (see Supplement 1B).

In Task 2, freezing during lower limb movements (FO-LL) included periods with a clean arrest and a nearly complete loss of movement, similar to FO-UL. Foot movements were not registered but 2 independent raters scored each trial as with or without FO-LL based on online observation.

Statistical Analysis

For all statistical testing, we used STATISTICA (8.0; StatSoft, Inc.) with significance levels of .05. Group comparisons on the normal trials are not reported in this manuscript. In case of abnormality or a discrete nature of the outcome variable, nonparametric statistics were used.

Clinical variables were compared between groups using 1-way analysis of variance (ANOVA) (disease duration, UPDRS-III scores, levodopa-equivalent dose, comfortable speed), nonparametric Mann-Whitney *U* test (age, MMSE, SCOPA-COG, Hoehn and Yahr stage, and FOGQ), and logistic regression test (gender).

The occurrence of freezing episodes was compared between freezers and non-freezers by means of a Mann-Whitney *U* test and between the 2 levels of pattern (in-phase, anti-phase), amplitude (normal, small), and speed (normal, fast) using a generalized estimating equation (GEE) logistic regression that accounts for

TABLE 1. Demographic and disease characteristics of participants

Parameter	Non-freezers	Freezers	*P*
Age (years)[a]	70 (64–72)	69 (65–72)	.92
Disease duration (years)[b]	7 (6–9)	9 (6–11)	.43
Sex (M/F)[c]	9/2	10/2	.82
UPDRS-III *on* (0–108)[b]	36 (32–44)	31 (27–49)	.97
UPDRS-III *off* (0–108)[b]	35 (28–37)	38 (28–42)	.54
H&Y *off* (0–5)[d]	II (II–III)	III (II–III)	.32
FOGQ (0–28)[d]	0 (0–0)	9 (8–16)	<.01*
MMSE (24–30)[a]	30 (28–30)	28 (27–28)	<.01*
SCOPA-COG (0–43)[a]	31 (28–33)	29 (25–31)	.29
Levodopa-dose (mg)[b]	510 (413–626)	600 (468–708)	.54
Comfortable speed (Hz)[b]	1.13 (0.80–1.37)	1.31 (0.90–1.70)	.28

Demographic and clinical characteristics of 12 non-freezers, 11 freezers, and 11 control subjects (median and interquartile ranges).
[a]Nonparametric Kruskal-Wallis test was used.
[b]One-way ANOVA was used.
[c]Logistic regression was used.
[d]Nonparametric Mann-Whitney *U* test was used.
*Groups significantly different at $P < .05$.
UPDRS-III, Unified Parkinson's Disease Rating Scale part III; H&Y, Hoehn & Yahr stage; FOGQ, Freezing of Gait Questionnaire; MMSE, Mini Mental State Examination; SCOPA-COG, Scales for Outcomes in Parkinson's Disease–Cognitive part; *on*, while on medication; *off*, while off medication; ANOVA, analysis of variance.

clustered observations and binary outcomes (trial without FO-UL = 0, with FO-UL = 1).[34]

Nonparametric Spearman correlation tests (r_s) were applied to relate severity of FOG (measured by the FOGQ), FO-UL, FO-LL, and clinical outcomes within patients with FOG and/or FO-UL.

Amplitude and frequency regression coefficients (β values) of regular movement, not followed by FO-UL, were compared with β values of regular motion preceding an FO-UL episode, using nonparametric repeated-measures Friedman test within patients who presented FO-UL. Differences in FI between normal motion and freezing episodes were analyzed within patients with FO-UL by Friedman tests.

Significant effects were further analyzed by post hoc tests yielding *P* values that were corrected for multiple comparisons. Results are presented as mean and standard error of the mean (SEM).

Results

Subjects

Age, gender distribution, and comfortable movement speed were similar between groups (Table 1). Freezers and non-freezers had comparable disease profiles. SCOPA-COG scores did not differ between freezers and non-freezers. Freezers' scores on the MMSE were lower than non-freezers but fell well within normal reference values.[35]

Occurrence of Freezing Episodes

Nine freezers (82%) and 2 non-freezers (17%) ($P = .001$) demonstrated FO-UL. FO-LL was also more frequent in freezers (n = 8; 73%) than in non-freezers (n = 0) ($P = .002$). Similar to FOG,[4] duration of FO-UL episodes (total number = 114) was quite variable, ranging from 0.34 to 23.3 seconds, and 5.98 seconds on average.

Within a trial, FO-UL could be present bilaterally (31%) or unilaterally (69%). Unilateral FO-UL occurred more often on the disease-dominant (45 FO-UL trials, 75%) than the nondominant body side (n = 15; 25%) ($P = .0002$). The number of freezing trials was highest in the most complex condition (n = 15; 17%), entailing alternating, fast and small-amplitude movements, and lowest in the condition requiring simultaneous, slow and large-amplitude movements (n = 6; 7%). Using the GEE model, we found no difference in FO-UL frequency between in-phase and anti-phase ($P = .23$) and between normal and high-frequency conditions ($P = .47$). A trend for significance was found for the triggering effect of small versus large-amplitude conditions (50 vs 37 freezing trials; $P = .081$) (Fig. 2).

Correlation Between FO-UL, FOG, FO-LL, and Clinical Outcomes

Within patients with FOG and/or FO-UL, the FOGQ score significantly predicted the number of FO-UL trials ($r_s = 0.56$, $P < .05$) and the number of FO-LL trials ($r_s = 0.59$, $P < .05$). The FOGQ was also significantly correlated with the duration of FO-UL episodes within patients who presented FO-UL during testing ($r_s = 0.64$, $P < .05$) (Fig. 3). In contrast, FO-UL and FO-LL were not explained by PD severity (Table 2) and cognitive scores. Last, the number of

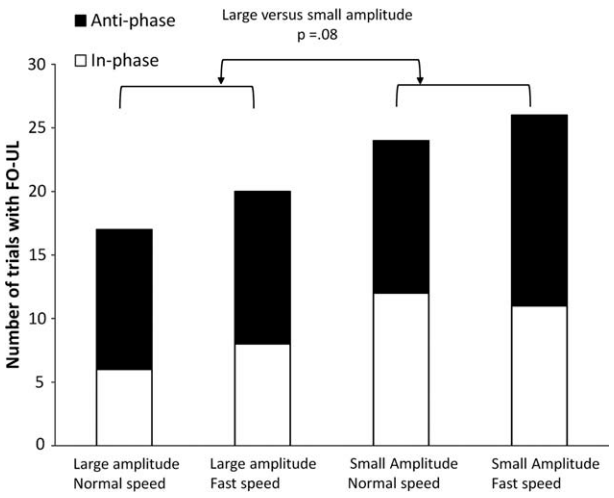

FIG. 2. The effect of manipulations in movement frequency, amplitude, and coordination pattern on the occurrence of upper-limb freezing episodes. Frequency of FO-UL in each movement condition. Most freezing episodes were elicited in the most complex movement condition; ie, small and fast movements in an anti-phase pattern. Small-amplitude conditions tended to provoke more freezing episodes compared to large amplitude conditions ($P = .08$).

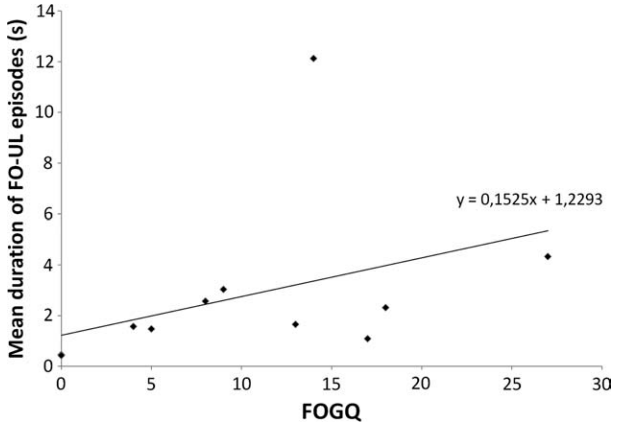

FIG. 3. Relation between severity of upper limb freezing (FO-UL) and FOG within 11 patients who demonstrated FO-UL during testing; ie, 9 freezers and 2 non-freezers. Spearman rank correlation (r_s) = 0.64, $P < .05$. Solid line represents a linear trend. (As data points of the 2 non-freezers are very similar (x = 0, y = 0.48; and x = 0, y = 0.43) they are collated on the figure).

FO-UL and FO-LL trials were highly intercorrelated ($r_s = 0.80$, $P < .05$).

Spatiotemporal Characteristics of Upper Limb Freezing Episodes

To evaluate the change in amplitude and frequency prior to a freezing episode, we compared the mean amplitude and frequency regression slopes of normal motion not followed by a freezing episode with the mean slopes of movement before FO-UL took place in 11 patients who presented FO-UL. In case of similar behavior of the left and right finger (both normal or both freezing), slopes were averaged for both body sides. In case of unilateral freezing, the slope of the freezing hand was entered in the category of "motion preceding freezing" whereas the slope of the non-freezing hand was added to the "motion not followed by freezing" category. For each subject, the average amplitude and frequency slope was computed for both categories. Amplitude β values were more negative during motion preceding a freezing episode (mean β = −0.23; SEM = 0.07) than in motion not followed by freezing (mean β = −0.12; SEM = 0.04; $P = .035$). Conversely, frequency β values were larger when preceding a freezing episode (mean β = 0.016; SEM = 0.007) than when motion was not followed by FO-UL (mean β = 0.0093; SEM = 0.006; $P = .034$). These findings indicate a strong amplitude decline and frequency increase prior to the freezing episode (Figs. 4 and 5). In fact, 71% of FO-UL episodes were preceded by frequencies above 2 Hz.

Ninety-three FO-UL episodes lasting longer than 1 second (82%) and 12 FOG episodes (retrieved from gait data of 1 freezer) were included for spectral analyses. Unlike regular finger movement and normal gait (Fig. 6A), the power distribution of freezing episodes during both upper limb movement and gait was blurred, including local maxima within the "freeze band" (3–8 Hz) (Fig. 6B). Freezing indices were significantly higher for FOG episodes than normal gait (FI = 1.26; SEM = 0.2 and 0.24; SEM = 0.04; $P < .001$). Similarly, FI values were higher during FO-UL episodes indicating a relative increase in high frequency components compared to regular finger motion (FI = 2.23; SEM = 0.16 vs 0.8; SEM = 0.008; $P < .01$).

TABLE 2. Spearman correlations between severity of freezing in different effectors and disease severity

	FO-UL number of freezing trials	FO-LL number of freezing trials
FOGQ (0–28)	0.56*	0.59*
FO-LL number of freezing trials (0–3)	–	0.80*
UPDRS-III *off* (0–108)	0.18	0.0047
H&Y *off* (0–5)	0.25	0.37
Disease duration (years)	−0.013	0.038

Spearman correlations between severity of freezing in different effectors (FOG, FO-UL, and FO-LL) and disease severity in 10 patients with FO-UL (8 freezers and 2 non-freezers).
*$P < .05$.
FO-UL, freezing of upper limb movement; FO-LL, freezing of lower limb movement; FOGQ, Freezing of Gait Questionnaire; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; H&Y, Hoehn & Yahr stage; *off*, while off medication; FOG, freezing of gait.

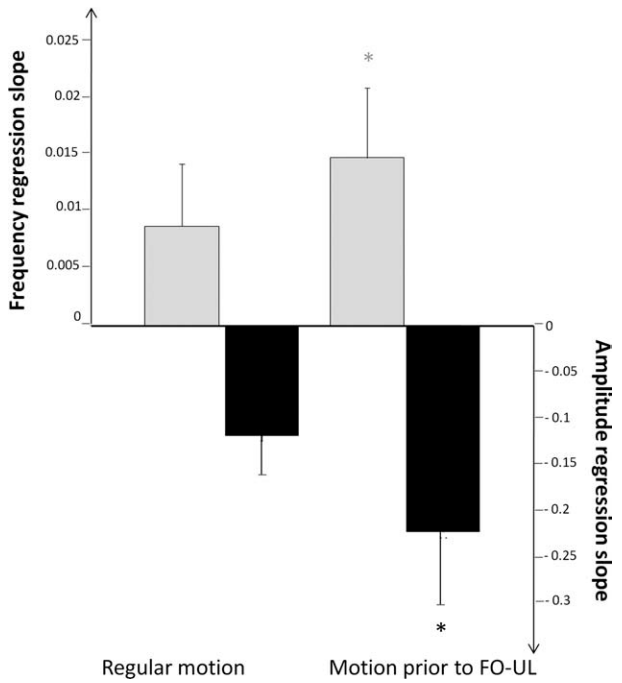

FIG. 4. Frequency and amplitude regression slopes in regular motion not followed by FO-UL and in motion preceding an FO-UL episode. Regression slopes of cycle-by-cycle frequency (upper part) and amplitude (lower part) in patients with FO-UL. Movement was scaled down more dramatically prior to an upper-limb freezing episode (more negative amplitude slope) than in normal motion not followed by FO-UL ("regular motion"). In contrast, movement was more hastened before FO-UL (larger frequency slope) compared to normal motion. (Data are represented by average slopes and standard error of measurements; *$P < .05$).

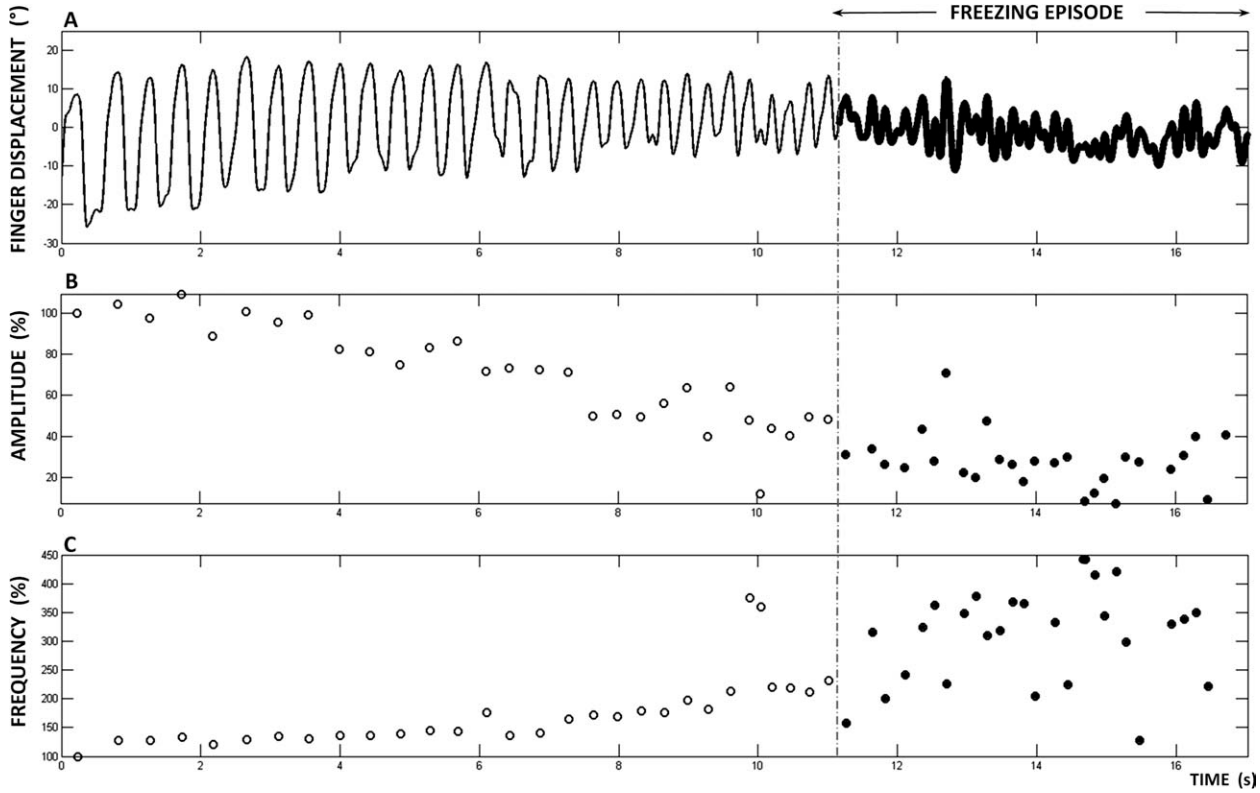

FIG. 5. Illustration of amplitude and frequency alterations preceding and during an upper limb freezing episode (FO-UL). **A**: This panel shows the angular displacement of the left index finger of a single subject while performing anti-phase movements with comfortable amplitude and frequency. The red dotted line indicates the beginning of the freezing episode. **B**: Movement amplitude is gradually reduced preceding the freezing episode. **C**: Movement frequency shows a progressive increase prior to FO-UL and is markedly variable (chaotic) during the episode. Amplitude and frequency are expressed as a percentage of the values obtained during the first movement cycle. Data from the first 17 seconds of the trial is shown. Normal movement was regained after the freezing episode but is not shown to aid clarity.

Discussion

Our results support the hypothesis that a generic motor control problem underlies FOG. This effector-independent deficit interferes with amplitude and timing regulation during repetitive movement leading up to freezing events during upper- as well as lower-limb motion. First, imposing small amplitudes during bimanual finger movements increased the tendency of freezing. This is congruent with the results of Chee et al.,[19] who showed a strong association between reduced stride length and the occurrence of FOG. Second, the number and duration of upper- and lower-limb freezing episodes were related to FOG severity, not to disease severity or cognitive outcomes. Third, FO-UL episodes were preceded by a strong amplitude decrease and hastened movements. Fourth, FO-UL was characterized by high-frequency components just like FOG.

FO-UL occurred more frequently in the present internally generated finger movement task without vision than in a hand drawing task, which was guided by vision.[28] Also, FO-UL was only observed in the absence of the initial auditory pacing. Interestingly, 1 of the 2 non-freezers who experienced FO-UL developed FOG a few months later. Possibly, this patient already had mild FOG symptoms at the time of testing pointing to the problems of distinguishing freezers from non-freezers using a questionnaire methodology.[28] Alternatively, FO-UL could be a precursor for the future development of FOG. Freezing as a generic deficit may be topographically distributed, reaching either upper or lower limbs first, dependent on disease progression. This could also explain why 2 patients did not show FO-UL but did have FOG. It appears that the true nature of freezing is not as "clear cut" as currently considered in clinical practice and research, but is better reflected by a continuous spectrum of abnormality with possibly a more gradual onset and affecting different body parts.[36]

Unilateral Upper Limb Freezing

Another novel finding was that, contrary to FOG, which is typically seen as a bilateral event, FO-UL sometimes emerged unilaterally while the contralateral limb kept moving regularly. FO-UL was not related to global disease severity but occurred more frequently in the disease-dominant hand, consistent with the fact that during gait the first leg to enter a freezing state is usually the one at the disease-dominant side.[22] A unilateral onset and/or manifestation of FOG and FO-UL suggest that freezing originates from difficulties with

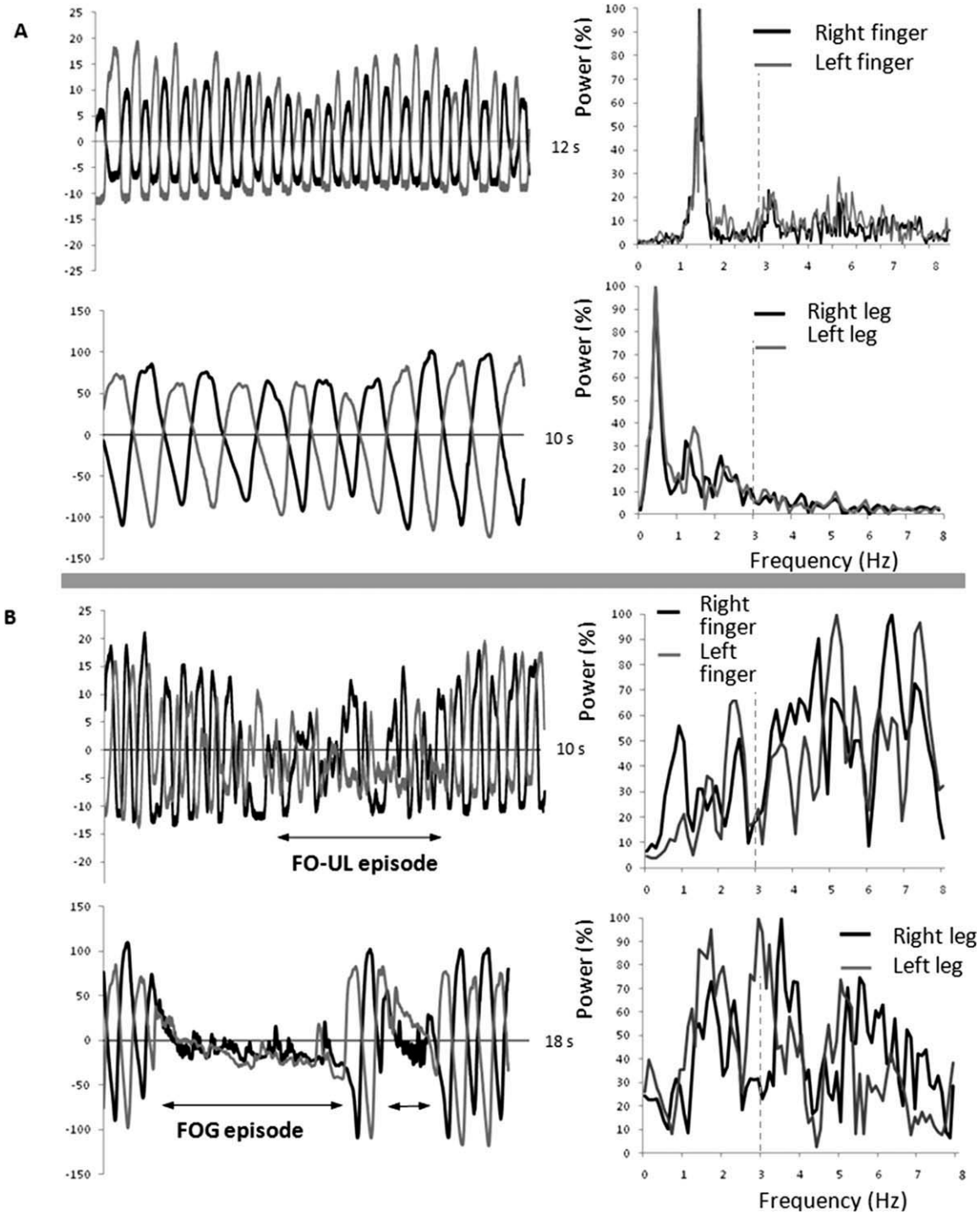

FIG. 6. Spectral analysis of gait (normal and freezing) and upper-limb motion (normal and freezing). **A**: Trials without freezing episodes during upper-limb motion (upper row) and gait (lower row). A clear peak in the power spectrum (right side) represents the main movement frequency within the normal motion band (0.5–3 Hz, left of vertical dashed line). **B**: Trials with freezing episodes during upper limb motion (upper row) and gait (lower row). Both types of freezing are characterized by a blurred energy distribution with increased energy in the freeze band (3–8Hz, right of vertical dashed line).

within-limb spatiotemporal processing rather than from between-limb motor deficit. A pilot study by our group (unpublished data) also demonstrated that UL freezing could be elicited in single-limb finger tapping. The within-limb spatiotemporal deficit may be aggravated by bilateral coordination complexity, although freezing did not occur more often during alternating than simultaneous movements. Future studies on single (upper) limb movements might provide further insights on the relative contribution of bimanual coordination complexity to spatiotemporal impairments in the freezing problem.

Motor Triggers of Freezing

Contrary to the notorious difficulty to provoke FOG in laboratory settings, internally generated upper limb motion seems quite successful in triggering FO-UL. We found the highest number of FO-UL episodes in the most complex condition. However, there was only a trend toward significance when manipulations in frequency, amplitude, and coordination pattern were tested separately, probably due to limited statistical power. Almeida et al.[27] reported significantly more "freezing" during anti-phase compared to in-phase movements. Unlike in the present study, these authors did not control for pattern corrections, which are more likely to occur when coordination complexity increases.[37]

Small-amplitude finger movements tended to increase the number of freezing trials and amplitude decreased dramatically during movement preceding a freezing episode. This is consistent with earlier findings that a reduced stride length mediates the occurrence of FOG episodes,[19] which was interpreted as a basal ganglia deficit compromising appropriate feedforward signaling to cortical motor preparation areas.[17,38,39]

FO-UL episodes were preceded by a gradual increase in cycle frequency (higher frequency slopes), although this was not confirmed by more FO-UL episodes during fast than normal speed conditions. Stegemöller et al.[40] showed that a nearly complete loss of movement during metronome paced finger movement was triggered by frequencies above 2 Hz. These rate-dependent movement disruptions occurred in PD patients without a documented history of FOG. Our data do not support the idea that exceeding a critical movement rate elicits motor impairments independent of freezing. In our study, comfortable and imposed movement frequencies were similar in freezers and non-freezers, and still movement disruptions were rare in non-freezers. We found that 71% of FO-UL episodes were preceded by frequencies above 2 Hz. This means that internally generated repetitive movement becomes hastened in freezers, but not in non-freezers and resembles the increased stepping frequency that often precedes FOG.[15,41–43]

FOG is known to occur in situations which pose environmental negotiation and demand elevated attention supporting a possible frontal executive hypothesis for FOG.[12,13] However, in this study FO-UL was triggered without additional cognitive, limbic, or postural load, suggesting a primary deficit in sequential movement generation. We consciously employed a bimanual task paradigm because it better resembled the inter-leg coordination during gait. Finger movements may be less automated than gait but the spatiotemporal coupling between the fingers is considered part of a natural coordination repertoire.[37] Similarly to walking, the fingers become integrated into a common "motor gestalt" and can be performed effortlessly.[37,44] Attentional resources may have been invested by non-comfortable amplitude or frequency constraints but these should not interfere with the actual motor program. Anyhow, cognitive parameters were decreased but not abnormal in freezers in this study. Freezers scored less in the memory domain (MMSE) than non-freezers, but the SCOPA-COG, which is more sensitive to attention and executive functions, showed no significant differences between the subgroups. More importantly, cognitive functioning was not correlated to any of the freezing outcomes, emphasizing that freezing is most likely a motor deficit even though it might be aggravated by non-motor triggers.

High-Frequency Components During Freezing

High-frequency components are common characteristics of FOG episodes.[4,15,16,21] A novel finding of this study was that trembling-like movements during upper limb freezing were very similar to gait freezing.[18,21,45] As in FOG, the broadband spectral distribution during FO-UL included multiple local maxima in frequency bands above 3 Hz.[18,21] In gait, these temporal changes have been linked to multiple anticipatory adjustments[8] or to attempts to overcome the motor block.[4] However, the complexity of the energy spectrum during FOG and FO-UL proposes multiple oscillatory inputs to the legs and fingers[16,21] rather than a compensatory phenomenon. In relation to FOG, the disturbed signaling is thought to be driven by misfiring central pattern generators (CPGs).[16,21] These spinal motor neurons remain silent during rest due to tonic inhibition from the basal ganglia to brainstem motor regions.[46,47] The high depolarization threshold in synapses of basal ganglia nuclei is crucial for the selective facilitation of movement.[47] Faulty facilitation may hamper the cortico-subcortical top down movement pathways or affect pathways from the mesencephalic locomotor region.[48,49] This in turn can hinder fine-tuned orchestration of limb-specific CPGs resulting in misfiring oscillations and uncontrolled trembling during FOG and FO-UL. Understanding the significance of these abnormal phenomena may be crucial for the development of novel treatment targets for FOG.

Assessment of Freezing in PD

A consensus on how to identify freezing episodes is presently lacking (see Supplement 2). We included as freezing episodes periods with a severely disrupted motion and a nearly but not complete loss of movement. The spatial and temporal criteria used in this study ensured an objective and reproducible detection method, which was investigator independent. A fully objective identification can only be reached using automated software. Spectral analyses seem promising

to identify freezing episodes using a specific threshold of the freezing index, possibly defined separately for each subject.[18,21] A similar technique can be considered to detect FO-UL episodes, although delineation of "normal" and "freezing" frequency bands might need to be adjusted when detecting non-gait freezing. For the purpose of this study, foot movements were studied in an exploratory way. Although interrater agreement of FO-LL detection was sufficient, we acknowledge that future registration of these signals also might provide valuable information with regard to scaling and timing difficulties in these movements. Complete akinesia and initiation difficulties were not observed during finger movements. These types of freezing might be more under intentional control and more dramatically observed in gait due to postural constraints. It is also possible that the hypothesized underlying mechanism of impaired amplitude-rhythm control is restricted to movement breakdown preceding and during freezing of ongoing motion.

Conclusions

This study demonstrated that hastened movement and a dramatic breakdown in movement amplitude constituted a prelude to freezing episodes during rhythmic upper limb motion which were highly correlated with FOG and exhibited highly similar motor changes. The results suggest that freezing can be conceptualized as primarily originating from impaired timing-amplitude control which is not restricted to the gait network but possibly represents a generic motor control problem.

Legend to Video

Video 1: A short fragment of a Parkinson patient (freezer) performing the bilateral upper limb task in a simplified experimental setting (measuring equipment not shown). The freezing episode starts at 6 seconds and is characterized by small-amplitude and high-frequency movements that resemble the trembling-like leg movements described for FOG. Between 6 seconds and 10 seconds nearly-normal movement cycles or half movement cycles still occur. After 10 seconds both fingers are clearly "stuck" in uncontrolled dysrhythmic behavior. In this example, the patient is not able to regain regular movement before the end of the video. ■

Acknowledgments: We are grateful to all participants for their time and patience during testing. We thank our statistician Steffen Fieuws for his valuable advice. Wim Vandenberghe is a Senior Clinical Investigator of the Research Foundation Flanders (FWO).

References

1. Giladi N, Treves TA, Simon ES, et al. Freezing of gait in patients with advanced Parkinson's disease. J Neural Transm 2001;108: 53–61.
2. Giladi N, Nieuwboer A. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. Mov Disord 2008;23(Suppl 2):423–425.
3. Kerr GK, Worringham CJ, Cole MH, Lacherez PF, Wood JM, Silburn PA. Predictors of future falls in Parkinson disease. Neurology 2010;75:116–124.
4. Schaafsma JD, Balash Y, Gurevich T, Bartels AL, Hausdorff JM, Giladi N. Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease. Eur J Neurol 2003;10:391–398.
5. Ferraye MU, Debû B, Fraix V, et al. Effects of subthalamic nucleus stimulation and levodopa on freezing of gait in Parkinson disease. Neurology 2008;70:1431–1437.
6. Fasano A, Herzog J, Seifert E, et al. Modulation of gait coordination by subthalamic stimulation improves freezing of gait. Mov Disord 2011;26:844–851.
7. Spildooren J, Vercruysse S, Desloovere K, Vandenberghe W, Kerckhofs E, Nieuwboer A. Freezing in Parkinson's disease: the impact of dual-tasking and turning. Mov Disord 2010;25:2563–2570.
8. Jacobs JV, Nutt JG, Carlson-Kuhta P, Stephens M, Horak FB. Knee trembling during freezing of gait represents multiple anticipatory postural adjustments. Exp Neurol 2009;215:334–341.
9. Snijders AH, Weerdesteyn V, Hagen YJ, Duysens J, Giladi N, Bloem BR. Obstacle avoidance to elicit freezing of gait during treadmill walking. Mov Disord 2010;25:57–63.
10. Almeida QJ, Lebold CA. Freezing of gait in Parkinson's disease: a perceptual cause for a motor impairment? J Neurol Neurosurg Psychiatry 2010;81:513–518.
11. Cowie D, Limousin P, Peters A, Day B. Insights into the neural control of locomotion from walking through doorways in Parkinson's disease. Neuropsychologia 2010;47:2750–2757.
12. Amboni M, Cozzolino A, Longo K, Picillo M, Barone P. Freezing of gait and executive functions in patients with Parkinson's disease. Mov Disord 2008;23:395–400.
13. Naismith SL, Shine JM, Lewis SJ. The specific contributions of set-shifting to freezing of gait in Parkinson's disease. Mov Disord 2010;25:1000–1004.
14. Giladi N, Hausdorff JM. The role of mental function in the pathogenesis of freezing of gait in Parkinson's disease. J Neurol Sci 2006;248:173–176.
15. Nieuwboer A, Dom R, De Weerdt W, Desloovere K, Fieuws S, Broens-Kaucsik E. Abnormalities of the spatiotemporal characteristics of gait at the onset of freezing in Parkinson's disease. Mov Disord 2001;16:1066–1075.
16. Bloem BR, Hausdorff JM, Visser JE, Giladi N. Falls and freezing of gait in Parkinson's disease: a review of two interconnected, episodic phenomena. Mov Disord 2004;19:871–884.
17. Iansek R, Huxham F, McGinley J. The sequence effect and gait festination in Parkinson disease: contributors to freezing of gait? Mov Disord 2006;21:1419–1424.
18. Moore ST, MacDougall HG, Ondo WG. Ambulatory monitoring of freezing of gait in Parkinson's disease. J Neurosci Methods 2008;167:340–348.
19. Chee R, Murphy A, Danoudis M, Georgiou-Karistianis N, Iansek R. Gait freezing in Parkinson's disease and the stride length sequence effect interaction. Brain 2009;132:2151–2160.
20. Plotnik M, Giladi N, Balash Y, Peretz C, Hausdorff JM. Is freezing of gait in Parkinson's disease related to asymmetric motor function? Ann Neurol 2005;57:656–663.
21. Hausdorff JM, Schaafsma JD, Balash Y, Bartels AL, Gurevich T, Giladi N. Impaired regulation of stride variability in Parkinson's disease subjects with freezing of gait. Exp Brain Res 2003;149: 187–194.
22. Nieuwboer A, Chavret F, Willems AM, Desloovere K. Does freezing in Parkinson's disease change limb coordination? A kinematic analysis. J Neurol 2007;254:1268–1277.
23. Plotnik M, Giladi N, Hausdorff JM. Bilateral coordination of walking and freezing of gait in Parkinson's disease. Eur J Neurosci 2008;27:1999–2006.
24. Moreau C, Ozsancak C, Blatt JL, Derambure P, Destee A, Defebvre L. Oral festination in Parkinson's disease: biomechanical analysis and correlation with festination and freezing of gait. Mov Disord 2007;22:1503–1506.

25. Fahn S. The freezing phenomenon in parkinsonism. Adv Neurol 1995;67:53–63.
26. Ziv I, Avraham M, Dabby R, Zoldan J, Djaldetti R, Melamed E. Early-occurrence of manual motor blocks in Parkinson's disease: a quantitative assessment. Acta Neurol Scand 1999;99:106–111.
27. Almeida QJ, Wishart LR, Lee TD. Bimanual coordination deficits with Parkinson's disease: the influence of movement speed and external cueing. Mov Disord 2002;17:30–37.
28. Nieuwboer A, Vercruysse S, Feys P, Levin O, Spildooren J, Swinnen S. Upper limb movement interruptions are correlated to freezing of gait in Parkinson's disease. Eur J Neurosci 2009;29: 1422–1430.
29. Goetz CG. Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS): a new scale for the evaluation of Parkinson's disease. Rev Neurol 2010;166:1–4.
30. Nieuwboer A, Rochester L, Herman T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. Gait Posture 2009;30: 459–463.
31. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.
32. Fahn S, Elton RL, UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, editors. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan; 1987:153–163.
33. Marinus J, Visser M, Verwey N, et al. Assessment of cognition in Parkinson's disease. Neurology 2003;61:1222–1228.
34. Liang K-Y, Zeger S. Longitudinal data analysis using generalized estimating equations. Biometrika 1986;73:13–22.
35. Verbaan D, Marinus J, Visser M, et al. Cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 2007;78:1182–1187.
36. Snijders AH, Nijkrake MJ, Bakker M, Munneke M, Wind C, Bloem BR. Clinimetrics of freezing of gait. Mov Disord 2008;23: 468–474.
37. Kelso JA. Phase transitions and critical behavior in human bimanual coordination. Am J Physiol 1984;246:R1000–R1004.
38. Bartels AL, Leenders KL. Brain imaging in patients with freezing of gait. Mov Disord 2008;23(Suppl 2):461–467.
39. Morris ME, Iansek R, Galna B. Gait festination and freezing in Parkinson's disease: pathogenesis and rehabilitation. Mov Disord 2008;23(Suppl 2):451–460.
40. Stegemöller EL, Simuni T, MacKinnon C. Effect of movement frequency on repetitive finger movements in patients with Parkinson's disease. Mov Disord 2009;24:1162–1169.
41. Giladi N, Shabtai H, Rozenberg E, Shabtai E. Gait festination in Parkinson's disease. Parkinsonism Relat Disord 2001;7:135–138.
42. Okuma Y, Yanagisawa N. The clinical spectrum of freezing of gait in Parkinson's disease. Mov Disord 2008;23(Suppl 2):S426–S430.
43. Browner N, Giladi N. What can we learn from freezing of gait in Parkinson's disease? Curr Neurol Neurosci Rep 2010;10:345–351.
44. Swinnen S, Wenderoth N. Two hands, one brain: cognitive neuroscience of bimanual skill. Trends Cogn Sci 2004;8:18–25.
45. Delval A, Snijders AH, Weerdesteyn V, et al. Objective detection of subtle freezing of gait episodes in Parkinson's disease. Mov Disord 2010;25:1684–1693.
46. Knikou M. Neural control of locomotion and training-induced plasticity after spinal and cerebral lesions. Clin Neurophysiol 2010;121:1655–1668.
47. Grillner S, Hellgren J, Ménard A, Saitoh K, Wikström MA. Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. Trends Neurosci 2005;28:364–370.
48. Karachi C, Grabli D, Bernard FA, et al. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson's disease. J Clin Invest 2010;120:2745–2755.
49. Snijders A, Leunissen I, Bakker M, et al. Gait-related cerebral alterations in Parkinson patients with freezing of gait. Brain 2010; 134:59–72.