The Neural Correlates of Upper Limb Motor Blocks in Parkinson’s Disease and Their Relation to Freezing of Gait

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Due to basal ganglia dysfunction, bimanual motor performance in Parkinson patients reportedly relies on compensatory brain activation in premotor–parietal–cerebellar circuits. A subgroup of Parkinson’s disease (PD) patients with freezing of gait (FOG) may exhibit greater bimanual impairments up to the point that motor blocks occur. This study investigated the neural mechanisms of upper limb motor blocks and explored their relation with FOG. Brain activation was measured using functional magnetic resonance imaging during bilateral finger movements in 16 PD with FOG, 16 without FOG (PD + FOG and PD − FOG), and 16 controls. During successful movement, PD + FOG showed decreased activation in right dorsolateral prefrontal cortex (PFC), left dorsal premotor cortex (PMd), as well as left M1 and bilaterally increased activation in dorsal putamen, pallidum, as well as subthalamic nucleus compared with PD − FOG and controls. On the contrary, upper limb motor blocks were associated with increased activation in right M1, PMd, supplementary motor area, and left PFC compared with successful movement, whereas bilateral pallidum and putamen activity was decreased. Complex striatofrontal activation changes may be involved in the difficulties of PD + FOG to perform bimanual movements, or sequential movements in general. These novel results suggest that, whatever the exact underlying cause, PD + FOG seem to have reached a saturation point of normal neural compensation and respond belatedly to actual movement breakdown.

Keywords: bimanual coordination, fMRI, freezing of gait, motor blocks, neuroimaging, Parkinson’s disease, upper limb freezing

Introduction

In Parkinson’s disease (PD), dopaminergic depletion in the substantia nigra disturbs the basal ganglia–cortical circuits that drive motor and nonmotor behavior (Gale et al. 2008). Impairments in bimanual coordination are common in PD, especially when performing rapid and antiphase movements (Almeida et al. 2002; Van Gemmert et al. 2003; Ponsen et al. 2006). These difficulties have been related to hypoactivation in the basal ganglia and their main cortical projections (Sabatini et al. 2000; Buhmann et al. 2003; Wu and Hallett 2005; Yu et al. 2007; Jahanshahi et al. 2010; Wu et al. 2010). Proficient bimanual performance in PD was shown to rely on a compensatory switch from the deficient basal ganglia–frontal pathways to alternative circuitries involving premotor, parietal, and cerebellar regions (Sabatini et al. 2000; Buhmann et al. 2003; Wu and Hallett 2005; Yu et al. 2007; Jahanshahi et al. 2010; Wu et al. 2010).

It is currently unclear why a subgroup of PD patients, namely those who experience freezing of gait (FOG), have greater spatiotemporal abnormalities in bimanual control up to the point that actual motor blocks occur (Nieuwboer, Vercruysse, et al. 2009; Vercruysse, Spildooren, Heremans, et al. 2012; Vercruysse, Spildooren, Vandenberghe, et al. 2012). Motor blocks or “freezing episodes” may occur in repetitive upper (Nieuwboer, Vercruysse, et al. 2009; Vercruysse, Spildooren, Vandenberghe, et al. 2012) and lower limb movements (Nutt et al. 2011; Shine et al. 2012; Vercruysse, Spildooren, Vandenberghe, et al. 2012). They refer to involuntary episodes of movement breakdown during which effective cyclical movement is lacking (Giladi and Nieuwboer 2008). Regarding gait, FOG is described as if patients’ feet are suddenly glued to the floor and is associated with falls and injuries (Kerr et al. 2010). FOG is common in advanced PD, but does not affect all patients (Giladi et al. 2001). Cyclical alternating foot movements have been found to particularly provoke motor blocks in patients with FOG (Shine et al. 2012; Vercruysse, Spildooren, Vandenberghe, et al. 2012). As well, upper limb motor blocks have been reported in various repetitive tasks such as finger tapping, bimanual sliding and drawing movements, and functional activities such as writing, tooth brushing, and typing (Fahn 1995; Ziv et al. 1999; Almeida et al. 2002; Nieuwboer, Vercruysse, et al. 2009; Vercruysse, Devos, et al. 2012).

Upper limb motor blocks, hereafter called “upper limb freezing (FOUL),” mostly occur when the motor system is stressed, for example, by imposing small and fast finger movements, rather than by finger movements at comfortable pace and amplitude (Vercruysse, Spildooren, Vandenberghe, et al. 2012). Furthermore, these motor blocks are episodic, variable, and unpredictable phenomena. Their abnormal kinematic output signals clearly evidence timing amplitude dyscontrol (Vercruysse, Spildooren, Vandenberghe, et al. 2012). Importantly, scaling and timing difficulties persist during continuous bimanual movement generation in PD with FOG, that is, outside freezing episodes, as evidenced by more variable, asymmetric, and small-amplitude movement cycles (Nieuwboer, Vercruysse, et al. 2009; Vercruysse, Spildooren, Heremans, et al. 2012). These spatiotemporal difficulties outside freezing episodes relate well with the more pronounced abnormalities in step length and step timing in patients with FOG during ongoing gait (Hausdorff, Schaafsma, et al. 2003; Plotnik et al. 2005, 2008, 2012; Iansek et al. 2006; Nieuwboer et al. 2007).

The neural mechanisms of FOG and related freezing phenomena in PD are still unclear. Comparing subgroups of PD with and without FOG, anatomical and functional differences were found in the basal ganglia, fronto-parietal regions (Matsui et al. 2005; Bartels et al. 2006; Bartels and Leenders 2012). It is currently unclear why a subgroup of PD patients, namely those who experience freezing of gait (FOG), have greater spatiotemporal abnormalities in bimanual control up to...
with a deep brain stimulator or excessive rest tremor as determined by a neurologist were excluded. A group of 16 healthy age-matched subjects served as controls. None of the participants were diagnosed with a neurological disease other than PD or demonstrated signs of clinical dementia [Mini-Mental State Examination (MMSE) score >24]. Executive functioning assessed by the cognitive section of the Scales for Outcomes in PD—Cognitive part (SCOPA-COG; Marinus et al. 2003) and other clinical variables were similar across groups, except for the levodopa equivalent dose which was higher in freezers (Table 1). Participants gave informed consent consistent with the sixth version of the Declaration of Helsinki. Ethics approval was received by the local Medical Ethics Committee of the University Hospitals Leuven.

**Behavioral Task and Overall Protocol**

Subjects performed a bimanual task consisting of rhythmic flexion and extension movement of the index fingers, validated to elicit upper limb motor blocks (Vercruysse, Spildooren, Vandebossche, et al. 2012). Movement difficulty was manipulated by variation in naturally preferred coordination patterns (i.e. simultaneous in-phase and alternating antiphase coordination), movement amplitude (comfortable and small), and movement frequency (comfortable and fast). In the interest of comparable task difficulty across participants, amplitude and frequency requirements were expressed as a percentage of subject-specific preferred values. The design included 2 freezing-resistant and 2 freezing-provoking movement conditions that were chosen based on previous work (Vercruysse, Spildooren, Vandebossche, et al. 2012). Freezing-resistant conditions allowed comfortable amplitude movements at a comfortable frequency while the 2 index fingers were moved in-phase (Condition 1) or antiphase (Condition 2). Freezing-eliciting conditions required small-amplitude movements (i.e. 50% of comfortable amplitude) at high frequency (i.e. 133% of comfortable frequency) according to an in-phase (Condition 3) or antiphase coordination pattern (Condition 4). Movement conditions were presented in a random order and alternated with a rest condition using a block design. Each movement condition was prompted by a short instruction projected on the screen in the scanner at the end of the rest period. Subjects were given sufficient time (5 s) to prepare and were instructed to start moving when an auditory pacing signal started. Auditory pacing enabled frequency manipulations and was present during the first 6 movement cycles. Movement was continued after the pacing signal was withdrawn until the instruction to rest reappeared on the screen. Each movement trial lasted 30 s.

One or 2 days before scanning, patients were invited to the laboratory to receive testing instructions and to familiarize themselves with the bimanual motor task. On this day, patients were on medication and practiced the behavioral task first in a seated position (about 20 min) and then while lying in a dummy scanner. They performed 2 runs of 5.6 min in which each of the 4 movement conditions was repeated twice.

### Table 1

Clinical details of participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls (W = 16)</th>
<th>PD without FOG (W = 16)</th>
<th>PD with FOG (W = 16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F), frequencies</td>
<td>11/5</td>
<td>12/4</td>
<td>13/3</td>
<td>0.72</td>
</tr>
<tr>
<td>Age (years), mean (±SD)</td>
<td>67.4 (61.1–73.4)</td>
<td>67.4 (62.3–72.6)</td>
<td>66.1 (59.2–73.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>SCOPA-COG (0–43), mean (±SD)</td>
<td>30.7 (28.0–35.4)</td>
<td>30.3 (28.2–34.0)</td>
<td>27.6 (22.3–32.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hoehn and Yahr staging (0–5)</td>
<td>2.5 (2.0–2.5)</td>
<td>2.5 (2.0–3.0)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years), mean (±SD)</td>
<td>7.4 (6.2–12.2)</td>
<td>9.5 (6.2–12.7)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>UPDRS motor score (0–108)</td>
<td>34.0 (26.0–44.3)</td>
<td>443.8 (258.8–628.7)</td>
<td>659.7 (453.0–884.4)</td>
<td>0.01*</td>
</tr>
<tr>
<td>L-dopa dose (mg/day), mean (±SD)</td>
<td>0 (0–0)</td>
<td>17.5 (12.0–20.25)</td>
<td>&lt;0.01*</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; IQR: interquartile range (Q1–Q3); SCOPA-COG: Scales for Outcomes in Parkinson’s Disease—Cognitive part; UPDRS motor score: Unified Parkinson’s Disease Rating Scale part III (motor examination); L-dopa dose: Levodopa equivalent dose; NFOS-Q: new freezing of gait questionnaire.

<sup>a</sup>*Test was used.

<sup>b</sup>Two-sample t-tests was used.

<sup>c</sup>Nonparametric Wilcoxon 2-sample t-tests was used.

*Groups significantly different at P < 0.05.
Testing in the actual MRI scanner took place in the early morning after patients had withdrawn medication for at least 12 h (off medication). They again performed one antiphase trial of 30 s to determine comfortable frequency and amplitude during “off” and performed one additional practice run. Subjects were lying supine in the scanner with the upper arms positioned along the body and elbows slightly flexed. Care was taken to avoid head movements using foam padding and a bite bar when required. The forearms were positioned in an orthosis, enabling only flexion and extension movements of the index fingers in the sagittal plane. The angular displacements of the index bite bar when required. The forearms were positioned in an orthosis, enabling only flexion and extension movements of the index fingers in the sagittal plane. The angular displacements of the index fingers were registered by nonferromagnetic shaft encoders fixed to the rotation axis of the orthosis, which was aligned with the metacarpophalangeal joint axis of the index finger. The shaft encoders recorded movement with a spatial resolution of 1° and a sampling frequency of 200 Hz.

**Functional MRI Procedure**

Imaging was carried out in a 3-T Magnetom Trio Magnetic Resonance scanner (Siemens, Erlangen, Germany). For each subject, we acquired high-resolution $T_2$-weighted anatomical scans and $T_2$-weighted functional images using the following gradient echo-planar imaging (EPI) pulse sequence: 50 transversal slices, slice thickness: 2.8 mm, slice gap: 0.28 mm, time echo $= 30$ ms, time repetition $= 3000$ ms, flip angle $= 90^\circ$, matrix: $80 \times 80$, in-plane resolution $= 2.5$ mm $\times 2.5$ mm. The protocol consisted of 5 runs in which each of the 4 movement conditions was repeated twice. Accordingly, each run lasted 5.6 min and consisted of 8 active conditions of 30 s and 8 rest conditions of 12 s.

**Data Analysis**

**Behavioral Data Analysis**

We processed kinematic time series using Matlab 7.7 (Mathworks, Sherborn, MA, USA) in 2 steps. First, FOUL episodes were detected using objective criteria. Similar to our previous work (Vercruyssse, Spildooren, Vandenbergboesse, et al. 2012), we defined FOUL as “a period of involuntary stop or the clear absence of effective cyclical movements.” Thus, both periods with a complete halt and severely disrupted motion with a nearly complete loss of movement were classified as freezing episodes. As validated previously (Vercruyssse, Spildooren, Vandenbergboesse, et al. 2012), ineffective cyclical movements were characterized when at least 2 of the following 3 conditions were met: (1) Abnormally reduced amplitude <50% of the reference cycle; (2) irregular frequency, and (3) a freezing index (FI) of >1. A FI is a temporal feature obtained through spectral analysis and reflects the presence of high-frequency components in a signal (Moore et al. 2008). FI is defined as the ratio of power in the “freeze” band (3–8 Hz) to the power in the “normal motion band” (0–5 Hz) in accordance with Moore et al. (2008). Previous research successfully applied the FI to detect gait freezing on- and offline (Moore et al. 2008; Delval et al. 2010). We previously validated a critical threshold of FI >1 to detect freezing episodes during upper limb movements (Vercruyssse, Spildooren, Vandenbergboesse, et al. 2012). FOUL episodes were demarcated by means of visual markers (Fig. 1). Reproducibility of the FOUL detection method was established by a reliability study between 2 independent clinical experts blinded for freezing status of the subjects (intraclass correlation coefficient (2,2) = 94%). Number and duration (in seconds) of FOUL episodes per movement trial were the primary outcome parameters.

Secondly, amplitude and frequency measures were computed for the remaining continuous (nonfreezing) motor signals based on peak-to-peak measures of the end-effector motions. Mean amplitude and frequency per movement cycle were the main outcome parameters. Group comparisons between amplitude and frequency were restricted to continuous movement after cue withdrawal during the freezing-resistant conditions. For this purpose, kinematic outcome parameters were pooled across the freezing-resistant Conditions 1 and 2, hereafter called “CONT.” Conditions 3 and 4 were excluded from the between-group analysis due to the high number of freezing episodes and thus, the relatively low amount of normal movement data in patients with FOUL. As such, we ensured a comparable amount of normal movement data in the 3 groups to be included in both behavioral and functional imaging analyses (see below). Mean amplitude and frequency during CONT were compared between PD with FOG, PD without FOG, and controls using 1-way analysis of variance (ANOVA). Significant group effects were further addressed with Tukey’s HSD post hoc test. In the text, all data are reported by means and standard errors.

**Functional Imaging Analysis**

Functional imaging data were preprocessed and analyzed with SPM5 (Wellcome Department of Imaging Neuroscience, University College, London, UK) implemented in Matlab. EPIs were spatially realigned to the mean EPI image, unwarped, slice time corrected to account for differences in slice acquisition time by temporal interpolation to the middle slice (reference slice $= z = 30$, $\pm 15$, $\pm 5$) and spatially coregistered to the individual’s anatomical $T_1$ image. Anatomical images were normalized to the Montreal Neurological Institute template using the SPM5 segmentation procedure, and the resulting transformation parameters were applied to all realigned EPI images. Finally, the normalized functional images were smoothed with an isotropic 8-mm full-width at half maximum Gaussian kernel.

At the first level, the preprocessed fMRI data of each subject were analyzed on a voxel-by-voxel basis using an epoch-related approach in the context of a General Linear Model. REST, ongoing motion in Conditions 1 and 2 (“CONT”), and 2 (“FOUL”), as well as FOUL epochs were modeled as box-car functions convolved with the canonical hemodynamic response function. Despite our efforts to exclude patients with tremor, rest tremor was present in 5 patients and was modeled as a separate epoch and, as such, excluded from the rest periods. Additionally, we included regressors of the mean signal intensity values calculated for each EPI within white matter, cerebral spinal fluid, and out-of-brain compartments as covariates of no interest.

At the second level, 2 types of analyses were performed. The first analysis included the contrast image representing the effect of CONT versus REST that was defined in all subjects. CONTvsREST contrast images (1 per subject) were entered into a second-level random-effects analysis in the context of the General Linear Model with preplanned comparisons using t-tests within and between groups ($P < 0.05$, false discovery rate, FDR, corrected). Cerebral activation was compared between (1) PD with FOG versus PD without FOG, (2) PD with FOG versus controls, and (3) PD without FOG versus controls. We restricted the search volume for between-group analyses to gray matter voxels that showed task-related activation as defined by the CONTvsREST contrast. The second analysis involved a fixed-effects model including all runs (across all subjects) in which FOUL had occurred. In contrast to random-effects models, fixed-effects models do not take intersubject variability into account and therefore only allow limited inference of the findings. Contrast images representing the effect of FOUL versus CONT were specified per FOUL run and were used for within-group analysis (preplanned comparison of FOUL vs. CONT within those with FOUL, $P < 0.05$, FDR corrected).

**Region of Interest Analysis**

Recent studies pointed to deficits in the neural circuitry connecting the basal ganglia, brainstem structures, and cortical regions as probable origin of FOG (Nutt et al. 2011). We therefore included bilateral putamen, caudate nucleus, subthalamic nucleus (STN), pallidum, pedunculopontine nucleus (PPN), and the MLR as regions of interest (ROIs) and extracted contrast estimates using Marsbar (Brett et al. 2002). The caudate nucleus, pallidum, and dorsal and ventral parts of the putamen were delineated according to Postuma and Dagher (2006). The coordinates for the MLR ROI were based on the maximal activation loci during a gait imagery task in the fMRI study of Snijders et al. (2011). The MLR ROI was thus defined as an $8 \times 8 \times 8$ mm cube centered around coordinate $x$, $y$, $z = 0$, $-28$, $-20$. The STN ROI was centered around coordinate $x$, $y$, $z = \pm 10$, $+15$, $-5$ (Lennissen et al. 2013). Stereotactic coordinates reported by Zrinzo et al. (2008) were used for the PPN ROI with $x$, $y$, $z$ coordinates ranging from $\pm 5$ to $\pm 7$, $-25$ to $-30$, and $-7$ to $-16$. For all ROIs, contrast values of CONTvsREST were extracted for each run in all subjects and of FOULvsCONT for each run with FOUL.
Results

Data are reported in 2 sections: (1) The behavioral and brain imaging results of the successful continuous motion in the 3 groups; (2) the behavioral and brain imaging data for the FOUL episodes within the PD group demonstrating FOUL.

Continuous Movement

Group Comparison of Kinematics During Continuous Movement (CONT)

We found a main effect of group for movement amplitude ($F_{2,45} = 6.83; P = 0.003$) and movement frequency ($F_{2,45} = 5.48; P = 0.007$). Post hoc analysis revealed that, during CONT, mean amplitude was larger in controls ([55.25° (4.55)] compared with patients without FOG [37.55° (3.73), $P = 0.009$] and with FOG [36.42° (4.55), $P = 0.006$; Fig. 2A]. Mean frequency was higher in patients with FOG [1.49 Hz (0.12)] than controls [1.13 Hz (0.06), $P = 0.009$] and patients without FOG [1.11 Hz (0.08), $P = 0.009$; Fig. 2B].

Whole-Brain Analysis Within Groups During CONT

All groups activated a classical sensorimotor network (see Supplementary Material) consisting of primary sensorimotor cortex (SM1), dorsal premotor cortex (PMd), supplementary motor area (SMA), cerebellum (vermis, bilateral lobules 4, 5, 6, and 8, crus 2), basal ganglia, as well as middle prefrontal areas and bilateral superior frontal gyrus. However, activity was generally reduced in PD patients compared with healthy controls who exhibited larger clusters and additional activity in angular gyrus, left middle temporal gyrus, and medial areas (precuneus and cingulum).

Whole-Brain Analysis Between Groups During CONT

To ascertain that differences in brain activation between PD with FOG, PD without FOG, and controls were not confounded by differences in behavioral performance, we included a regressor containing the mean frequency values during CONT for each subject as a covariate of no interest in the second-level ANOVA model. The comparison of brain
activation during CONT between PD with and without FOG, corrected for differences in mean movement frequency, showed relatively decreased activation in PD with FOG in the right middle frontal gyrus (anterior dorsolateral prefrontal cortex, PFC) and the left PMd and M1 (2-sample t-tests, \( P < 0.05 \) FDR corrected, see Fig. 3 and Table 2). Similarly, a strong tendency toward decreased activation in the right anterior dorsolateral PFC and the left PMd was found in PD with FOG compared with control subjects (2-sample t-tests, \( P = 0.057 \) FDR corrected, see Fig. 4 and Table 2). No areas showed increased activation in PD with FOG compared with PD without FOG or controls. Without statistically correcting for multiple comparisons, activation in the right putamen was found increased in PD with FOG compared with control subjects (2-sample t-tests, \( P = 0.035 \)) and tended to be higher than in PD without FOG (\( P = 0.088 \)). For all these areas, PD with FOG exhibited clearly increased activity during CONT when compared with PD without FOG.

**ROI Analysis Between Groups During CONT**

PD subjects with FOG activated bilateral STN more compared with PD without FOG (ROI analysis, 2-sample t-tests corrected for differences in movement frequency, \( P = 0.017 \), Fig. 5) and showed increased activation in the bilateral dorsal putamen compared with controls (ROI analysis, 2-sample t-tests corrected for movement frequency, \( P = 0.011 \)). Activity in the pallidum was also increased in PD with FOG compared with controls (\( P = 0.035 \)) and tended to be higher than in PD without FOG (\( P = 0.088 \)). For all these areas, PD with FOG exhibited clearly increased activity during CONT when compared with PD without FOG.

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**Figure 2.** Kinematic group comparison during CONT. Mean movement amplitude (A) and frequency (B) during continuous movement (CONT) of controls (\( N = 16 \)), PD without FOG (\( N = 16 \)), and PD with FOG (\( N = 16 \)). Vertical bars represent standard error of measurement (SEM). *Groups significantly different at \( P < 0.05 \).

**Figure 3.** Differences in brain activation during continuous movement between PD without FOG and PD with FOG. Anatomical location (left side) and contrast values (right side) of brain regions that were less activated in PD with FOG compared with PD without FOG. Results are based on 2-sample t-tests with movement frequency as covariate of no interest and are significant at \( P < 0.05 \) with FDR correction. The subject group with a white bar was not included in the given contrast, but is shown to provide the reader with a complete view on contrast values in all 3 groups. Abbreviations: PMd: dorsal premotor cortex; M1: primary motor area; Ant. PFC: anterior prefrontal cortex; DLPFC: dorsolateral prefrontal cortex.
compared with rest, which was not the case for the controls who exhibited even a slight deactivation. PD without FOG showed increased activation in the dorsal putamen compared with controls ($P = 0.03$). Brain activation in the MLR, PPN, and ventral putamen did not differ between groups ($P > 0.2$).

### Table 2

Brain areas with different activation patterns between groups during continuous movement (A) and within patients with FOUL when comparing FOUL with CONT (B)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Functional label</th>
<th>BA</th>
<th>Coordinates</th>
<th>$T$</th>
<th>$P$ (FDR)</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Whole-brain analysis during CONT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD with FOG &lt; PD without FOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>Ant. DLPFC</td>
<td>10,46</td>
<td>40 46 6</td>
<td>4.46</td>
<td>0.042</td>
<td>63</td>
</tr>
<tr>
<td>Left precentral gyrus</td>
<td>PMd and M1</td>
<td>6,4</td>
<td>−22 −22 58</td>
<td>5.25</td>
<td>0.042</td>
<td>82</td>
</tr>
<tr>
<td>PD with FOG &lt; controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>Ant. DLPFC</td>
<td>10,46</td>
<td>40 46 10</td>
<td>4.58</td>
<td>0.057</td>
<td>84</td>
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<td>Left precentral gyrus</td>
<td>PMd</td>
<td>6</td>
<td>−24 −12 70</td>
<td>4.87</td>
<td>0.057</td>
<td>47</td>
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<td>PD with FOG &gt; controls</td>
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<tr>
<td>Right putamen</td>
<td></td>
<td></td>
<td>26 −6 10</td>
<td>3.51</td>
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<tr>
<td><strong>B. Whole-brain analysis during FOUL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>FOUL &gt; CONT</td>
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<td></td>
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</tr>
<tr>
<td>Right superior frontal gyrus</td>
<td>SMA</td>
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<td>8 8 48</td>
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<td>Right precentral gyrus</td>
<td>PMd and M1</td>
<td>6,4</td>
<td>42 −22 58</td>
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<tr>
<td>Left superior frontal gyrus</td>
<td>Ant. PFC</td>
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<td>−18 66 18</td>
<td>5.08</td>
<td>0.018</td>
<td>18</td>
</tr>
</tbody>
</table>

Notes: A. Whole-brain analysis of task-related activation during continuous movement (CONT) between PD with FOG ($N = 16$), PD without FOG ($N = 16$), and controls ($N = 16$) using 2-sample $t$-tests. All areas and reported cluster sizes are significant at $P < 0.001$ (uncorrected). $P$-values after FDR correction for multiple comparisons at the voxel level are shown. B. Whole-brain analysis of activation during FOUL and CONT based on a 1-sample $t$-test within patients who demonstrated FOUL ($n = 8$). All areas and reported cluster sizes are significant at $P < 0.05$ after FDR correction at the voxel level. Coordinates of local maxima at $x$, $y$, $z$ are in MNI space.

PD: Parkinson’s disease; FOG: freezing of gait; FOUL: freezing of upper limb; Ant.: anterior; PFC: prefrontal cortex; M1: primary motor cortex; SMA: supplementary motor area.

**Figure 4.** Differences in brain activation during continuous movement between controls and PD with FOG. Anatomical location (left side) and contrast values (right side) of brain regions that were differently activated in PD with FOG compared with controls. Results are based on 2-sample $t$-tests with movement frequency as covariate of no interest and are significant at $P < 0.001$ (uncorrected). Exact $P$-values after FDR correction can be found in Table 2. The subject group with a white bar was not included in the given contrast, but is shown to provide the reader with a complete view on contrast values in all 3 groups. Abbreviations: PMd: dorsal premotor cortex; Ant. PFC: anterior prefrontal cortex; DLPFC: dorsolateral prefrontal cortex.
Correlation Analysis
We tested whether group differences in motor-related brain activation (right PMd, left primary motor and premotor areas and prefrontal areas, right putamen, bilateral STN, and bilateral pallidum) were related to disease duration using Pearson correlations. Within patients with FOG, a longer disease duration was associated with a stronger reduction in activity of the right PFC ($R = -0.56$, $P < 0.05$) and with a stronger increase in activity of the dorsal and ventral putamen (dorsal putamen: $R = 0.57$, $P = 0.02$ and ventral putamen: $R = 0.60$, $P = 0.02$). No such correlation was found in Parkinson patients without FOG (dorsal putamen: $R = 0.32$, $P = 0.23$ and ventral putamen: $R = 0.01$, $P = 1.00$). No areas showed significant correlations with cognitive variables (MMSE and SCOPA-COG), disease severity (Hoehn and Yahr stage), the FOG-Q, L-DOPA dose, and movement amplitude or frequency.

Upper Limb Motor Blocks

Occurrence of FOUL Episodes
FOUL was detected in 9 patients with FOG and 1 without FOG. There were 289 FOUL episodes in total, with 150 being bilateral (51.90%), 93 unilateral left FOUL (32.18%), and 46 unilateral right FOUL (15.92%). The duration varied among FOUL episodes with a median of 4.89 s (interquartile range, IQR = 2.10–14.97 s; Fig. 6A). More and longer freezing episodes were observed during freezing-provoking conditions (small-amplitude, fast-frequency conditions) compared with freezing-resistant conditions (comfortable amplitude and speed; Fig. 6B). Within patients with FOUL, the correlation between total FOUL time with FOG severity ($R = 0.41$) was not significant ($P = 0.27$). As expected, the FI was significantly elevated during FOUL $[2.36 (1.08 SD)]$ when compared with CONT $[0.63 (0.13 SD)]$ (repeated-measures ANOVA $F_{1,8} = 23.01$, $P = 0.0013$). Patients with FOG who demonstrated FOUL had a similar clinical profile as FOG patients without FOUL (nonparametric Wilcoxon $t$-test $P > 0.2$ for age, UPDRS, disease duration, Hoehn and Yahr score, LED, FOG-Q, SCOPA-COG, and preferred movement frequency), but movement amplitude during continuous motion (freezing-free movement under Conditions 1 and 2) in FOG patients with FOUL was smaller $[FOG with FOUL: 26.89° (13.03) vs. FOG without FOUL: 48.95° (7.97); nonparametric Wilcoxon $t$-test, $P = 0.0097$].

Whole-Brain Analysis During FOUL
Brain activation during FOUL was compared with CONT using a fixed-effects model. Five runs with only short periods of FOUL (summed duration of FOUL episodes <5% of total
motion time, see Fig. 6B) were excluded from the analysis in view of the slowness of the blood oxygen level-dependent signal. This cutoff value proved efficient to exclude outlying contrast values for the FOULvsCONT contrast that could not be optimally estimated in these runs. The 5 excluded runs belonged to 3 different subjects, and 2 of them did not have other runs with FOUL to include in the model. Therefore, the following results are based on 274 FOUL episodes (out of 289 in total) distributed over 35 runs in 8 subjects [7 PD with FOG and 1 PD without FOG; median FOUL duration = 5.76 s (IQR = 2.25–15.73 s)]. The right SMA, right PMd, as well as M1 and left superior frontal gyrus (anterior PFC) showed increased activation during FOUL compared with CONT ($P < 0.05$, FDR corrected, see Fig. 7 and Table 2). No areas showed decreased activation during FOUL versus CONT.

ROI Analysis During FOUL
Brain activation in the STN, MLR, and PPN did not differ between FOUL and CONT ($P > 0.3$), but the results showed decreased activity in the pallidum bilaterally during FOUL compared with CONT (ROI analysis, $P = 0.03$, Fig. 7), and there was a trend toward decreased activation in the ventral and dorsal putamen during FOUL compared with CONT (ROI analysis, $P = 0.073$ for ventral putamen and 0.078 for dorsal putamen).

Discussion
The present study aimed to identify the neural correlates of motor blocks or “freezing episodes” during a bimanual motor task and to investigate their relation with FOG. Our study revealed 2 main findings: First, during successful performance of repetitive upper limb movement, patients with FOG showed decreased activation in cortical frontal areas (left PMd and M1, and right PFC) and increased subcortical activity in the right dorsal putamen, bilateral pallidum, and STN compared with patients without FOG and controls. Secondly, FOUL episodes were associated with increased cortical (right SMA, PMd and M1, and left PFC) brain activity while subcortical activity in the bilateral pallidum and putamen was decreased. This study is one of the first to measure freezing-related brain activation by eliciting upper limb motor blocks in an fMRI environment. The novel findings indicate that the neural drive for rhythmic movement generation and, more specifically, the balance between subcortical and cortical activation, is altered in patients with FOG.

Reduced Cortical and Increased Subcortical Brain Activity During Continuous Upper Limb Motion in Patients with FOG
Previous functional MRI studies of upper limb motion in PD have consistently shown increased activation in premotor-parietal and cerebellar regions, presumably to compensate for the dysfunctional striato-supplementary motor loop (Wu and Hallett 2005; Jahanshahi et al. 2010; Wu et al. 2010). Recruitment of these compensatory pathways was facilitated by using external cues that guide movement generation (Debaere et al. 2003). Wu et al. (2010) showed that a compensatory shift in functional connectivity between SMA and other motor regions enhanced bimanual performance in PD, especially during anti-phase movements.

Recent findings of more pronounced scaling-timing difficulties in PD patients with FOG during repetitive drawing or finger movements and less beneficial cueing effects than those without FOG (Nieuwboer 2008; Nieuwboer, Vercruyssse, et al. 2009; Vercruyssse, Spildooren, Heremans, et al. 2012) suggest that neural compensatory mechanisms may be unsatisfactory in freezers. In line with this, the current study showed increased frontal activation in PD without FOG compared with controls, but not in those with FOG. Instead, freezers had decreased activation in M1, PMd, and dorsolateral prefrontal cortex (DLPFC) and exaggerated activity in the putamen, STN, and pallidum during continuous movement, compared with the other subgroups. The combination of hyperactivity in these 3 subcortical regions and cortical hypoactivity during movement execution in freezers is an important finding. One interpretation might be that subcortical overactivation inhibits cortical activity during continuous cyclical movement in freezers, implying an increased involvement of the so-called indirect basal ganglia (BG) pathway. The indirect pathway is
thought to suppress cortical motor regions through the external part of the globus pallidus and STN (Obeso et al. 2008) and is thus crucial for inhibitory action control (Nambu et al. 2002; Wylie et al. 2010). Although the interpretation that increased BG activity induces inhibition of cortical regions remains speculative in the context of fMRI, it could influence ongoing upper limb movement in 2 ways. As suggested above, it may hinder compensatory cortical recruitment, making upper limb movement more susceptible to progressive spatiotemporal abnormalities that may culminate into a sudden motor block. This interpretation would be in line with findings of a recent study comparing cerebral activation during motor imagery in PD patients with and without FOG. The authors interpreted decreased activation of mesial frontal and posterior parietal cortices in freezers (Snijders et al. 2011), as insufficient compensatory brain activity which may result in difficulties in stride length regulation, ultimately leading to FOG (Iansek et al. 2006; Snijders et al. 2011).

An alternative interpretation contends that basal ganglia overactivation may be protective by inhibiting nonselective action programs that would otherwise interfere with the intended motor goal (Mink 1996; Yu et al. 2007). Accordingly, reduced cortical activation would reflect a beneficial mechanism to prevent the emergence of motor blocks.

The whole-brain analysis showed that overactivation in the putamen in PD patients with FOG was specific to the posterior part, which is the main motor structure of the BG. This is consistent with our primarily motor-oriented paradigm of FOUL.

Figure 7. Differences in brain activation during FOUL compared with CONT within patients with FOUL. Anatomical location (left side) and contrast values (right side) of brain regions that showed increased (green) or decreased (red) activation during FOUL. Results of the whole-brain analysis are based on 1-sample t-tests and are thresholded at $P < 0.05$ (FDR correction). Abbreviations: SMA: supplementary motor area; PMC: premotor cortex; M1: primary motor area; Ant. PFC: anterior prefrontal cortex; ROI: region of interest.
This part of the nucleus is more severely affected by dopamine depletion than the anterior or ventral striatum in PD (Bartels et al. 2006). With regard to upper limb coordination, putamen activity is particularly increased during the movement initiation phase (Kraft et al. 2007). Hence, patients with FOG may need additional subcortical input to preserve movement continuity although not resulting in increased cortical engagement. This finding also relates well with the increased glucose metabolism found in the putamen of freezers as revealed by fluorodeoxyglucose positron emission tomography compared with nonfreezers (Bartels et al. 2006).

In addition to cortical motor regions, our results revealed that the DLPFC and anterior PFC were part of the network related to the continuous cyclical motor abnormalities in patients with FOG. These regions play an important role in cognitive control. This line of reasoning coincides with the fact that FOG often occurs in situations that are demanding on cognitive resources. Whether disturbed output signaling from the basal ganglia related to the continuous cyclical motor abnormalities in patients with FOG seems to be consistent across different types of freezing.

Increased Cortical and Decreased Subcortical Brain Activity During Upper Limb Motor Blocks

Quite opposite to the neural activation patterns during continuous movement, upper limb motor blocks were associated with increased engagement of SMA, PMd, M1, and the anterior PFC and decreased subcortical activity. Behaviorally, FOUL episodes were characterized by highly abnormal motor output resembling the kinematic changes during FOG. These entail severely reduced amplitude, irregular frequency, and the presence of high-frequency tremulous-like components, although complete akinetic types of freezing exist as well (Nieuwboer et al. 2001; Hausdorff, Balash, et al. 2003; Schaafsma et al. 2003; Bloem et al. 2004; Nutt et al. 2011; Vercruysse, Spildooren, et al. 2012). Given the drastically reduced movement amplitude, the increased cortical activation during FOUL is unlikely to be a result of increased motor output per se. However, the rapid, trembling-like movements could have induced an increase in afferent sensory input to cortical regions of the proprioceptive network (Naito et al. 2007; Goble et al. 2012).

In line with the discussion of brain activation during continuous movement, we raise 2 alternative hypotheses, which do not exclude proprioceptive influences. First, following the idea that freezers exhibited less compensatory cortical activation during continuous movement, the inverse pattern during motor blocks may imply that cortical drive increases belatedly in freezers, namely only when motor output is severely at odds with the intended motor program. As such, the temporary increase in cortical activation may represent a last minute attempt to restore movement and overcome the motor block. Why increased cortical activation only occurred in freezers when FOUL emerged is currently unclear. One assumption is that impaired integration of sensorimotor and proprioceptive information in freezers (Tan et al. 2011) impedes a gradual shift to a compensatory cortical drive during movement generation, which could have prevented movement breakdown. In keeping with this, PD with FOG showed more pronounced gray matter atrophy and reduced functional connectivity in fronto-parietal regions (Kostic et al. 2012; Tessitore, Amboni, Esposito, et al. 2012). Whatever the exact underlying cause, our results indicate that freezers seem to have reached a saturation point of normal compensation and respond belatedly to actual movement breakdown.

Alternatively, the increased cortical activation during FOUL could be symptom-related instead of overdue compensation. As mentioned above, decreases in BG outflow could also release cortically defined competing motor signals. Indeed, fMRI and transcranial magnetic stimulation studies have revealed that increased M1 and PMC activation may also be pathological, rather than subserving normalized motor function (Yu et al. 2007; Berardelli and Suppa 2011).

Whether symptom-related or compensatory the pattern of decreased BG activation and increased cortical (pre)motor activation seems to be consistent across different types of freezing. In addition to the current study, Shine, Matar, Ward, Bolitho, Gilat, et al. (2013) reported a similar activation pattern during motor arrests in cyclical foot movements. Their paradigm involved cognitive triggers of freezing which likely explains why freezing-related changes were also found in prefrontal and parietal regions.

Brain Activation During Upper Limb Motor Blocks: What Does it Tell Us About Freezing of Gait?

Difficulties in maintaining adequate timing and amplitude of movement sequences may be generic to freezing in different effectors (Vercruysse, Spildooren, Vandenbossche, et al. 2012; Vercruysse, Spildooren, Heremans, et al. 2012). Nevertheless, in addition to repetitive stepping movements, proficient locomotion obviously depends on posture and balance control and on its dynamic adaptation in the face of obstacles. Evidently, this more complete and complex picture of FOG is not fully captured by upper limb movements, and this likely explains why brainstem motor regions associated with FOG (Schweder et al. 2010; Snijders et al. 2011; Shine, Matar, Ward, Bolitho, Gilat, et al. 2013) were not related to FOUL. Importantly, it has been put forward that disturbed output signaling from the brainstem-central pattern generator pathways may result in the abnormal high-frequency output during FOG (Bloem et al. 2004; Nieuwboer et al. 2001; Hausdorff, Balash, et al. 2003; Schaafsma et al. 2003; Nutt et al. 2011) and FOUL (Vercruysse, Spildooren, Heremans, et al. 2012). The current results argue against this as no changes in brainstem activation were found during FOUL. Consequently, the role of brainstem motor areas in the origins of freezing is not necessarily related to the generalized impairment of scaling and timing control underlying motor blocks in different body parts. The recent finding that PPN stimulation reduces the number of FOG episodes, but
does not improve background abnormalities in stride length and timing control (Tevathasan et al. 2012), appears to support this hypothesis. The fact that freezing-related changes in MLR activation were found in other fMRI studies is likely because their motor imagery of gait (Snijders et al. 2011) and virtual reality paradigm (Shine, Matar, Ward, Bolitho, Gilat, et al. 2015) better mimic the sense of forward progression during gait or relied more on cognitive control.

Interpretational Issues
In this study, we partially relied on relatively liberal statistical thresholds to estimate between-group effects due to the high variability in the neural profiles of the patient population involved. In addition, a fixed-effects model was used to directly compare brain activation during ongoing movement with freezing episodes, which only allows inference from our results to the sample tested in our study.

Secondly, not all PD patients with FOG showed FOUL. This may be due to the scanner environment, which is likely to enhance “test arousal.” Interestingly, 12 of the 16 patients with FOG reported motor blocks in other functional tasks other than gait using a motor block questionnaire (Vercruysse, Devos, et al. 2012). The presence of motor blocks in daily functional tasks may be more easily provoked than in an experimental context. This is in line with the well-documented difficulty of eliciting FOG in a laboratory setting (Nutt et al. 2011; Snijders et al. 2012). There were no clinical differences between patients with FOG who demonstrated FOUL during testing (n = 9 of 16) and those who did not (n = 7 of 17). Interestingly, those with FOUL had a smaller movement amplitude, adding further strength to the major role of scaling difficulties in freezing (Iansek et al. 2006; Chee et al. 2009). Consequently, future imaging studies that benefit from a high sample of freezing episodes may want to consider screening patients for scaling difficulties.

Matching of freezers and nonfreezers occurred through a clinical assessment at the patients’ home while on medication. Consistent with a prior study (Vercruysse, Devos, et al. 2012), levodopa dose was higher in freezers compared with nonfreezers. The contrasts between the subgroups were somewhat reduced in some brain areas when correcting for these differences, but given the complexity and nonlinearity of the relationship between FOG and dopamine depletion (Espay et al. 2012), applying statistical correction for levodopa doses also has its limitations. Moreover, in the off state, the general motor output during the upper limb tests was comparable between patient groups for movement amplitude and none of the group differences in neural activation were correlated with levodopa doses.

Conclusion
When compared with nonfreezing and control participants, Parkinson patients with FOG showed marked alterations within the striatofrontal circuitry during successful upper limb movement and actual motor blocks. We found subcortical hyperactivity and cortical hypoactivity in motor and cognitive control areas in freezers, which may be responsible for timing and scaling abnormalities during upper limb movement. In contrast, an increase in cortical drive and a reduction in basal ganglia activity occurred in freezers when actual UL freezing emerged. FOUL did not yield changes in activation of regions downstream of the basal ganglia, suggesting that brainstem motor regions exercise a gait-specific role in freezing in PD.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/


