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Gait-related cerebral alterations in patients with Parkinson's disease with freezing of gait

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Freezing of gait is a common, debilitating feature of Parkinson's disease. We have studied gait planning in patients with freezing of gait, using motor imagery of walking in combination with functional magnetic resonance imaging. This approach exploits the large neural overlap that exists between planning and imagining a movement. In addition, it avoids confounds introduced by brain responses to altered motor performance and somatosensory feedback during actual freezing episodes. We included 24 patients with Parkinson's disease: 12 patients with freezing of gait, 12 matched patients without freezing of gait and 21 matched healthy controls. Subjects performed two previously validated tasks—motor imagery of gait and a visual imagery control task. During functional magnetic resonance imaging scanning, we quantified imagery performance by measuring the time required to imagine walking on paths of different widths and lengths. In addition, we used voxel-based morphometry to test whether between-group differences in imagery-related activity were related to structural differences. Imagery times indicated that patients with freezing of gait, patients without freezing of gait and controls engaged in motor imagery of gait, with matched task performance. During motor imagery of gait, patients with freezing of gait showed more activity than patients without freezing of gait in the mesencephalic locomotor region. Patients with freezing of gait also tended to have decreased responses in mesial frontal and posterior parietal regions. Furthermore, patients with freezing of gait had grey matter atrophy in a small portion of the mesencephalic locomotor region. The gait-related hyperactivity of the mesencephalic locomotor region correlated with clinical parameters (freezing of gait severity and disease duration), but not with the degree of atrophy. These results indicate that patients with Parkinson's disease with freezing of gait have structural and functional alterations in the mesencephalic locomotor region. We suggest that freezing of gait might emerge when altered cortical control of gait is combined with a limited ability of the mesencephalic locomotor region to react to that alteration. These limitations might become particularly evident during challenging events that require precise regulation of step length and gait timing, such as turning or initiating walking, which are known triggers for freezing of gait.

Keywords: Parkinson's disease; motor planning; gait; pedunculopontine nucleus

Abbreviations: FOG = freezing of gait; MI = motor imagery; VI = visual imagery

Introduction

Freezing of gait (FOG) is an episodic gait disorder during which the feet appear 'glued to the floor' (Bloem *et al.*, 2004). The pathophysiology underlying FOG remains largely unknown. Behavioural studies have identified several gait alterations in patients with Parkinson's disease with FOG ('patients with FOG'), even when the patient is not experiencing an actual FOG episode. Alterations include premature timing of muscle activations (Nieuwboer *et al.*, 2004), increased variability of gait (Hausdorff *et al.*, 2003), increased temporal gait asymmetry (Plotnik *et al.*, 2008) and faulty generation of postural adjustments before step initiation (Jacobs *et al.*, 2009a). A recent article suggested that FOG may be caused by a failure to generate adequate amplitudes for the intended movement. This leads to a progressive reduction of step size that may culminate in a FOG event (Chee *et al.*, 2009). This so-called sequence effect could result from defective stride length amplitude setting by the supplementary motor area and its maintenance by the basal ganglia, leading to a mismatch between intention and automation (Chee *et al.*, 2009). However, empirical tests of this hypothesis are difficult, because most non-invasive neuroimaging methods are not suitable for assessing gait (Bakker *et al.*, 2007b).

Some experimental approaches can bypass these difficulties, allowing researchers to study the cerebral correlates of FOG (Fabre *et al.*, 1998; Matsui *et al.*, 2005; Bartels *et al.*, 2006; la Fougere *et al.*, 2010). One possibility is to focus on the planning phase of walking movements, rather than the manifestation of actual FOG episodes. Motor imagery (MI) (asking subjects to imagine a particular movement) exploits the large functional and neural overlap between motor planning and MI (Jeannerod, 1994; Cisek and Kalaska, 2004; Miller *et al.*, 2010). Imagining a movement is sensitive to motor control variables (Gentili *et al.*, 2004), it is contingent on the current physical configuration of the subject (Nico *et al.*, 2004; de Lange *et al.*, 2006) and it relies on neural processes similar to those evoked during performance and planning of the same movement (Stephan *et al.*, 1995; la Fougere *et al.*, 2010). We have shown recently that MI of gait follows similar motor constraints as actual walking (Bakker *et al.*, 2007a). Accordingly, MI of gait has been used repeatedly to study human walking using functional MRI (Bakker *et al.*, 2008; la Fougere *et al.*, 2010) or positron emission tomography (Malouin *et al.*, 2003).

Although MI of gait is likely to engage only a portion of the cerebral circuits controlling walking, it has several advantages for investigating FOG. First, MI provides opportunities for studying alterations in the planning of gait, which may be a crucial element in FOG pathophysiology (Chee *et al.*, 2009; Jacobs *et al.*, 2009b). Second, meaningful cerebral comparisons between patients and controls require matched behavioural performance (Price and Friston, 2002). This condition can be met with MI of gait, whereas real motor performance will often differ between patients and controls. Third, MI of gait allows us to isolate cerebral responses related to walking, distinct from alterations in motor performance and somatosensory feedback produced by actual FOG episodes (Almeida *et al.*, 2005).

Accordingly, we used MI of gait in combination with functional MRI to study the cerebral correlates of gait planning in patients with and without FOG. Stimulated by current hypotheses concerning FOG pathophysiology—which mainly deal with deficits in regulating step length and gait timing (Plotnik *et al.*, 2008; Chee *et al.*, 2009)—we also included a behavioural control experiment where actual gait was electrophysiologically quantified. Finally, we used voxel-based morphometry to assess whether between-group differences in imagery-related activity were related to structural differences.

Materials and methods

Subjects

We included 25 patients with Parkinson's disease: 13 with FOG and 12 without FOG who were matched for disease severity and duration (Table 1, one patient with FOG was excluded from the analyses due to his inability to engage in imagery, see below). Patients were diagnosed according to the UK Brain Bank criteria (Hughes *et al.*, 1992). All patients except one used dopaminergic medication (levodopa or dopamine agonists). Patients were examined in the morning, at least 12 h after intake of the last dose of antiparkinsonism medication. Disease severity was assessed using the Hoehn and Yahr stages and Unified Parkinson's Disease Rating Scale (UPDRS). Patients with marked resting tremor were excluded. In the remaining patients, we carefully controlled for tremor influences on scanning results by recording electromyography (see below). Twenty-one healthy volunteers, matched for age and gender, served as controls (Table 1).

Patients with FOG were identified by three criteria: (i) convincing subjective reports of FOG, based on consistent and characteristic accounts of the phenomenon (including the typical feeling of the feet being glued to the floor); (ii) patient's recognition of typical phenotype when this was demonstrated to them by an experienced clinician, or using the New Freezing of Gait Questionnaire (NFOG-Q) video

Table 1 Clinical characteristics

Parameter	Group	n	Mean (SD)	P-value
Gender	Patients	24	9F/15M	0.18
	Controls	21	9F/12M	
	With FOG	12	4F/8M	0.22
	Without FOG	12	5F/7M	
Age (years)	Patients	24	60.2 (8.9)	0.25
	Controls	21	57.0 (9.1)	
	With FOG	12	58.7 (9.0)	0.2
	Without FOG	12	62.6 (7.1)	
Disease duration	With FOG	12	9.8 (4.6)	0.1
	Without FOG	12	7.1 (3.0)	
UPDRS III	With FOG	12	34.6 (9.6)	0.2
	Without FOG	12	28.6 (12.2)	
Frontal Assessment Battery	With FOG	12	16.5 (1.4)	0.22
	Without FOG	12	17.1 (0.8)	

Statistical inferences are based on independent samples *t*-test (chi-squared test for gender).

F = female; M = male; UPDRS III = Unified Parkinson's Disease Rating Scale Part 3.

(Nieuwboer *et al.*, 2009); and (iii) a standardized and videotaped gait trajectory was performed containing specific elements known to provoke FOG (Snijders *et al.*, 2008). These videos were rated offline for the presence of FOG by two different experts. Nine of the 12 patients with FOG (75%) also showed FOG during physical examination. None of the patients without FOG experienced subjective freezing, recognized the phenotype when this was demonstrated to them or manifested freezing during physical examination. The median New Freezing of Gait Questionnaire score (Nieuwboer *et al.*, 2009) for patients with FOG was 12.4, range 5–27. The score for patients without FOG was 0.

All subjects were right handed according to the Edinburgh Handedness Inventory, had no cognitive dysfunction (Mini-Mental State Examination >24, Frontal Assessment Battery >13) and no vestibular, orthopaedic, neurological or psychiatric diseases. Before participation, subjects received the (unrevised) Vividness of Motor Imagery Questionnaire (Isaac *et al.*, 1986) to screen for ability to perform MI. When a subject was unable to perform MI (Vividness of Motor Imagery Questionnaire score >200), the subject was excluded (one patient with FOG with a score of 240). Patients and controls were equally able to perform MI [one-way ANOVA, effect of group: $F(2,41) = 1.4$, $P = 0.24$], with scores comparable to age-matched healthy subjects (Mulder *et al.*, 2007). The study was approved by the local ethics committee and written informed consent was obtained from all subjects prior to the experiment according to the Declaration of Helsinki.

Tasks

We used a behaviourally validated protocol (Bakker *et al.*, 2007a) described in a previous functional MRI study of young healthy subjects (Bakker *et al.*, 2008). Briefly, subjects performed two tasks: MI of gait, during which they had to imagine walking along a path, and a matched visual imagery control task (VI), during which they imagined seeing a disc moving along the path (Fig. 1). Subjects were presented with a picture of a path with a target placed on it. They were asked to either imagine themselves walking towards the target (MI), or to imagine a disc moving towards the target (VI). During both tasks, the motion-relevant portion of the path could have two different widths (narrow, broad) and five different distances (2, 4, 6, 8 and 10 m). These manipulations allowed us to monitor the subject's ability to perform MI in the scanner (Bakker *et al.*, 2008). Specifically, imagery times for both VI and MI should vary with alterations in path length. Furthermore, only MI times should be susceptible to path width alterations, because a narrow path requires precision gait. Conversely, the VI task (a moving disc) should not be influenced by path width (Bakker *et al.*, 2008). The MI and VI tasks were performed in two successive sessions of 25 min each, separated by a break outside the scanner. The order of the sessions was counterbalanced across subjects. To control for actual movements related to tremor or overt leg movements, muscle activity from the forearm and lower leg was measured during the functional MRI experiment. For further details, see Supplementary Material.

After the imagery sessions, we tested subjects' actual walking along the same paths as displayed during the imagery session. Performance on each of the 10 experimental conditions (two different path widths over five different distances) was sampled once, recording the actual walking time with a stopwatch. These measurements served to confirm the relationship between imagined and actual walking performance (Bakker *et al.*, 2007a).

Behavioural analysis

We objectively monitored task performance by testing whether imagery times were modulated by the width and length of the path presented to the subjects. For each trial, imagery time was defined as the time between the button presses indicating the onset and offset of imagery. Trials in which subjects failed to press the button (either at the onset or offset of the imagery phase) were excluded from analyses [patients with FOG mean (range): 1.1 (0–4) trials; patients without FOG: 0.5 (0–3) trials; controls: 0.5 (0–5) trials]. Afterwards, the standard deviation (SD) of the mean picture inspection duration and imagery time was computed. Trials outside the mean ± 3 SD range were considered outliers and removed [patients with FOG mean (range): 1.2 (0–3) trials; patients without FOG: 0.6 (0–2) trials; controls: 0.8 (0–2) trials].

We considered the effect of 'Group' (Analysis 1: patients versus controls; Analysis 2: patients with FOG versus patients without FOG), 'Task' (MI, VI), 'Path Width' (narrow, broad) and 'Path Length' (2, 4, 6, 8, 10 m) on imagery time. The significance of the experimental factors was tested within the framework of the General Linear Model using two $2 \times 2 \times 2 \times 5$ mixed-effects ANOVAs. When interactions were significant, the simple main effects were investigated by additional ANOVAs. The α -level of all behavioural analyses was set at $P < 0.05$. In a separate analysis, we used Spearman's correlation to assess the relationship between actual walking times and mean imagery times across the different experimental conditions for patients and controls.

Preprocessing of imaging data

Functional data were preprocessed and analysed with Statistical Parametric Mapping (SPM5, www.fil.ion.ucl.ac.uk/spm). Details on MRI preprocessing can be found in the Supplementary Material.

Statistical analysis of imaging data

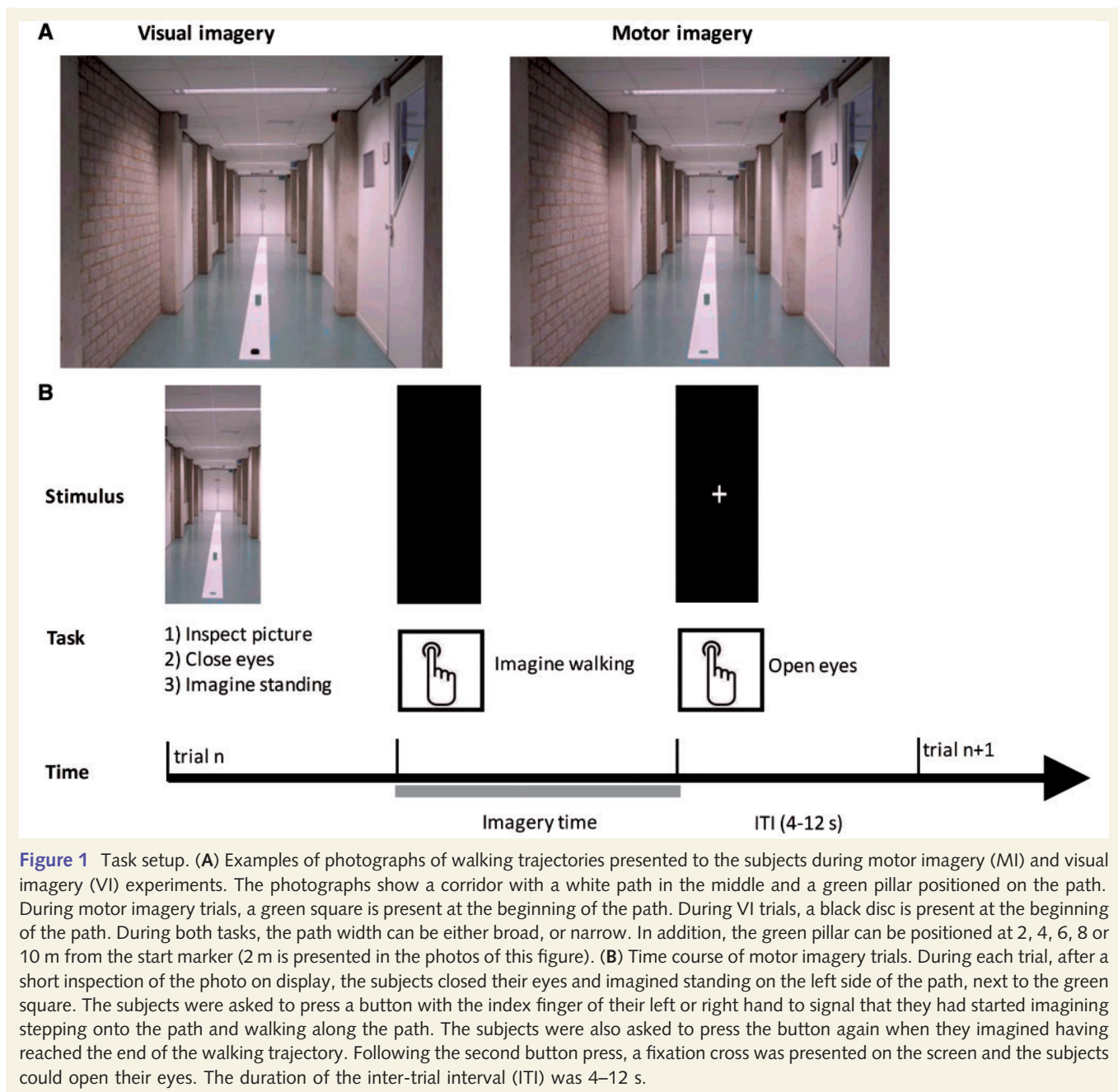
First level

The ensuing preprocessed functional MRI time series were analysed on a subject-by-subject basis using an event-related approach in the context of the General Linear Model (Friston *et al.*, 1995). The model was aimed at finding regions in which the cerebral response changed as a function of 'Task' (MI, VI) and/or 'Path Width'. 'Path Length' was also considered in the analysis, which gave rise to a model with 20 different regressors of interest. The model also included separate regressors of no interest, modelling blood oxygenation level-dependent imaging activity evoked by picture inspection, button presses and incorrect trials separately for each session. Further details can be found in the Supplementary Material.

Second level

We report the results of a random effects analysis. The statistical significance of the estimated evoked haemodynamic response was assessed using t -statistics in the context of the General Linear Model. For each subject, four contrast images (MI-broad, MI-narrow, VI-broad and VI-narrow) were calculated and entered into a second-level random effects analysis. Analogously to the analysis of the behavioural data, we considered two analyses: Analysis 1 compared controls with patients; Analysis 2 compared patients with FOG with patients without FOG.

First, we identified the cerebral correlates of MI of gait within each group, searching for brain responses that were larger for MI than for



VI (Analysis 1: control MI > control VI, Patient MI > Patient VI; Analysis 2: without FOG MI > without FOG VI, with FOG MI > with FOG VI). Second, we identified regions where task-related activity differed between groups, assessing the 'Group*Task' interaction [Analysis 1: (control MI > control VI) > (patient MI > patient VI), (patient MI > patient VI) > (control MI > control VI); Analysis 2: (with FOG MI > with FOG VI) > (without FOG MI > without FOG VI), (without FOG MI > without FOG VI) > (with FOG MI > with FOG VI)]. Third, we looked for the shared effects (across groups) of environmental constraints (i.e. 'Path Width') on MI-related activity, searching for brain responses that were larger during imagined walking on a narrow path than during imagined walking on a broad path (Analysis 1: control MI-narrow > control MI-broad, patient MI-narrow > patient MI-broad; Analysis 2: without FOG

MI-narrow > without FOG MI-broad, with FOG MI-narrow > with FOG MI-broad). Fourth, we assessed differential effects of 'Path Width' between groups, looking at the 'Group to Path Width' interaction.

Statistical inference ($P < 0.05$) was performed at the cluster level, correcting for multiple comparisons over the search volume (i.e. the whole brain) using family-wise error, given an intensity threshold of $t > 3.4$ (Friston *et al.*, 1996).

Region of interest analysis

Besides whole brain analyses, statistical inference was also performed on regions of interest that were based on our previous study in healthy controls (Bakker *et al.*, 2008) (Refer to Supplementary Material for

nomenclature and stereotactic coordinates of regions of interest). More precisely, we considered the local maxima of the clusters that were previously found to be significantly activated in the following contrasts: (i) 'MI > VI' for the analyses considering the effects of 'Task' and 'Group' described above; and (ii) 'MI-narrow > MI-broad' for the analyses considering the effects of 'Path Width' and 'Group'. More specifically, we drew spherical regions of interest centred at these coordinates with a radius of 8 mm. Statistical inference was performed at the voxel-level, with a family-wise error correction for multiple comparisons ($P < 0.05$).

Gait assessment

In a separate behavioural experiment, gait characteristics were measured with an electronic pressure-sensitive walkway (GAITrite, CIR Systems Inc., USA). This system consists of a 4.6 m long walkway, containing six sensor pads encapsulated in a roll-up carpet to produce an active area 61 cm wide and 366 cm long. This system captures the geometry and relative arrangement of each footfall as a function of time, and can detect gait alterations that are typical for Parkinson's disease (Almeida *et al.*, 2005). Subjects were asked to walk at their normal speed. This procedure was repeated three times. We compared normalized step length (step length/leg length) and gait asymmetry (natural logarithm) of the difference in the swing time of the slowest and swing time of fastest foot) between patients with FOG, patients without FOG and controls using univariate ANOVA and *post hoc* independent sample *t*-tests.

Brain-disease, brain-behaviour and structural–functional relationships

We tested whether the activity related to MI of gait was correlated with clinical characteristics (disease severity, disease duration and freezing severity). We considered the significant between-groups effects obtained in the second level analysis of the imaging data, and correlated subject-specific β -values (relative to the contrast MI minus VI) with the Unified Parkinson's Disease Rating Scale score, disease duration and New Freezing of Gait Questionnaire score, using Pearson's correlation with an α -level set at $P < 0.05$. We used Part 2 of the New Freezing of Gait Questionnaire score, looking at severity of FOG.

We also examined whether the activity in motor imagery-related areas was correlated to the kinematic characteristics of gait movements, and whether this effect varied among the three groups. We only considered effects that were robust to the removal of potential outliers (Z-score above/below 2.5 U). We considered the significant between-groups effects obtained in the second-level analysis of the imaging data, and we used a generalized linear model with subject-specific β -values (relative to the contrast MI minus VI) as a dependent variable, fixed factor of 'Group' and the gait parameters as covariates. The General Linear Model uses the Wald statistic with chi-square distribution to compute the individual contribution of predictors (Field, 2009). If a significant effect ($P < 0.05$) was found, *post hoc* univariate ANOVA was performed on the different groups with the gait parameter as a covariate.

In addition, we evaluated whether the between-group differences in imagery-related activity was associated with structural differences, performing a voxel-based morphometry analysis (Ashburner and Friston, 2000). We tested whether there were between-groups differences in grey matter, white matter or CSF volume (Analysis 1: controls versus

patients; Analysis 2: patients with FOG versus patients without FOG). We assessed regional differences, as well as differences over regions of interest based on the results of the whole-brain functional MRI analyses (mesencephalic locomotor region, Table 4), testing for the relevance of structural differences by correlating them to the magnitude of the functional differences (i.e. β -weights for the MI versus VI contrast). Statistical inference was performed at the voxel level, with a family-wise error correction for multiple comparisons ($P < 0.05$). For further details on the voxel-based morphometry analysis, refer to the Supplementary Material.

Anatomical inference

Anatomical details of significant signal changes were obtained by superimposing the statistical parametric maps on the anatomical sections of a representative subject of the MNI series. The atlas of Duvernoy was used to identify relevant anatomical landmarks (Duvernoy *et al.*, 1991). The Statistical Parametric Map Anatomy Toolbox was used for regions where cytoarchitectonic maps were available (Eickhoff *et al.*, 2005; Scheperjans *et al.*, 2008). We used the WFU PickAtlas Tool version 2.4 to translate MNI into Talairach coordinates (where necessary for relating our findings to existing literature). To define coordinates of mesencephalic locomotor regions, we used maps and coordinates (Zrinzo *et al.*, 2008; Eippert *et al.*, 2009; Keren *et al.*, 2009). The functional labelling of premotor cortical areas was based on criteria from Mayka *et al.*, (2006) and Picard and Strick (1996).

Results

During electrophysiological gait testing, patients had a smaller step length and an increased temporal gait asymmetry compared with controls (Table 2).

Behavioural results

Imagery times are shown in Fig. 2 and statistical values in Table 3. During the MI experiment, none of the patients with FOG experienced 'imagined' FOG. Although patients without FOG were numerically slower than patients with FOG (and controls) across both imagery tasks, imagery times for VI and MI were not statistically

Table 2 Gait data

Parameter	Group	Mean (SD)	P-value
Normalized step-length	Patients	0.71 (0.08)	0.009
	Controls	0.78 (0.08)	
Gait asymmetry	With FOG	0.66 (0.15)	0.17
	Without FOG	0.73 (0.07)	
	Patients	0.036 (0.027)	0.003
	Controls	0.015 (0.011)	
With FOG	0.040 (0.027)	0.5	
Without FOG	0.033 (0.029)		

Normalized step length: step length/leg length.

Gait asymmetry: natural logarithm of the difference in swingtime between the feet.

Statistical test: independent samples *t*-tests.

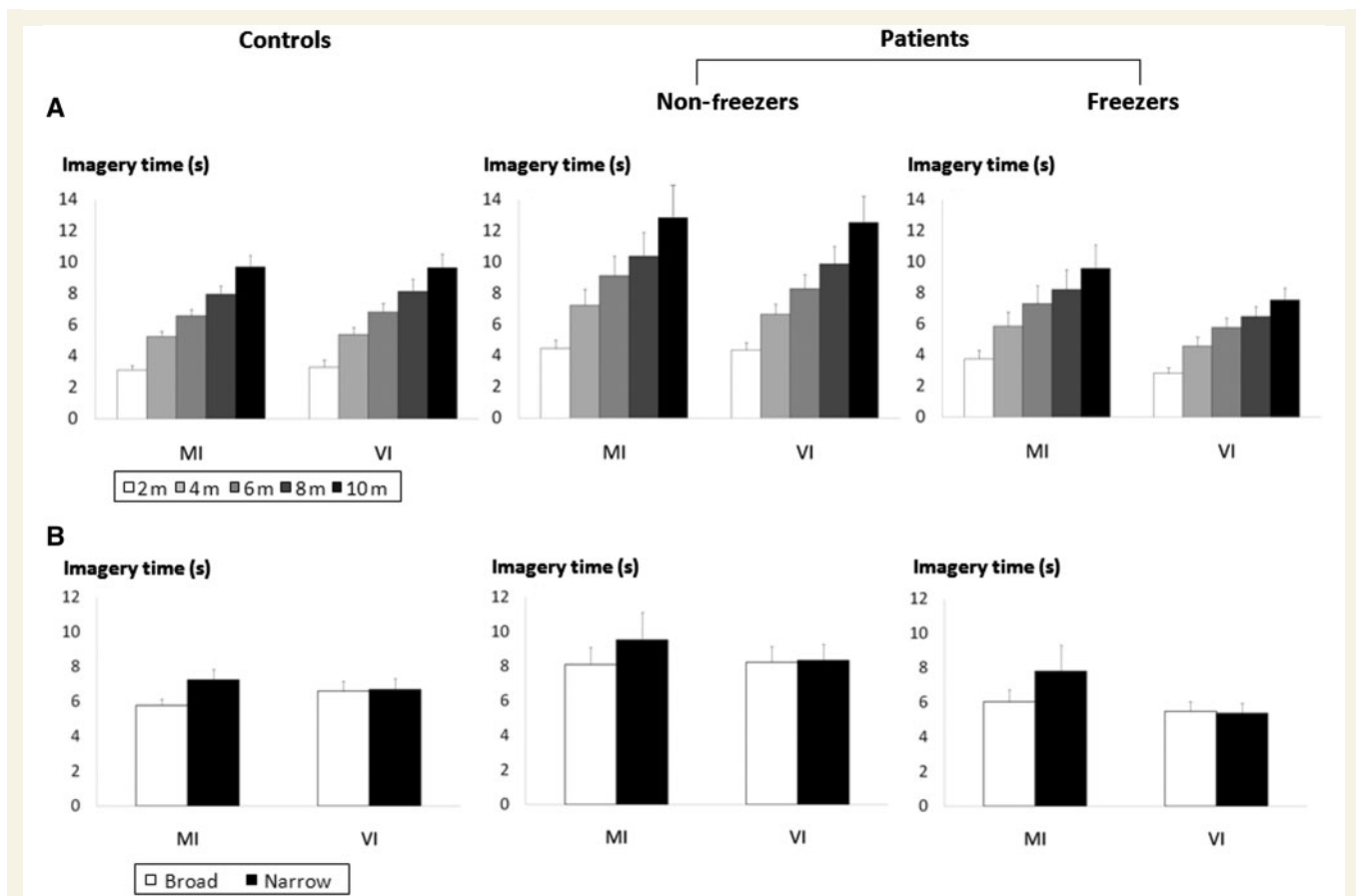


Figure 2 Behavioural performance during scanning. Average imagery times (\pm SEM) measured in patients with FOG (freezers), patients without FOG (non-freezers) and controls. (A) Imagery times for trials with different path lengths (2, 4, 6, 8 and 10 m) and (B) for trials with different path widths (broad, narrow).

Table 3 Behavioural performance (between-groups comparisons on imagery times)

Effect:	Patients versus Controls		With FOG versus Without FOG	
	F-statistics (df)	P-value	F-statistics (df)	P-value
Group	<1 (1,43)	0.35	3.7 (1,22)	0.07
Task (MI versus VI)	1.3 (1,43)	0.26	2.5 (1,22)	0.13
Task \times Group	2.3 (1,43)	0.13	<1 (1,22)	0.44
Path length	69.8 (4,172)	<0.001	62.1 (4,88)	<0.001
Path length \times Group	1.5 (4,172)	0.23	2.8 (4,88)	0.61
Task \times path width	17.5 (1,43)	<0.001	8.8 (1,22)	0.007
Task \times path width \times Group	<1 (1,43)	0.734	<1 (1,22)	0.80

Statistical test: repeated measures ANOVA.

different between groups (no effect of 'Group', Table 3, Fig. 2). In addition, there was no difference between MI and VI (no effect of 'Task', Table 3). The effect of task on imagery times did not differ between groups (no 'Task*Group' interaction, Table 3, Fig. 2B) and showed that all groups performed the imagery adequately. First, there was an effect of increasing path length in both tasks, and this effect was not different between groups (significant effect 'Path Length' and no interaction 'Group*Path Length', Table 3, Fig. 2A). Second, the effect of path width on imagery times differed for the different tasks, which was not different

between groups (significant 'Task*Path Width' interaction, no interaction 'Task*Path Width*Group', Table 3, Fig. 2B). A smaller path width resulted in longer imagery times in the MI task [$F(1,42) = 17.7$, $P < 0.001$], but had no effect on imagery times in the VI task [$F(1,42) = 0.4$, $P = 0.52$]. Actual and imagined walking times were significantly correlated, both in controls ($\rho = 0.78$, $P < 0.001$) and in patients ($\rho = 0.54$, $P < 0.001$). The correlation was also significant for the patient with FOG and patients without FOG subtype separately (patients with FOG: $\rho = 0.77$, $P < 0.001$, patients without FOG: $\rho = 0.53$, $P < 0.001$).

Electromyography

There were no differences in EMG activity between VI and MI [effect 'Task' $F(1,43) = 1.7$, $P = 0.20$]. Patients showed more EMG activity than controls [effect 'Group' $F(1,43) = 5.4$, $P = 0.03$]. Crucially, there were no differences in EMG activity between the two groups (controls, patients) across tasks [Analysis 1: 'Task*Group' interaction: $F(1,43) = 1.3$, $P = 0.26$], nor between patients with FOG and patients without FOG across task [Analysis 2: 'Task*Group' interaction: $F(1,22) < 1$, $P = 0.50$]. Hence, differences in actual movements (related to tremor or overt leg movements during MI of gait) did not account for changes in differential (MI compared with VI) cerebral activity between groups.

Cerebral activity during motor imagery of gait for each group

Controls and patients (Analysis 1)

We could confirm the presence of significant MI effects in controls (control MI > control VI) in those areas previously reported in young healthy controls (Bakker *et al.*, 2008; control MI > control VI; region of interest (ROI) analysis; left and right supplementary motor cortex, left and right superior parietal lobule, right anterior cingulate lobule, left putamen; for statistical data see Supplementary Material). In the patient group, there was a significant effect of MI in the right supplementary motor cortex (patient MI > patient VI; ROI analysis, see Supplementary Table 1). Furthermore, a *post hoc* analysis assessing the cerebral effects evoked during MI of walking (as compared with the baseline provided by the inter-trial epochs) revealed clear responses in other portions of the known locomotor network (Jahn *et al.*, 2008), in particular, cerebellar and striatal regions both in patients and controls (Table 2, Fig. 2 and Supplementary Material).

Patients without and patients with freezing of gait (Analysis 2)

In patients without FOG, activity in both the right and the left supplementary motor cortex was larger during MI than during VI (without FOG MI > without FOG VI; ROI analysis; see Supplementary Material). In patients with FOG, none of the areas previously reported were significantly activated during MI (with FOG MI > with FOG VI; ROI analysis), but whole-brain analysis revealed a strong effect in the posterior mid-mesencephalon [mesencephalic locomotor region, local maximum (2 –30 –18), cluster size = 330, $Z = 5.2$, P (cluster-level corrected) = 0.004].

Differential cerebral activity during motor imagery of gait across groups

Controls and patients (Analysis 1)

ROI analysis of the differential MI-related activity of controls compared with patients [(control MI > control VI) > (patient MI > patient VI)], revealed a reduced activity in patients

compared with controls in the superior parietal lobule (Brodmann areas 5L and 7) and in the anterior cingulate cortex (caudal cingulate motor area, Brodmann area 24; Fig. 3; Table 4; Picard and Strick, 1996; Scheperjans *et al.*, 2008).

Patients without and patients with freezing of gait (Analysis 2)

Comparing patients without FOG to patients with FOG [(without FOG MI > without FOG VI) > (with FOG MI > with FOG VI); ROI analysis], there was no above threshold between-group difference, although there was a statistical trend towards increased activity in patients without FOG compared with patients with FOG in the left supplementary motor cortex (Brodmann area 6) and the right superior parietal lobule (Figs 3 and 4; Table 4).

Comparing patients with FOG to patients without FOG [(with FOG MI > with FOG VI) > (without FOG MI > without FOG VI); whole-brain analysis], there was increased imagery-related activity in the posterior mid-mesencephalon of patients with FOG (Fig. 4, Table 4).

The maximum of the cluster was located dorsomedial to the pedunculopontine nucleus, just including the pedunculopontine nucleus (Zrinzo *et al.*, 2008). The cuneiform nucleus and the periaqueductal grey were included in the cluster (Eippert *et al.*, 2009; Keren *et al.*, 2009). The locus coeruleus is located on the lower dorsal border of our cluster (Keren *et al.*, 2009). The mesencephalic locomotor region is a neurophysiologically defined region that includes the pedunculopontine nucleus, cuneiform nucleus, periaqueductal grey and locus coeruleus (Jordan, 1998). The activity we found most likely includes several nuclei of the mesencephalic locomotor region, especially the cuneiform nucleus and the periaqueductal grey.

Specific effects of environmental constraints on cerebral activity during motor imagery

We found no significant differential activity for MI of gait along a narrow compared with a broad path, nor was there a 'Group*Task' interaction for path width.

Brain-disease, brain-behaviour and structural–functional relationships

Differential mesencephalic locomotor region activity in patients with FOG (MI minus VI) correlated to FOG severity as measured by Part 2 of the New Freezing of Gait Questionnaire (Fig. 5A, $r = 0.60$, $P = 0.041$). Mesencephalic locomotor region activity correlated to disease duration, only significantly when taking both patient groups into account (Fig. 5B, patients with FOG $r = 0.53$, $P = 0.08$, all patients $r = 0.58$, $P = 0.003$). MI-related activity (MI > VI) in the supplementary motor cortex was associated with greater step length (General Linear Model effect STEP LENGTH Wald $\chi^2 = 41.0$, $P < 0.001$). *Post hoc* ANOVA showed a significant relation between supplementary motor cortex activity and step length in controls [$F(1,14) = 9.6$, $r^2 = 0.38$, $P = 0.01$] but not in patients with FOG [$F(1,8) < 1$, $r^2 = 0.10$, $P = 0.71$ after removal of outlier] or patients without FOG [$F(1,9) = 2.9$, $r^2 = 0.26$, $P = 0.12$]. MI-related activity (MI > VI) in the mesencephalic locomotor region, superior parietal lobule or caudal

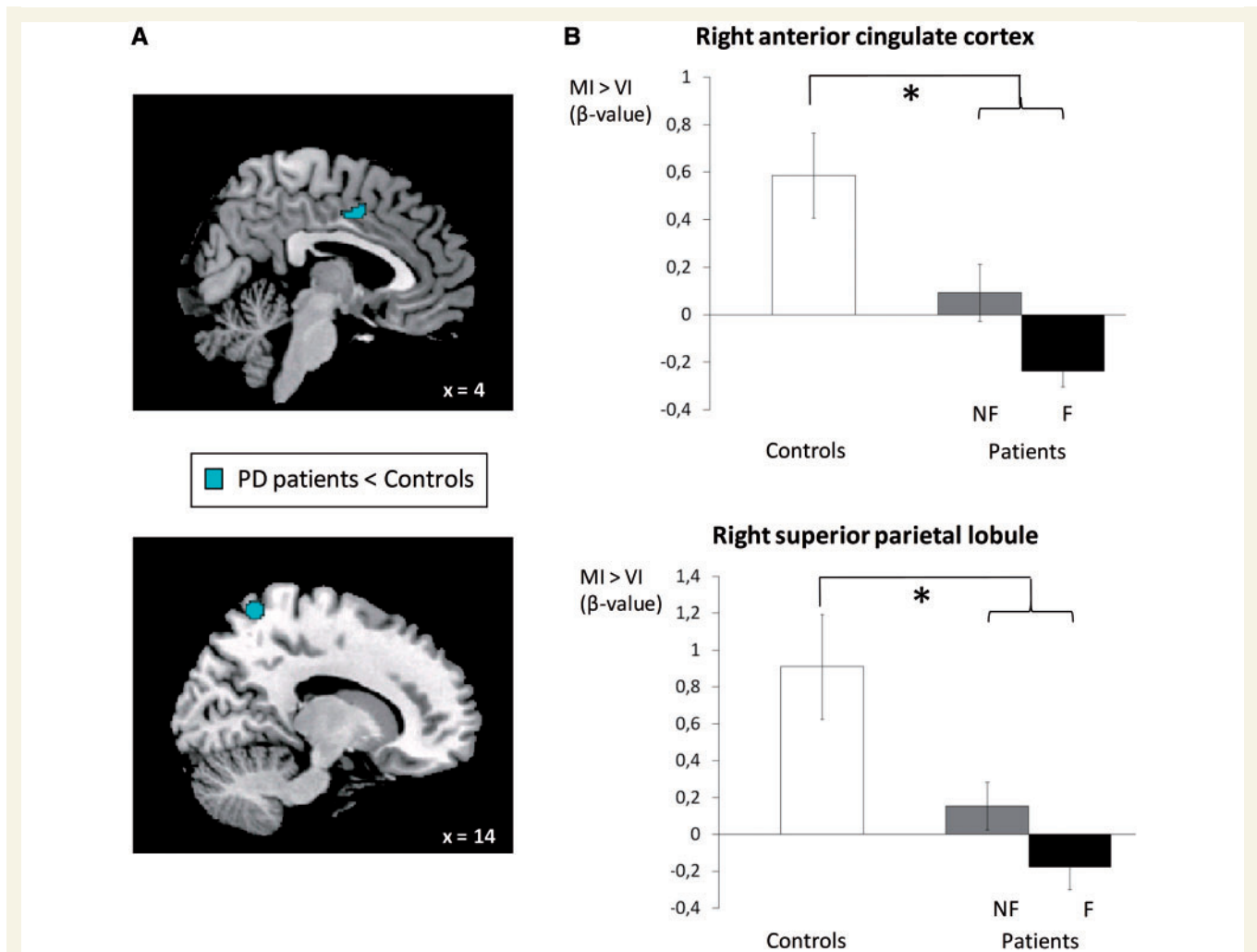


Figure 3 Imagery-related brain activity. Brain areas in which the relative increase in activity for motor imagery (MI) versus visual imagery (VI) was greater in controls than patients (region of interest analysis, $P < 0.05$ corrected for multiple comparisons using family-wise inference on voxel level). (A) Statistical parametric maps of increased activity in the right superior parietal lobule and right anterior cingulate cortex, superimposed on a sagittal brain section (*top*: superior parietal lobule, *bottom*: caudal cingulate motor area). (B) β -weights of the contrast between motor imagery and VI (mean \pm SEM) from right caudal cingulate motor area cluster (*top*) and the right superior parietal lobule cluster (*bottom*) in controls, patients without FOG and patients with FOG. PD = Parkinson's disease; F = patients with FOG; NF = patients without FOG. Top: caudal cingulate motor area, bottom: superior parietal lobule. And ADD: * = significant difference of $P < 0.05$.

Table 4 Stereotactic coordinates of local maxima with differential cerebral activity during MI of gait across groups

Contrast	Search volume	Anatomical label	Functional label	Cluster size	Hemi-sphere	Z-value	P-value	x	y	z
Analysis 1: Controls versus Patients										
(control MI > control VI) > (Patient MI > Patient VI)	Region of interest	Superior parietal lobule	Area 5L	144	Right	3.1	0.019	14	-58	66
		Anterior cingulate cortex	Area 24	65	Right	3.0	0.025	2	2	40
Analysis 2: Patients Without FOG versus patients With FOG										
(without FOG MI > without FOG VI) > (with FOG MI > with FOG VI)	Region of interest	Superior parietal lobule	Area 5L	93	Right	2.6	0.074	22	-50	72
		Superior frontal gyrus	Supplementary motor cortex	64	Left	2.6	0.061	-10	-16	72
(with FOG MI > with FOG VI) > (without FOG MI - without FOG VI)	Whole brain	Posterior mid-mesencephalon	Mesencephalic locomotor region	170		4.5	0.049	0	-28	-20

Results of whole-brain analysis are corrected for multiple comparisons for search over the whole brain using cluster-level family-wise inference ($P < 0.05$).

Results of region of interest analysis are corrected for multiple comparisons over the region of interest volume using voxel-level family-wise inference ($P < 0.05$).

Stereotactic coordinates are reported in Montreal Neurological Institute space. Details on the anatomical and functional labelling can be found in the Materials and methods section.

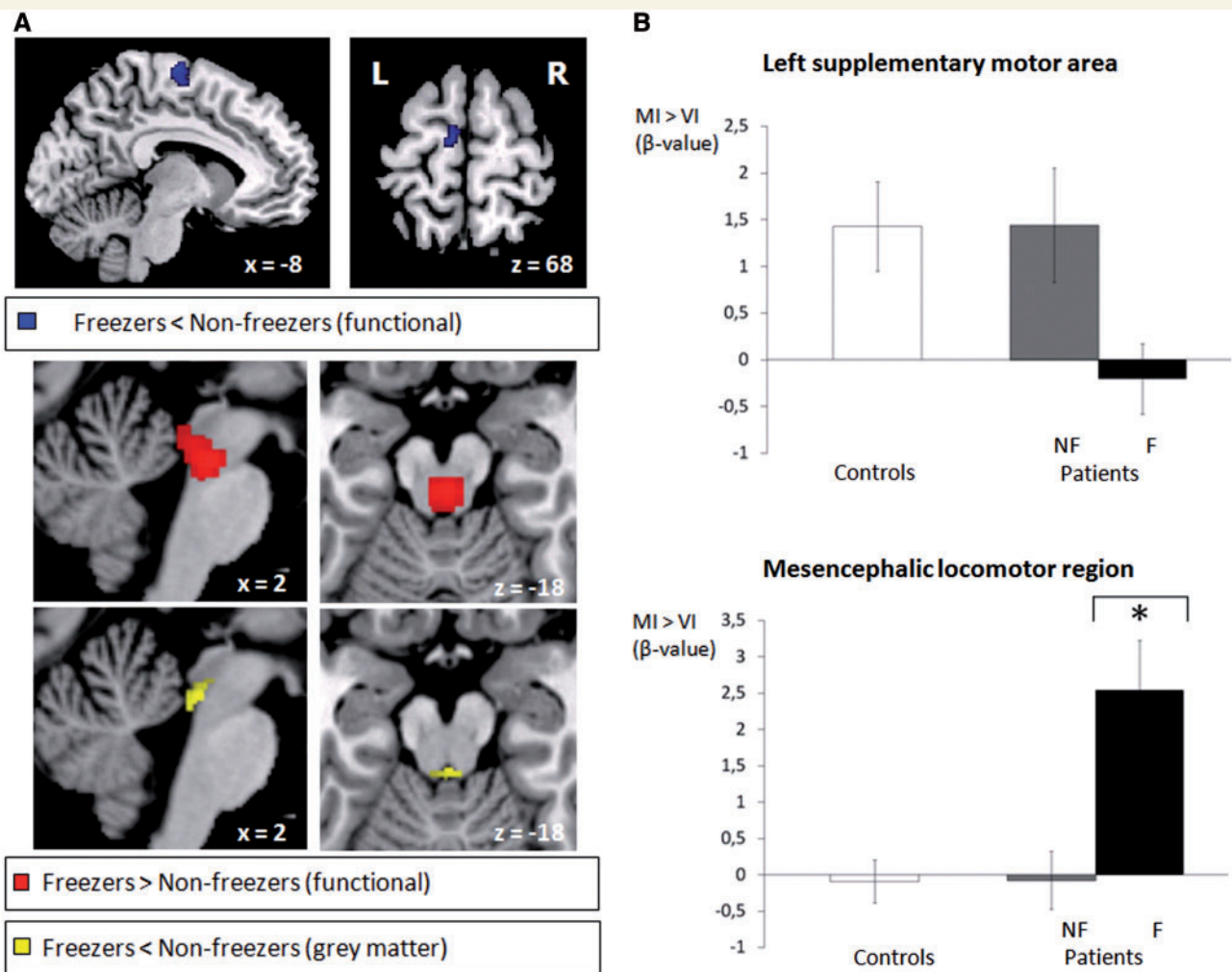


Figure 4 Imagery-related brain activity. Brain areas in which the relative increase in activity for motor imagery (MI) versus visual imagery (VI) differed between patients with FOG (freezers) and patients without FOG (non-freezers; supplementary motor cortex): region of interest analysis, $P = 0.06$ corrected for multiple comparisons using family-wise inference on voxel level; mesencephalic locomotor region whole brain search, $P < 0.05$ corrected for multiple comparisons using family-wise error (cluster level). (A) Statistical parametric map of decreased activity in the supplementary motor cortex and increased activity in the mesencephalic locomotor region, superimposed on a sagittal brain section (top-left: supplementary motor cortex, middle-left: mesencephalic locomotor region) and a transversal brain section (top-right: supplementary motor cortex, middle-left: mesencephalic locomotor region). The bottom brain sections include the small cluster with significant difference in grey matter between patients with FOG and patients without FOG in the mesencephalic locomotor region. (B) β -weights of the contrast between MI and VI (mean \pm SEM) from the supplementary motor cortex cluster (top) and the mesencephalic locomotor region cluster (bottom) in controls, patients without FOG and patients with FOG. F = patients with FOG; NF = patients without FOG. * = significant difference of $P < 0.05$.

cingulate motor area was not associated with step length or gait asymmetry.

There were no differences in global grey matter, white matter or CSF volume between groups (patients versus controls; patients with FOG versus patients without FOG) [voxel-based morphometry Analysis 1: grey matter: $F(1, 41) = 0.753$, $P = 0.391$; white matter: $F(1, 41) = 0.215$, $P = 0.645$; CSF: $F(1, 41) = 0.329$, $P = 0.569$; Analysis 2: grey matter: $F(1, 20) = 0.401$, $P = 0.534$; white matter: $F(1, 20) = 0.321$, $P = 0.577$; CSF: $F(1, 20) = 0.406$, $P = 0.531$]. The analysis of regional volume differences between groups did not show any differences in local grey matter, white

matter or CSF between groups at a whole-brain corrected threshold of $P < 0.05$. When focusing on the mesencephalic locomotor region cluster found in the comparison between patients with FOG and patients without FOG [(with FOG MI > with FOG VI) > (without FOG MI > without FOG VI)], there was a significantly larger grey matter volume in the latter group [2, -33, -18; $Z = 2.89$, P (voxel-level corrected) = 0.028, Fig. 4, Supplementary Fig. 1]. The magnitude of this structural difference did not correlate to FOG severity ($r = 0.28$, $P = 0.37$). Crucially, the gait-related difference found in the mesencephalic locomotor region did not correlate to the proportion of grey matter in this

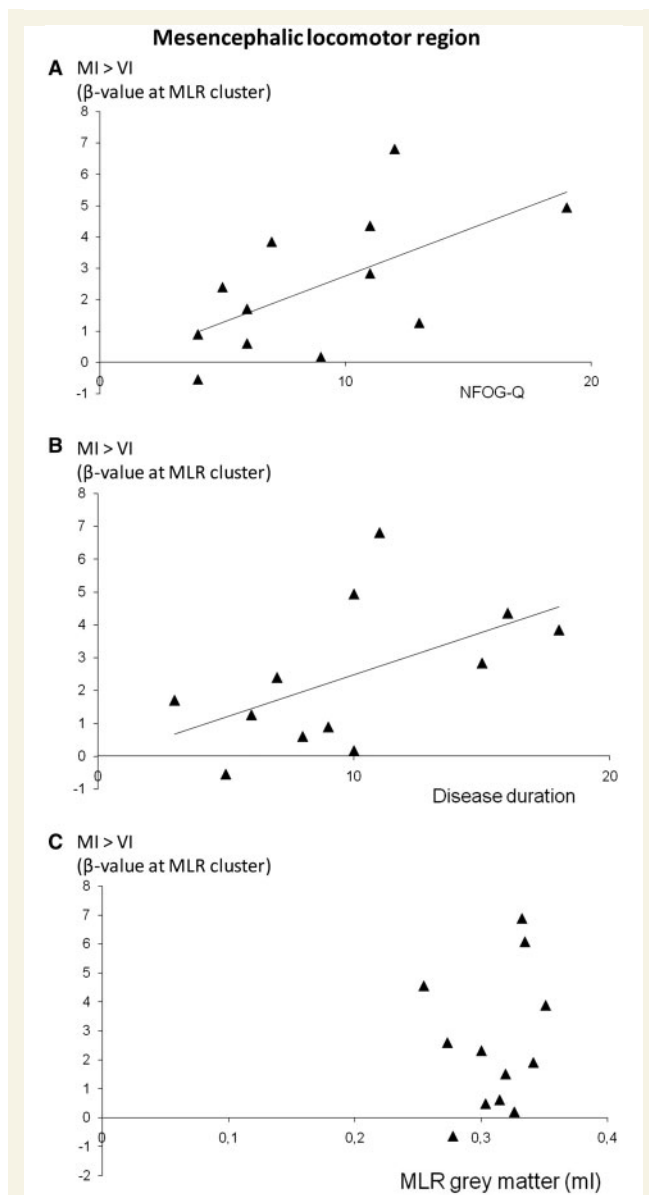


Figure 5 Brain-disease and structural–functional relationships. Relation between differential cerebral activity and clinical/structural parameters in patients with FOG. (A) Scatterplot of β -weights of the contrast between MI and VI from the mesencephalic locomotor region (MLR) cluster (y-axis) against score on the New Freezing of Gait Questionnaire Part 2 (NFOG-Q; x-axis; Pearson's correlation $r = 0.60$, $P = 0.04$). (B) Scatterplot of β -weights of the contrast between MI and VI from the mesencephalic locomotor region cluster (y-axis) against disease duration (in years; x-axis; $r = 0.53$, $P = 0.08$). (C) Scatterplot of β -weights of the contrast between MI and VI from the mesencephalic locomotor region cluster (y-axis) against grey matter volume of the same cluster (x-axis; $r = -0.17$, $P = 0.44$).

same region (MI versus VI; $r = 0.17$, $P = 0.60$, Fig. 5C). This indicates that differential brain atrophy between the patients with FOG and patients without FOG cannot account for the gait-related differences we observed in this region.

Discussion

We used MI to investigate alterations in cerebral activity related to planning of walking in patients with Parkinson's disease with or without FOG. We showed that the mesencephalic locomotor region, just dorsomedial to the pedunculopontine nucleus, contributed to MI of gait in patients with FOG but not in patients without FOG or controls. This altered cerebral activity was not confounded by the effects of altered motor execution, somatosensory processing, task performance or brain atrophy, and it was related to subjective FOG severity. In addition, controls and patients without FOG recruited the supplementary motor cortex during MI of gait, while patients with FOG did not. Patients with FOG and patients without FOG, taken together, showed less MI-related activity in the superior parietal lobule (Brodmann areas 5L and 7) and in the anterior cingulate cortex (Brodmann area 24) than controls.

Increased gait-related activity

Mesencephalic locomotor region

Patients with Parkinson's disease with FOG solved the MI task by evoking additional activity in the posterior mid-mesencephalon. This region includes several components of the mesencephalic locomotor region, namely the pedunculopontine nucleus, the cuneiform nucleus and the periaqueductal grey. The pedunculopontine nucleus has been implied in the pathophysiology of akinesia and gait disorders in Parkinson's disease, based on several observations. In animal experiments and human case studies, lesions of the pedunculopontine nucleus yield akinesia, while stimulation or disinhibition of the pedunculopontine nucleus alleviates akinesia (Masdeu *et al.*, 1994; Pahapill and Lozano, 2000; Plaha and Gill, 2005; Stefani *et al.*, 2007). Direct electrical stimulation of the pedunculopontine nucleus in humans has, so far, resulted in only modest and non-significant effects on gait (Ferraye *et al.*, 2010). Analysis of electrode positions among the few patients that received the greatest benefit from pedunculopontine nucleus stimulation suggested that a more posterior stimulation may afford greater beneficial effects on gait (Ferraye *et al.*, 2010; P. Pollak, Personal communication). In another study, this more posterior part of the mesencephalon was activated by mimicked gait in patients with Parkinson's disease (Piallat *et al.*, 2009). Those findings suggest that either the pedunculopontine nucleus lies more posterior than previously suspected, or that the subcuneiform/cuneiform nucleus was stimulated. The cluster found in the present study included the pedunculopontine nucleus, with the local maximum located in the cuneiform nucleus, and reaching the periaqueductal grey, a structure severely affected by Parkinson's disease (Zweig *et al.*, 1989; Braak *et al.*, 2000). We also found grey matter atrophy in the mesencephalic locomotor region in patients with FOG compared with patients without FOG, although this did not account for the differences in gait-related mesencephalic locomotor region activity. Taken together, these observations suggest that the mesencephalic locomotor region, and in particular, the cuneiform nucleus and the periaqueductal grey, may be involved in FOG.

Compensation or pathology?

The mesencephalic locomotor region is recruited during actual gait in humans (Hanakawa *et al.*, 1999). Output from this structure is probably inhibited during MI of gait, to prevent the mesencephalic locomotor region from driving the actual walking generators (Kaas *et al.*, 2010). Accordingly, the increased gait-related mesencephalic locomotor region activity we observed in patients with Parkinson's disease with FOG may be pathological, reflecting a decreased inhibition from the basal ganglia. Other findings support this interpretation. First, increased mesencephalic locomotor region activity was associated with higher subjective FOG severity scores. Second, the magnitude of mesencephalic locomotor region activity evoked during MI of gait was correlated to disease duration. This finding fits with the observation that longer disease duration increases the likelihood of developing FOG (Macht *et al.*, 2007), with the mesencephalic locomotor region becoming more affected as Parkinson's disease progresses (Braak *et al.*, 2000). Third, ischaemic lesions in the dorsomedial mesencephalic locomotor region cause gait ataxia, but not a hypokinetic-rigid gait (Hathout and Bhidayasiri, 2005).

However, if gait-related activity in the mesencephalic locomotor region of patients with FOG were exclusively pathological in nature, then how could patients with FOG have solved the task as adequately as patients without FOG and controls, despite their altered cortical responses during imagery of gait? This could point to a possible compensatory role of the mesencephalic locomotor region. This possibility is supported by recent findings, showing increased mesencephalic locomotor region activity when healthy controls perform MI of gait involving frequently repeated periods of gait initiation and termination, but less prominent activation during stable gait (la Fougere *et al.*, 2010). The latter finding fits with the absence of gait-related mesencephalic locomotor region activity in our controls, who also imagined a stable gait. Crucially, we showed that patients with FOG deviate from this pattern, showing strong mesencephalic locomotor region activity even during imagery of stable gait. This observation also fits with the increased mesencephalic locomotor region electrophysiological activity observed in patients with FOG during mimicked stepping movements (Piallat *et al.*, 2009). Taken together, these findings suggest that the mesencephalic locomotor region might play both a compensatory and a pathological role, dependent on the computational demands imposed on this structure and on disease progression. We speculate that early in the disease, possibly even at a presymptomatic stage (Buhmann *et al.*, 2005), medial frontal areas (supplementary motor cortex) of prospective patients with FOG fail to regulate step length. At such early stages, increased mesencephalic locomotor region activity could play a compensatory role, supporting gait planning and execution. However, the mesencephalic locomotor region's ability to control gait may be limited, especially when the structure becomes more severely affected with disease progression. Additional requirements to finely adapt gait parameters to time-varying demands, as during turning and step initiation, might then lead to a collapse of this compensatory system. This scenario would reconcile a compensatory role of the mesencephalic locomotor region during stable gait, with a pathological contribution under more demanding circumstances.

Decreased gait-related cortical activity

Cingulate and supplementary motor areas

Gait-related activity in the caudal cingulate motor area was decreased in patients with Parkinson's disease compared with controls. The caudal cingulate motor area is involved in updating and switching action plans (Rushworth *et al.*, 2002; Helmich *et al.*, 2009). We suggest that alteration of gait-related cingulate motor area activity might create a precondition for the manifestation of FOG, limiting the ability of patients with Parkinson's disease to switch between motor programmes. This is especially required by situations that require rapid gait adjustments like turning and step initiation.

Failures in additional gait-related cerebral structures may be necessary to actually evoke FOG. One example is the supplementary motor cortex. Unlike controls and patients without FOG, patients with Parkinson's disease with FOG solved the MI task without evoking additional activity in the supplementary motor cortex, as compared with a VI control task. The observed cluster falls within the portion of the supplementary motor cortex concerned with leg movements (Fink *et al.*, 1997). This portion of the supplementary motor cortex is also hypoactive in patients with age-related white matter changes and gait disturbances such as freezing of gait (Iseki *et al.*, 2010). Hypoactivity in the supplementary motor cortex is associated with hypokinesia in Parkinson's disease (Sabatini *et al.*, 2000; Nachev *et al.*, 2008), and movement amplitude in patients with Parkinson's disease improves when supplementary motor cortex activity is normalized (e.g. after medication, motor cortex stimulation or deep brain stimulation) (Tani *et al.*, 2007; Fasano *et al.*, 2008; Nachev *et al.*, 2008; Ballanger *et al.*, 2009). Furthermore, decreased supplementary motor cortex activity is related to higher cadence and decreased step length in patients with Parkinson's disease (Hanakawa *et al.*, 1999). Accordingly, in this study we show a relation between brain activity in the supplementary motor cortex (during MI) and step length (during actual walking outside the scanner). These findings suggest that the decreased supplementary motor cortex activity observed in patients with FOG may be related to altered regulation of step amplitude. The emphasis here is on abnormal regulation, since patients with FOG could produce step amplitudes largely overlapping with those of patients without FOG and controls. As such, this finding qualifies the hypothesis that a failure to generate steps of adequate amplitude could lead to a progressive decrease in step amplitude, and ultimately produce FOG (Chee *et al.*, 2009).

Superior parietal lobule

During MI of gait, cerebral activity in the right superior parietal lobule was reduced in patients compared with controls. This confirms previous SPECT findings related to gait execution in Parkinson's disease (Hanakawa *et al.*, 1999). We suggest that the reduced activity in the superior parietal lobule of patients with Parkinson's disease during imagery of gait underlies their difficulty in predicting the somatosensory consequences of a motor plan (Wolpert *et al.*, 1998; Blakemore and Sirigu, 2003). This interpretation fits with the known impairments of patients

with Parkinson's disease in integrating proprioceptive information into a motor plan (Lewis and Byblow, 2002; Almeida *et al.*, 2005; Keijsers *et al.*, 2005).

Interpretational issues

Patients were classified as 'patients with FOG' when there was an evident history of FOG. All patients with FOG reported the characteristic gluing of the feet and recognized the typical phenotype when this was demonstrated to them. Most patients also showed FOG during neurological examination. We included patients with relatively mild FOG, as this facilitated a proper match between patients with FOG and patients without FOG with respect to disease severity and duration. This may explain why three patients with mild freezing did not demonstrate FOG during clinical examination, despite convincing subjective accounts of FOG. *Post hoc* exploratory analyses suggested that the mesencephalic locomotor region activation in these patients without objective FOG was intermediate between fully overt patients with FOG and patients without FOG, perhaps reflecting a spectrum of severity (data not shown).

All three groups performed the task proficiently, without overall differences in imagery times between groups. Patients without FOG showed a trend towards slower imagery times, but this included both the MI and VI task. Hence, this tendency for different imagery times cannot explain the differential (MI > VI) functional brain activity. Moreover, in all groups, imagery times were equally sensitive to the length and width of the path and correlated to actual walking times. These findings indicate that both patients and controls were equally effective in solving the MI task. This excludes task difficulty as an explanation for between-group cerebral differences during MI.

The basal ganglia are affected in Parkinson's disease and are involved in MI of gait in young healthy subjects (Bakker *et al.*, 2008). Moreover, other studies have suggested that failure of the caudate nucleus may contribute to FOG (Bartels *et al.*, 2006). However, we found no differences in cerebral activity in the basal ganglia between patients and controls. This is probably a sign of the extreme selectivity of our functional comparison (MI versus VI), rather than a lack of sensitivity (Supplementary Table 2 and Fig. 2).

Conclusion

We have shown that patients with Parkinson's disease with FOG performing MI of gait use different cerebral structures than matched patients with Parkinson's disease without FOG or healthy controls. These cerebral differences were observed in the context of matched behavioural performance across groups, and could not be explained by brain atrophy. During imagined walking, patients with Parkinson's disease with FOG showed increased activity in the mesencephalic locomotor region, which was related to subjective FOG severity. In addition, patients with Parkinson's disease with FOG tended to have reduced activity in mesial frontal and posterior parietal regions. These findings provide new insights into the pathophysiology of FOG; the cause of FOG may be altered

cortical regulation of movement execution, together with a progressively impaired ability of mesencephalic structures to flexibly compensate for that alteration. This may explain the manifestation of FOG during changes in motor behaviour, such as turning or initiating walking. These gait adaptations not only require a switch of motor programme, but also more precise regulation of step length and gait timing.

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Supplementary material

Supplementary material is available at *Brain* online.

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