Brain Advance Access published March 12, 2013

BRAIN
A JOURNAL OF NEUROLOGY

Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease

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Freezing of gait is a devastating symptom of advanced Parkinson's disease yet the neural correlates of this phenomenon remain poorly understood. In this study, severity of freezing of gait was assessed in 18 patients with Parkinson's disease on a series of timed 'up and go' tasks, in which all patients suffered from episodes of clinical freezing of gait. The same patients also underwent functional magnetic resonance imaging with a virtual reality gait paradigm, performance on which has recently been shown to correlate with actual episodes of freezing of gait. Statistical parametric maps were created that compared the blood oxygen level-dependent response associated with paroxysmal motor arrests (freezing) to periods of normal motor output. The results of a random effects analysis revealed that these events were associated with a decreased blood oxygen level-dependent response in sensorimotor regions and an increased response within frontoparietal cortical regions. These signal changes were inversely correlated with the severity of clinical freezing of gait. Motor arrests were also associated with decreased blood oxygen level-dependent signal bilaterally in the head of caudate nucleus, the thalamus and the globus pallidus internus. Utilizing a mixed event-related/block design, we found that the decreased blood oxygen level-dependent response in the globus pallidus and the subthalamic nucleus persisted even after controlling for the effects of cognitive load, a finding which supports the notion that paroxysmal increases in basal ganglia outflow are associated with the freezing phenomenon. This method also revealed a decrease in the blood oxygen level-dependent response within the mesencephalic locomotor region during motor arrests, the magnitude of which was positively correlated with the severity of clinical freezing of gait. These results provide novel insights into the pathophysiology underlying freezing of gait and lend support to models of freezing of gait that implicate dysfunction across coordinated neural networks.

Keywords: functional magnetic resonance imaging; freezing of gait; Parkinson's disease; basal ganglia; subthalamic nucleus
Abbreviation: BOLD = blood oxygen level-dependent

Introduction

Freezing of gait is a common symptom of Parkinson's disease in which patients experience the feeling that their feet become glued to the floor whilst walking (Giladi *et al*., 2001). Although the pathophysiology remains poorly understood (for reviews see Nutt *et al*., 2011; Shine *et al*., 2011*a*), it is well recognized that a number of specific triggers can either provoke freezing, such as

Received November 11, 2012. Revised December 31, 2012. Accepted January 22, 2013

the clinical 'OFF' state (Almeida *et al*., 2007), walking through a narrow doorway (Almeida and Lebold, 2010) and dual-task walking (Hausdorff *et al*., 2005) or relieve freezing, such as visual and auditory cues (Nieuwboer *et al*., 2007). In addition, freezing behaviour in Parkinson's disease is not limited to gait, with a number of studies showing that it also affects other domains, including upper limb movements and speech (Giladi *et al*., 1992; Almeida *et al*., 2002; Nieuwboer *et al*., 2009; Naismith and Lewis, 2010), suggesting that the mechanism underlying freezing in Parkinson's disease is because of dysfunction across neural regions supporting more general functions (Nutt *et al*., 2011; Shine *et al*., 2011*a*).

Identifying the neural correlates of freezing of gait has been limited by the restrictions that accompany the neuroimaging of gait *per se* (Bakker *et al*., 2007). Previous research has relied on temporally insensitive techniques, such as PET, or on the combination of functional MRI with non-motor tasks such as imagined walking paradigms (Jahn *et al*., 2004; Snijders *et al*., 2011) or watching a first-person perspective video recording of an actor walking (Wang *et al*., 2007). Alternatives to modelling gait in the neuroimaging setting are seen in studies that have utilized bimanual lower limb tasks that successfully stimulate the ongoing interhemispheric coordination requisite for normal gait (Kapreli *et al*., 2006, 2007). While by definition these tasks cannot measure some important variables in the production of gait such as balance and gravity, they provide a unique insight into the preparation and execution of bipedal motor tasks.

In spite of these limitations, much insight into freezing of gait has been gained from neuroimaging techniques (Bartels and Leenders, 2008). A number of studies of functional metabolism and the role of specific modulatory neurotransmitters have proposed that freezing of gait is likely to be because of dysfunction within a distributed network of frontal and parietal cortical regions (Wu and Hallett, 2005; Bartels *et al*., 2006; Bartels and Leenders, 2008; Wu and Hallett, 2008; Wu *et al*., 2010; Tessitore *et al*., 2012*a*, *b*). Such a formulation is consistent with a number of previously proposed freezing of gait hypotheses (Almeida *et al*., 2005; Hallett, 2008; Lewis *et al*., 2009). In addition to these corticostriatal networks, a recent functional MRI study using motor imagery in a group of patients with freezing of gait has shown preferential activation in localized areas of the brainstem (such as the mesencephalic locomotor region), that have been previously implicated in models of locomotor dysfunction (Jacobs and Horak, 2007; Snijders *et al*., 2011).

Although much of the symptomatology observed in Parkinson's disease relates to the relative lack of dopamine in the basal ganglia, to our knowledge no neuroimaging study has specifically explored the role of subcortical dysfunction in freezing of gait. Indeed, subcortical regions are likely to play an important role in the pathophysiology of freezing of gait, either through the striatal integration of sensory and motor corticothalamic activity during gait (Almeida *et al*., 2007), the effective switching of activity between competing yet complimentary neural networks (Lewis and Barker, 2009; Naismith *et al*., 2010), the mediation of ongoing activity within cortical regions such as the pre-supplementary motor area (Jacobs *et al*., 2009) and/or by exerting top-down control over the caudal brainstem structures controlling gait (Jahn *et al*., 2004; Snijders *et al*., 2011).

To investigate the neural correlate of freezing behaviour, our group has developed a novel (virtual reality) paradigm in which subjects navigate a non-immersive, yet realistic 3D environment using footpedals to control their 'walking'. The virtual reality task requires bipedal motor activity whilst processing cognitive and environmental information. Performance on this virtual reality task has previously been correlated with self-reported freezing of gait symptoms (Naismith and Lewis, 2010) and more recently, with the severity of actual recorded episodes of freezing of gait (Shine *et al*., 2012*b*). In addition, the task has recently been successfully combined with functional MRI in a proof-of-concept study in a single patient with freezing of gait (Shine *et al*., 2011*b*). Together, these results suggest that the virtual reality task represents an ecologically valid model of the freezing phenomenon in Parkinson's disease.

The current study utilized this virtual reality gait paradigm to determine the specific cortical and subcortical neural correlates associated with freezing behaviour in a group of patients with Parkinson's disease who experience significant freezing of gait while in their clinical OFF state.

Materials and methods

Patient details

The 18 patients in this study were all males with idiopathic Parkinson's disease and an average age of 66.8 years (see Table 1 for further demographics). All patients were assessed on section III of the Unified Parkinson's Disease Rating Scale (Goetz *et al*., 2007) immediately prior to scanning in their clinically defined OFF state, having withdrawn from dopaminergic medications overnight. This 'washout' period may not be sufficient to exclude all of the effects from longer acting medications; however, only three patients were taking

Table 1 Demographic, neuropsychiatric and virtual reality characteristics

	Range	Mean	SD
Demographics			
n = 18			
Age (years)	50–84	66.8	8.2
Hoehn and Yahr stage	2–4	2.2	0.5
UPDRS-III	13–71	39.2	13.6
FOG-Q (total score)	5–21	12.4	4.3
Disease duration (years)	1–26	6.2	5.7
Time frozen on timed up and go tasks (%)	2–62	18.2	18.0
Number of freezing episodes during timed up and go	2–49	16.0	4.2
Virtual reality measures			
Motor arrests, total	7–116	55.7	40.1
Motor arrests: low cognitive load block	0–51	23.3	27.5
Motor arrests: high cognitive load block	6–72	32.4	22.3
Motor arrests following indirect cues	0–28	15.2	7.7
Motor arrests following narrow doorways	0–51	17.8	13.3

UPDRS-III = Unified Parkinson's Disease Rating Scale (Part III); FOG-Q = Freezing of Gait-Questionnaire.

dopamine agonists. The University of Sydney Human Research and Ethics Committee approved the study and written informed consent was obtained from each patient. Patients were initially selected for the study by answering positively to item three of the Freezing of Gait Questionnaire ['Do you feel that your feet get glued to the floor while walking, making a turn or when trying to initiate walking (freezing)?'] (Giladi *et al*., 2000). This question has previously been shown to be a reliable screening tool for patients with freezing of gait (Giladi *et al*., 2009).

Patients were confirmed as experiencing freezing of gait during the performance of six timed up and go trials in which they were required to make tight 180° turns to the left and right. Freezing of gait was defined as having one or more episodes of foot movement cessation during this brief assessment (Schaafsma *et al*., 2003). Similar to a recent study (Shine *et al*., 2012*a*), each timed up and go trial was video-recorded and analysed *post hoc* for the number and duration of freezing episodes. In addition, the percentage of time spent frozen during the timed up and go trials was also calculated for each patient (Shine *et al*., 2012*a*), as this measure has been shown to represent a more robust measure of freezing severity (Morris *et al*., 2012).

Virtual reality paradigm

A single 10-min virtual reality paradigm was performed in the scanner. Patients were positioned so that they could clearly view the screen on which the virtual reality task was displayed, with their feet resting on a pair of magnetic resonance-compatible foot pedals (Shine *et al*., 2011*b*). To complete the task, patients were required to navigate a first-person view of a realistic 3D corridor with environmentally salient features (such as doorways) by the use of the foot pedals that were fixed to a board at the base of the MRI scanner. Forward progression within the virtual reality environment was accomplished by the alternate depression of left and right foot pedals at a rhythm consistent with their normal gait (~2–4 Hz). This action required that the patient plantar flex the ankle of one foot ~30° below parallel, activating a binary trigger mechanism, whilst performing simultaneous dorsiflexion of the contralateral ankle. The use of foot pedals here, in contrast to the use of hand buttons in earlier studies (Naismith and Lewis, 2010), is in keeping with previous work that has reported that alternate stepping in place is a sensitive and specific method for capturing arrests in motor output in freezers (Nantel *et al*., 2012). Navigation of the virtual reality could only be achieved with alternating 'physiological' footstep sequences (i.e. left-right-left-right) and forward progression did not occur during 'out of sequence' steps (i.e. left–left or right–right), thus ensuring that movement through the virtual reality environment was only associated with alternating left–right sequences. All foot pedal responses were recorded for further analysis.

Walking and stopping in the virtual reality environment was initiated by cue words that were displayed on the screen. These cue words were arranged into alternating blocks that carried low or high cognitive load (Fig. 1). In the low cognitive load blocks, patients were instructed to respond to 'WALK' cues that were displayed in green text, hereafter referred to as 'direct' cues (Fig. 1). Direct cues to stop walking during these low cognitive load blocks were signaled by a 'STOP' cue that appeared in red text (Fig. 1).

Task difficulty was manipulated by introducing inter-leaved blocks of high cognitive load, which contained 'indirect' cues for walking and stopping. These indirect cues utilized colour-word pairings based upon a modified version of the Stroop task (Stroop, 1935) (Fig. 1). In these high cognitive load blocks, the direct 'WALK' and 'STOP' cues were replaced with the presentation of either congruent (e.g. 'RED' written in red; Fig. 1) or incongruent (e.g. 'BLUE' written in red) colour word-pairings (i.e. 'indirect' cues). Prior to the experiment, patients were taught that a congruent colour-word pairing either represented a cue to 'WALK' or 'STOP'. For example, if congruent colour-word pairings represented 'WALK', then incongruent pairings represented 'STOP' and vice versa (Fig. 1). Conditions were randomly counterbalanced across patients, such that the congruent colour-word pairings represented 'WALK' for half of the group and 'STOP' for the other half.

Patients were generally 'active' throughout the task walking through the virtual reality environment and only stopped in response to a direct or indirect stop cue. After stopping appropriately to a stop cue for 1.5 s, a direct 'WALK' cue was presented after a delay of between 4 and 6 s, informing the patient to begin 'walking' again. All cues were presented for 1 s in the bottom third of the screen at pseudorandom intervals so that patients were unable to predict the cue-onset. The virtual reality paradigm was programmed such that cues appeared with a variable interval of between 5 and 40 steps (minimum 2 s). If a patient stopped inappropriately (either intentionally or otherwise) the cue was re-presented on the screen after a delay of 3 s. Similarly, if a patient did not appropriately respond to a stop cue, the cue was represented every 3 s until the patient responded by ceasing foot movements. Between 2 and 4 direct or indirect walk cues were presented prior to each direct or indirect stop cue and this pattern was repeated an average of three times per block. Prior to scanning, all participants were trained on the paradigm until they demonstrated that they understood the rules (>95% correct response to cue presentations during 2 min of practice). There were a total of 10 blocks in

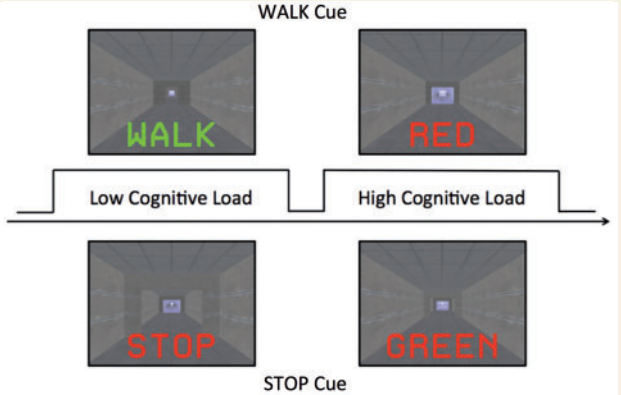

Figure 1 The experimental paradigm. Patients used a set of foot pedals to navigate a virtual corridor while lying supine in a 3 T MRI scanner. While stationary, the patient received a WALK cue, at which time they commenced tapping the foot pedals with alternate feet in a steady rhythm. Whilst walking, the patient was presented with a series of cues, which they interpreted in order to continue walking ('WALK' cue) or to stop ('STOP' cue). There were two alternating blocks within the experiment: a low cognitive load block, in which patients responded to direct cues (e.g. WALK = the word 'WALK' written in the colour green and STOP = the word 'STOP' written in the colour red); and a high cognitive load block, in which patients responded to indirect cues (e.g. WALK = congruent colour-word cues, such as the word 'RED' written in the colour red; and STOP = incongruent colour-word cues, such as the word 'GREEN' written in the colour red). Patients were asked to interpret these cues and determine whether to continue walking or to stop and await the next cue based on a prelearned rule.

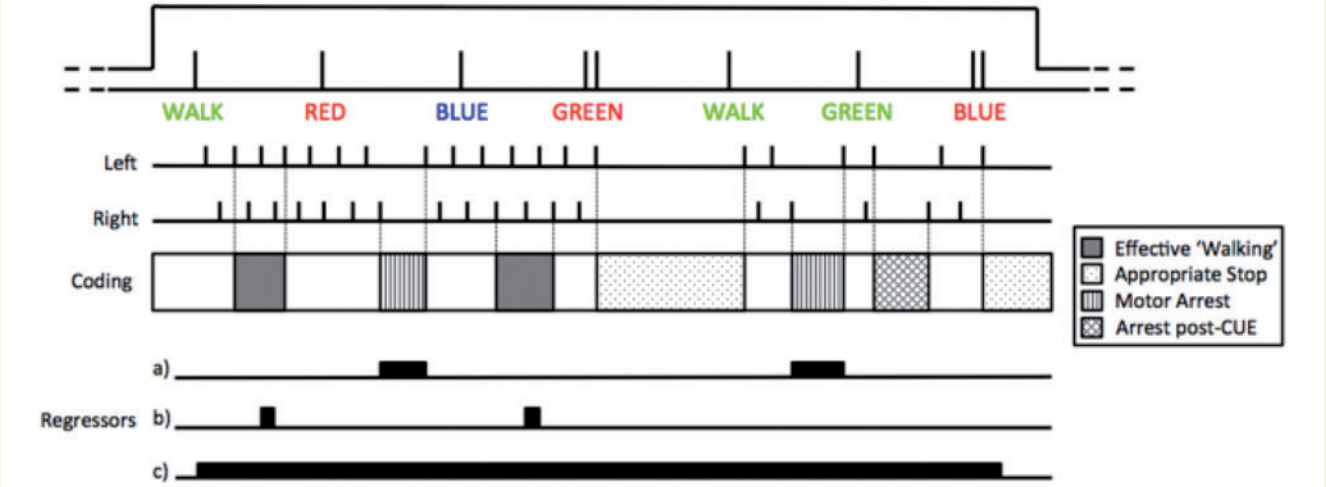

Figure 2 Explanation of the experimental paradigm and the methods employed to determine the onset time and durations of the regressors used in the functional MRI models. The top section of the figure is an example of the timing onsets of the indirect cues as a patient navigated a high cognitive load block in the experiment. The two lines below display the approximate onsets of each left and right foot pedal depression. The section below the footstep lines depicts the different 'coding' categories used to define the pattern of footstep response, including periods of effective 'walking', appropriate response to a STOP cue, motor arrests and arrests immediately following a WALK cue, which were discarded from the final analyses. The bottom section contains a depiction of the selection of time points and epochs for each regressor used in the functional MRI analyses: (a) epochs of motor arrest began at the last effective footstep prior to a long latency and end at the next effective footstep; (b) epochs of effective 'walking' were sampled from periods of the paradigm when a patient walked with a consistent 'modal' between-footstep latency without the presence of any motor arrests or WALK cues; and (c) the entire high cognitive load block was estimated from the first WALK cue until the final STOP cue in the block. The epoch analysis estimated the BOLD response differences between regressors (a) and (b) and the mixed analysis estimated the differences between regressors (a) and (c).

the experiment (five each of both low and high cognitive load), so that each patient responded to an equal number of direct and indirect cues. This meant that each patient performed a minimum of 800 foot pedal responses in the virtual reality.

Definition of motor arrests: behavioural freezing

As a primary outcome measure, we explored paroxysmal episodes of normal footstep cessation despite the intention to walk. Based on previous methodology (Naismith and Lewis, 2010), we identified all occasions when a patient suffered a motor arrest, which was defined as a period in time when a patient suffered from an abnormally long between-footstep latency (Fig. 2). To identify these epochs, we first determined the modal footstep latency for each patient by determining the most frequent between-footstep latency (within bins of 0.1 s) occurring throughout the virtual reality paradigm. The modal footstep latency was assumed to be a more robust measure of normal walking cadence than the mean footstep latency, which could be skewed by the presence of prolonged footstep latencies associated with motor arrest. Any epochs greater than a threshold of twice the modal footstep latency were defined as a motor arrest. This measure of behavioural freezing in the virtual reality has recently been correlated with the frequency and duration of actual clinical freezing of gait events suffered by patients whilst performing timed-up-and-go walking tasks (Shine *et al.*, 2012*b*). The cessation of the motor arrest was defined by the re-initiation of the normal walking pattern using the foot pedals.

Neuroimaging

Image acquisition

Imaging was conducted on a General Electric 3 T MRI. T_2*-weighted echo planar functional images were acquired in sequential order with repetition time = 3 s, echo time = 32 ms, flip angle = 90°, 32 axial slices covering the whole brain, field of view = 220 mm, interslice gap = 0.4 mm, and raw voxel size = 3.9 mm × 3.9 mm × 4 mm thick. High-resolution 3D T_1-weighted, anatomical images (voxel size 0.4 × 0.4 × 0.9 mm) were obtained for coregistration with functional data.

Image preprocessing

Statistical parametric mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/software/) was used for image processing and analysis. Functional images were pre-processed according to a standard protocol: (i) scans were slice-time corrected to the median (17th) slice in each scan; (ii) scans were then realigned to create a mean realigned image and measures of 6° of rigid head movements were calculated for later use in the correction of minor head movements; (iii) images were normalized to the echo planar image template; and (iv) scans were then smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel.

Due to the increased risk of head movements in this clinical population, each trial was subsequently analysed using ArtRepair (Mazaika *et al.*, 2007) and trials with a large amount of global drift or scan-to-scan head movements >1.5 mm (i.e. approximately half the size of the voxel collected in the echo planar images) were corrected using the Interpolation method. This correction was provided to ensure

that regular head movements throughout the task did not lead to spurious results; however, the sporadic nature of the motor arrests meant that a systematic relationship between head movements and the events of interest was extremely unlikely. Trials with >3 mm or 3° of scan-to-scan movement were considered an *a priori* exclusion criterion however, no patients exceeded this threshold.

Epoch analysis

Individual first-level statistical parametric maps were calculated for each subject using a general linear model analysis within an epoch-related design (Grinband *et al*., 2006) in a fixed-effects analysis using SPM8 software. The design matrix for each patient was created by entering two regressors for each trial (Fig. 2): a regressor that modelled the specific onset time and duration of a motor arrest (i.e. the entire epoch of time between two successful footsteps that lasted for greater than twice the modal footstep latency) and a regressor that modelled a period of time when the patient had successfully completed a modal footstep, with no external cues (such as a WALK cue or a doorway) or long latency footsteps within three 'steps' in either direction. Contrast images from the first-level analyses were then entered into a second-level random-effects design in order to determine the group-level effects of the condition of interest. The group-level brain maps were assessed at $P < 0.001$ uncorrected with cluster size >10.

Mixed block-event analysis

A mixed model was utilized to determine the blood oxygen level-dependent (BOLD) response pattern that was uniquely associated with freezing behaviour (Visscher *et al*., 2003; Petersen and Dubis, 2012). This technique allows the parsing of sustained, task-related effects from the transient patterns associated with the event of interest (Laurienti *et al*., 2003). That is, the results of the analysis can test for the presence of patterns of BOLD response that are specific to motor arrests, rather than to the mechanism that may have triggered the phenomenon (such as increased cognitive load in our experimental design). These analytic techniques are well known to over-ascribe significance to blocked regressors, as unmodelled variance in the event-related time course might create a spurious 'sustained' signal associated with the block regressor (Visscher *et al*., 2003; Petersen and Dubis, 2012). Practically, this means that results that survive the block correction are especially relevant to the event in question. To achieve this aim, a regressor modelling the duration of each High Cognitive Load block and a separate regressor modelling each motor arrest epoch were entered into a new fixed-event analysis for each patient (Fig. 2). A contrast image representing the direct statistical comparison of motor arrests and the block effects was extracted for each patient and placed into a random effects analysis at the second level. Resultant brain maps from these analyses were interpreted at $P < 0.001$, uncorrected for multiple comparisons; however, with a cluster threshold of 10 voxels (Lieberman and Cunningham, 2009). Due to the interrelated nature of the two imaging analyses, we could not directly compare the results of the two tests statistically.

Region of interest analysis

To investigate the specific *a priori* hypothesis from a previously proposed model of freezing of gait (Lewis and Barker, 2009), images from the first-level analysis were subsequently explored using a predefined regions of interest analysis. To avoid introducing bias, the coordinates of each region of interest were defined independently from the whole brain analyses. Spherical regions of interest were drawn in the following regions: the precentral sulcus, dorsal premotor area and the dorsal caudal putamen for the motor loop; the dorsolateral prefrontal cortex, posterior parietal cortex and the head of caudate for the cognitive loop; and the anterior insula, dorsal anterior cingulate cortex, medial prefrontal cortex and the ventral striatum for the affective loop, the globus pallidus internus, the subthalamic nucleus, the anterior thalamus and the mesencephalic locomotor regions (see Fig. 3 and Table 3 for the model and coordinates, respectively).

The coordinates for cortical regions of interest were defined using the peak clusters of activity from the Brain-Maps database (brainmap.org; also see Smith *et al*., 2009) and were created using the WFU Pickatlas template (fmri.wfubmc.edu/cms/software). The coordinates for the subcortical regions of interest were defined based on a study that traced basal ganglia regions of interest using an echo planar image template similar to the template used to normalize the functional scans in our study (Prodoehl *et al*., 2008). The coordinates for the mesencephalic locomotor region of interest were taken from the peak loci of activation from a recent paper that used imagined walking to explore deficits in patients with freezing of gait (Snijders *et al*., 2011). Care was taken to ensure that there was no overlap present

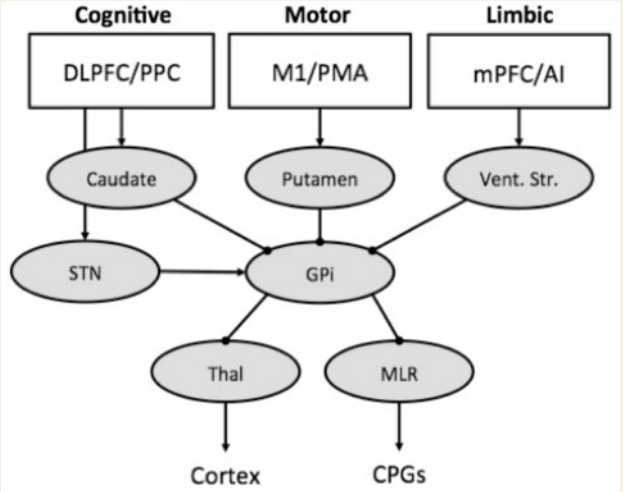

Figure 3 Model of frontostriatal loop function. Lines with arrows denote excitatory (glutamatergic) input and lines with spherical ends denote inhibitory (GABAergic) input. The cortical regions within the cognitive loop [comprising the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC)], the motor loop [comprising the precentral gyrus (Motor) and the dorsal premotor area (dPMA)] and the Affective Loop [comprising the medial prefrontal cortex (mPFC) and the anterior insulae (AI)] activate specific striatal nuclei [the head of caudate, the putamen and the ventral striatum (Vent. Str.), respectively], leading to the deactivation of the tonically-active globus pallidus internus (GPi). This releases the inhibition on relay nuclei in the thalamus (Thal) and the brainstem [including the mesencephalic locomotor region (MLR)] allowing normal corticothalamic information processing and activation of central pattern generators (CPGs), respectively. Hubs within the frontal regions of the cognitive loop also have direct connections with the subthalamic nucleus (STN), allowing for a direct and timely increase in the outflow of the globus pallidus internus, effectively decreasing thalamic and brainstem signalling.

Table 2 Brain regions displaying decreased BOLD response in the epoch analysis

Neural region	Hemisphere	x	y	z	Cluster size	T−value
Precentral gyrus	Left	−6	−22	73	190	−6.5
	Right	6	−19	64	190	−4.6
Head of caudate§	Left	−16	25	3	53	−2.8
	Right	11	25	3	31	−3.3
Anterior insula§/*	Left	−39	17	−8	16	3.0
	Right	45	20	−8	40	4.3
Dorsolateral prefrontal cortex§	Left	−45	23	28	167	3.9
	Right	60	14	28	33	3.6
Posterior parietal cortex§	Left	−45	−46	40	41	2.8
	Right	60	−52	43	19	3.2
VLPFC§	Left	−39	53	13	14	3.0
	Right	48	41	19	11	2.9
dACC§	Left	−12	29	25	12	3.0
	Right	9	29	28	10	2.9

MNI coordinates for neural regions that displayed decreased BOLD response in the epoch analysis. The coordinates represent the peak voxel within a cluster that was present above the statistical threshold in the whole-brain analysis. T-statistics are presented for clusters with $P < 0.001$ and >10 contiguous voxels.
§Denotes a member of the putative cognitive control network (Cole and Schneider, 2007).
*The anterior insula can also be viewed as a member of the Salience Network (Seeley *et al.*, 2007).

between the individual regions of interest. All regions of interest were defined in Montreal Neurological Index space.

The MarsBar toolbox in SPM8 (Brett *et al.*, 2002) was used to extract contrast values for each region of interest for each contrast. These values were then imported into Statistical Package for the Social Sciences software version 19 (SPSS Inc.) for group-level statistical testing. A two-sided paired sampled *t*-test was performed to determine whether each region of interest was significantly associated with a positive or negative contrast value in the motor arrest contrast when compared with the walking contrast. In addition, a similar analysis was used to compare the motor arrest contrast with the block effects in the mixed block-event analysis. Alpha levels were set to 0.05 and *P*-values were corrected for multiple comparisons using a family wise error correction. Finally, contrast values from each of the region of interest analyses were compared with the results from the clinical timed up and go tests using bivariate Spearman's rank-order correlations. Alpha levels were treated in a similar fashion to those from the rest of the region of interest analysis.

Results

Behavioural results

All patients in the study suffered from freezing episodes during both the timed up and go tests (16.0 ± 4.2) and the virtual reality paradigm (55.7 ± 40.1). As such, all patients in the study self-reported freezing behaviour and were also observed to experience freezing clinically. A greater number of events occurred during high cognitive load blocks (32.4 ± 22.3) than during low cognitive load blocks (23.3 ± 27.5), with 58% of the events occurring in the high cognitive load blocks ($t = 2.3$; $P < 0.05$). Table 1 contains further behavioural results from the virtual reality paradigm.

Imaging results

Epoch design analysis: motor arrests versus effective walking

When comparing the BOLD response between motor arrests and walking effectively, significant activation was observed in the bilateral posterior parietal cortex, the dorsolateral prefrontal cortex bilaterally and the ventrolateral prefrontal cortices along with the bilateral dorsal anterior cingulate regions and the bilateral anterior insula (see Table 2 for peak voxel co-ordinates and T-values and Fig. 4). In addition, there was a significant decrease in BOLD response in the bilateral sensorimotor regions, along with the head of caudate bilaterally.

Epoch design analysis: region of interest analysis

During the contrast comparing motor arrests and walking, there was a significant reduction in the BOLD response observed in the motor region of interest and the bilateral putamen of the motor loop; however, there was only a trend towards a decreased BOLD response in the right dorsal premotor area. In the cognitive loop, there was a significant increase in the dorsolateral prefrontal cortex and the posterior parietal cortex, with the right dorsolateral prefrontal cortex showing a strong inverse correlation with the severity of freezing behaviour (Spearman's rho = -0.600, $P = 0.008$).

In contrast there was a significant decrease in activation within the head of caudate nuclei. In the limbic loop, only the medial prefrontal cortex, the left anterior insula and the left ventral striatum showed significantly decreased activation. There was an additional decrease in the BOLD response within the bilateral globus pallidus internus and the bilateral anterior thalamus. There was also a significant decrease seen in the bilateral

Table 3 Results from the region of interest analysis for the epoch design and the mixed block-event design

Region	x	y	z	Size (mm)	Epoch	Mixed
Motor						
Precentral gyrus	±6	−31	67	8	$-1.7^{***}/-1.6^{***}$	$0.1^{ns}/0.1^{ns}$
Dorsal premotor area	±19	−16	67	8	$0.2^{ns}/0.4^{\#}$	$0.3^{ns}/0.2^{ns}$
Putamen	±28	3	6	6	$-0.3*/-0.6*$	$-0.1^{ns}/-0.1^{ns}$
Cognitive						
Dorsolateral prefrontal cortex[§]	±42	26	28	8	$0.9^{**}/0.9*$	$-0.3^{ns}/-0.1^{ns}$
Posterior parietal cortex[§]	±52	−49	47	8	$1.3*/1.1*$	$-0.1^{ns}/0.1^{ns}$
Head of caudate	±11	14	9	6	$-1.5^{**}/-1.6**$	$0.0^{ns}/0.1^{ns}$
Limbic						
Anterior insula	±33	23	−3	8	$0.7*/0.5^{ns}$	$0.0^{ns}/-0.1^{ns}$
Medial prefrontal cortex	±6	15	32	8	$-1.1*/-0.6^{ns}$	$0.3^{ns}/0.2^{ns}$
Ventral striatum	±9	10	−5	6	$-0.4^{\#}/-0.1^{ns}$	$-0.1^{ns}/-0.1^{ns}$
Shared						
Globus pallidus	±14	−2	3	4	$-0.5*/-1.0^{**}$	$-0.2*/-0.1^{\#}$
Subthalamic nucleus	±11	−14	−3	4	$-0.6^{***}/-0.5^{***}$	$-0.2^{***}/-0.3*$
Thalamus	±5	−12	3	4	$-1.4^{***}/-1.1^{**}$	$-0.2^{ns}/-0.2^{ns}$
Mesencephalic locomotor region[†]	±4	−30	−18	4	$0.6^{\#}/0.6^{\#}$	$-0.2*/-0.3^{**}$

MNI coordinates for neural regions that displayed decreased BOLD response in the epoch and the mixed block-event analyses. The coordinates represent the peak voxel within a cluster that was present above the statistical threshold in the whole-brain analysis. The values in the epoch and mixed columns reflect the average contrast value difference from the region of interest analysis for the left and right region, respectively.
Significance levels: ns = not significant; $^{ns}P > 0.1$; $^{\#}P < 0.1$; $*P < 0.05$; $**P < 0.001$; $***P < 0.0001$.
[§]negative correlation with the severity of clinical freezing of gait in the Epoch analysis.
[†]Positive correlation with the severity of clinical freezing of gait in the Mixed analysis.

subthalamic nucleus and a trend for an increase in the bilateral mesencephalic locomotor region.

Mixed block-event design analysis: region of interest analysis

When controlling for the activation that was related to the increased cognitive load in the blocks with the indirect walk and stop cues, no clusters survived in either contrast at $P < 0.001$ in a global brain analysis. However, the region of interest analysis revealed that motor arrests were associated with a significant decrease in the BOLD response in the right posterior parietal cortex, the left globus pallidus internus, the subthalamic nucleus bilaterally along with a significant decrease in BOLD response within the mesencephalic locomotor region, bilaterally. The BOLD response within the left mesencephalic locomotor region region was also strongly correlated with an increase in the severity of freezing behaviour (rho = 0.616, $P = 0.008$).

Discussion

The results presented here demonstrate the BOLD correlates of motor arrests that were provoked by a virtual reality gait task and have recently been shown to correlate with actual episodes of freezing of gait (Shine *et al*., 2012*b*). During these motor arrests, there was a significant increase in the BOLD response in the bilateral dorsolateral prefrontal cortex, posterior parietal cortices and anterior insulae and a concomitant decrease in BOLD response within the bilateral sensorimotor cortices (Fig. 4). In addition, a significant decrease in BOLD response was seen in a number of subcortical nuclei, including the bilateral caudate head, the anterior thalamus, the globus pallidus internus and the subthalamic nucleus. These findings are consistent with a recent review of the neuroimaging literature, which concluded that freezing behaviour in Parkinson's disease was likely to be because of impaired processing in frontal and parietal regions (Bartels, 2008).

After correction for multiple comparisons, there was a significant relative decrease in the BOLD response within the motor cortex during motor arrests when compared with effective walking. As the two contrasts both used one effective footstep, the relative decrease in BOLD response seen in our experiment is unlikely to be due to a simple motor mismatch but rather to the relative inability to recruit neural activity in the cortical regions that are responsible for the movement of the lower limbs (Shayoun *et al*., 2004; Wang *et al*., 2007). The lack of a significant decrease in the activation within the motor cortex in the mixed analysis, is likely to be due to the nature of the virtual reality task, which contains a large number of periods in which the subject must 'STOP', effectively negating the activity within motor regions during each block.

The prefrontal and parietal cortical regions with increased relative BOLD signal during motor arrests are well known to mediate a number of executive functions (Spreng *et al*., 2010) as well as affordance-based responses (Riddoch *et al*., 2006), both of which are well-aligned with the literature in freezing of gait (Nutt *et al*., 2011; Shine *et al*., 2011*a*). Indeed, these regions, including the dorsolateral prefrontal and posterior parietal cortices, as well as the head of caudate nucleus, have previously been shown to co-activate as a functional network, described as the cognitive control network (Cole and Schneider, 2007) or the Task Activation Ensemble (Seeley *et al*., 2007). Interestingly, this network is presumed to be responsible for the more domain-general

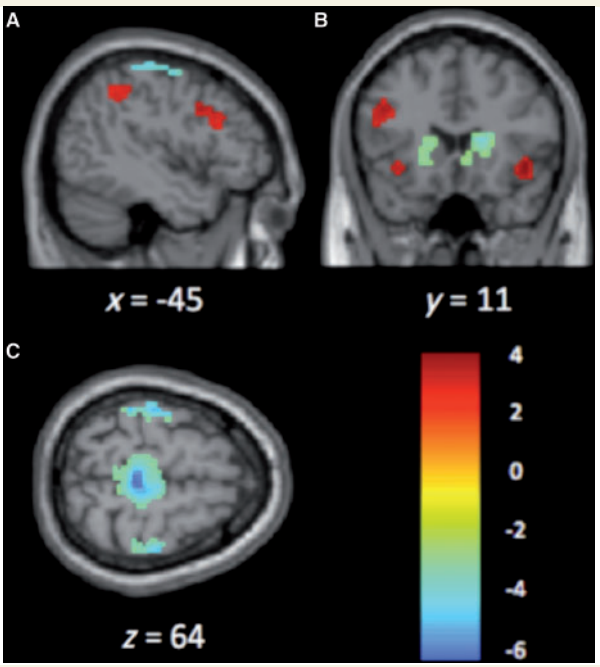

Figure 4 Comparison of BOLD activation and deactivation patterns during the contrast of the motor arrests and 'walking'. (**A**) Increased BOLD in the left dorsolateral prefrontal cortex and posterior parietal cortex with concomitant decrease in the sensorimotor cortices; (**B**) bilateral decreased BOLD in the caudate nuclei with increased BOLD in the bilateral insula and left dorsolateral prefrontal cortex; and (**C**) decreased BOLD in the sensorimotor cortices. Statistical maps were created with a voxel-level of $P < 0.001$ and a cluster threshold of 10 voxels. One cluster in the mesial precentral sulcus survived multiple comparisons correction at $P < 0.05$ using the theory of Gaussian random fields.

role of the processing of novel information, rather than merely activating during tasks requiring increased cognitive demand (Cole and Schneider, 2007).

While regions within the cognitive control network have been previously implicated in freezing of gait (Bartels and Leenders, 2008; Shine *et al*., 2011*a*), it is not yet clear what role these cortical hubs play in the freezing phenomenon. The increased BOLD signal within the cognitive control network during motor arrests may represent a compensatory adaptation with the recruitment of regions not typically involved in 'effective walking'. This observation is consistent with a number of hypotheses regarding the pathophysiology underlying freezing of gait, particularly those that highlight the complex interplay between these anatomically distinct yet functionally connected regions (Strauss and Sherman, 2006; Jacobs and Horak, 2007; Hallett, 2008; Lewis and Barker, 2009). It has also previously been proposed that 'breaking a freeze' relies on the generation of a goal-directed behaviour (Lewis and Barker, 2009) and thus activation of the cognitive control network may represent the recruitment of regions that are attempting to focus behaviour in order to overcome a freezing episode. This interpretation is consistent with the demonstration of a strong inverse relationship between clinical freezing of gait and cognitive control network activation during motor arrests in the virtual reality task. Therefore, although the cognitive control network appears to play a supportive role in freezing of gait, patients with severe freezing of gait are unable to effectively recruit activity within this network, predisposing their brains to freezing behaviour.

In view of the strong link between cognitive impairment and freezing of gait (Hausdorff *et al*., 2005), it is possible that the increased BOLD response seen in the cognitive control network may be simply reflective of the neural activity required to complete the cognitively complex portions of the virtual reality task. Indeed, this network of neural regions has previously been shown to co-activate in response to dual-task performance in patients with Parkinson's disease (Wu and Hallett, 2008). However, whilst motor arrests were more likely to occur during the experimental blocks with additional cognitive load, any events occurring within three steps of an indirect cue were removed from the analysis. Thus an alternative viewpoint is that dual-task performance and freezing of gait may share a similar neural substrate. As such, freezing of gait may reflect the transient 'overload' of the information processing capacity of this neural network, leading to a breakdown in motoric function. Though speculative, this interpretation is supported by a wealth of data from experiments spanning neuropsychological (Amboni *et al*., 2007; Naismith *et al*., 2010; Shine *et al*., 2012*a*), clinical (Hausdorff *et al*., 2005) and imaging modalities (Bartels *et al*., 2008).

Regions within the cognitive control network are known to co-activate with other neural networks to mediate goal-directed behaviour (Spreng *et al*., 2010) and recent research has implicated the basal ganglia in the mediation of these capacities (Bartels *et al*., 2006; Redgrave *et al*., 2010). Indeed, when compared with walking, periods of motor arrest were associated with a significant decrease in the BOLD in the bilateral head of caudate nucleus, the bilateral putamen and the right ventral striatum, along with bilateral globus pallidus internus. These regions have previously been shown to mediate the shift between competing neural networks (Kimura *et al*., 2004; Robbins *et al*., 2007), thus the decreased activation seen during motor arrests may represent a transient functional disconnection between subcortical and cortical regions (Jacobs *et al*., 2009; Lewis and Barker, 2009) thereby impairing information transfer between the neural hubs critical for the functional integrity of the neural networks.

Previously, it has been proposed that paroxysmal over-activity in the globus pallidus internus causes freezing of gait through inhibition of the thalami and the brainstem structures controlling gait (Lewis and Barker, 2009). This model hypothesizes that freezing of gait is due to an abrupt synchronization in the neuronal firing pattern within the basal ganglia outflow circuitry, which is triggered by complementary yet competing neural inputs. Therefore, the reduction in BOLD signal seen in the globus pallidus internus (the major outflow nucleus of the basal ganglia) may reflect a decrease in energy requirement due to the involvement of the globus pallidus internus in low frequency (<25Hz) synchronized oscillatory circuits, activity that is negatively correlated with the BOLD signal (Zumer *et al*., 2010). This interpretation is consistent with the known function of the globus pallidus internus, which exists in a low-energy oscillatory state unless directly inhibited

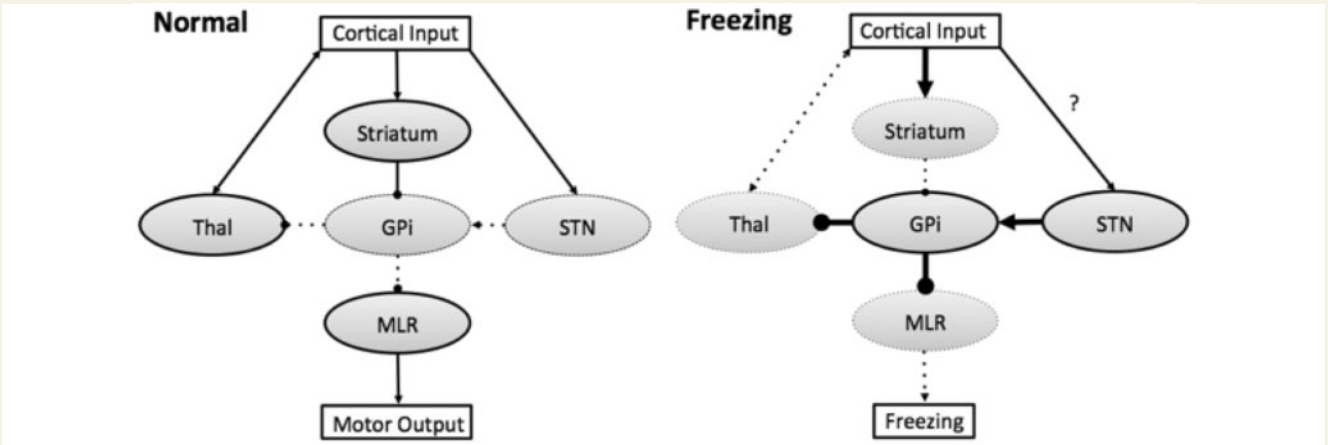

Figure 5 A graphical representation of the proposed mechanism underlying freezing behaviour. Lines with arrows denote excitatory (glutamatergic) input and lines with spherical ends denote inhibitory (GABAergic) input. In the healthy basal ganglia system (*left*), cortical input to the striatum leads to disinhibition of the thalamus (Thal) and the mesencephalic locomotor region (MLR), leading to efficient corticothalamic processing and normal motor output. In the presence of a dopaminergically-depleted basal ganglia (*right*), an overwhelming increase in cortical processing causes a transient overload of the striatum, leading to a loss of its inhibition over the globus pallidus internus (GPi). The globus pallidus internus, along with the subthalamic nucleus (STN), then begins firing in a low energy state secondary to synchronized oscillations, leading to overwhelming inhibition of the thalamic relay nuclei and the mesencephalic locomotor region, leading to cessation of motor output and 'freezing'. The increased activation within the subthalamic nucleus may be due to a decrease in communication within the hyper-direct pathway of the basal ganglia.

by GABAergic input from the striatum (Frank, 2006). By this means, the lower relative BOLD response in the globus pallidus internus may in fact reflect an increase in oscillatory neural activity, a state that has far lower energy requirements than asynchronous neural activity (Buzsaki and Draguhn, 2004).

The only subcortical regions that were significantly decreased during the mixed block-event analysis were the left globus pallidus internus and the bilateral subthalamic nucleus. Previous studies have demonstrated that the subthalamic nucleus is involved in the production of tonic oscillatory behaviour (Magill *et al*., 2001; Bevan *et al*., 2002) and as such, the BOLD response within the subthalamic nucleus likely follows a similar energetic pattern to that seen in the globus pallidus internus (Timmerman *et al*., 2007). Long presumed to be a hub within the 'indirect' pathway of the basal ganglia, the subthalamic nucleus has recently been shown to communicate with the pre-supplementary motor area (and other regions of the cortex) in the 'hyper-direct' pathway of the basal ganglia (Aron and Poldrack, 2006; Frank, 2006; Miller, 2008; Wiecki and Frank, 2010). While the exact functions of this pathway remain under investigation, it is clear that the subthalamic nucleus heavily influences response selection in both motor and cognitive tasks by effectively accelerating the activity within the globus pallidus internus, and thus inhibiting the downstream targets of the basal ganglia (Frank, 2006). As the pre-supplementary motor area was one of the only major hubs of the cognitive control network not activated in the epoch design, freezing may be due in part to impaired cortical communication within the hyper-direct pathway, ultimately leading to increased subthalamic nucleus firing and a subsequent increase in the inhibitory output of the basal ganglia. This interpretation is consistent with elements of current clinical practice, as deep brain stimulation surgery often targets the subthalamic nucleus (Modolo and Beuter, 2009), leading to improvements in freezing behaviour (Davis *et al*., 2006; Moreau *et al*., 2008). While this has yet to be confirmed, the results here suggest that freezing behaviour may be due to an overwhelming increase in the inhibitory output of the basal ganglia, leading to a paroxysmal decrease in firing within the efferent targets of the globus pallidus internus, such as the thalamic relay nuclei and the brainstem structures controlling gait, including the mesencephalic locomotor region (Fig. 5).

The results from the mixed design also help to make sense of the heretofore poorly understood finding of lower limb oscillatory activity in the 5–7 Hz range during episodes of freezing of gait (Moore *et al*., 2008). The classic parkinsonian tremor occurs in this same frequency range and studies using computational modelling have shown that the tremor can be explained mechanistically by emergent rhythmic activity between the subthalamic nucleus and the globus pallidus externus in the presence of a dopaminergically depleted basal ganglia (Frank, 2006). As our experiments revealed subcortical BOLD changes consistent with those proposed in the models of tremor, freezing behaviour may therefore be due to the paroxysmal occurrence of a similar mechanism. However, the emergent oscillatory pattern of rhythmic basal ganglia outflow would occur transiently during motor function rather than at rest, as is the case with the traditional tremor of Parkinson's disease. This interpretation is consistent with the finding that tremor and freezing are commonly present in separate parkinsonian phenotypes (tremor dominant and akinetic rigid, respectively; Lewis *et al*., 2005) and rarely co-occur in individual patients until advanced disease states. This suggests that the phenotypic differences within Parkinson's disease may be explained by the specific neural factors that determine whether the basal ganglia circuits oscillate at rest (patients with

tremor-dominant disease) or with motoric output (patients with freezing of gait). Further work will be required to elucidate the validity of this interpretation.

Interestingly, when accounting for the effects of the high cognitive load in the experiment, the heads of caudate nuclei were not significantly decreased, as was seen during the epoch-related design. This result may be due to the ongoing involvement of the caudate nuclei in the 'switching' between attentional sets (Kimura *et al*., 2004), a skill that is constantly probed by the virtual reality task (Naismith and Lewis, 2010). It is also possible that the relative lack of decreased BOLD response in the caudate nuclei is reflective of the 'breaking' of a freezing episode, which has been hypothesized to involve the reassociation of the striatum with the cortical structures from which they became disconnected during freezing (Lewis and Barker, 2009). Indeed, these results highlight an important caveat associated with functional MRI analyses, as the nature of the BOLD response enforces temporal smoothing (on the order of 5-6 s) on time-series data. As such, although this experiment helps to identify the pattern of disturbances associated with freezing behaviour in Parkinson's disease, it is not possible to identify the temporal sequence that gives rise to freezing events. Techniques such as dynamic causal modelling (Friston *et al*., 2003), seed-based functional connectivity analysis (Fox *et al*., 2005) or direct neuronal monitoring from deep brain electrodes (Brown and Williams, 2005) may help to address these issues. Alternatively, approaches with a higher temporal resolution and the capacity to analyse oscillatory waveforms (such as electroencephalography or magnetoencephalography) would potentially assist in establishing the temporal sequence of neural events associated with freezing behaviour.

There were no significant differences observed in the mesencephalic locomotor region in the contrast between effective walking and freezing, however we did see a significant decrease in the BOLD signal within the mesencephalic locomotor region during the mixed block-event analysis, suggesting that the mesencephalic locomotor region is actively involved in the mechanism underlying freezing of gait. These results are in contrast with a previous neuroimaging study, which used an imagined walking paradigm to explore the pathological basis of freezing of gait and found that patients with the disorder were more likely to show activation in the mesencephalic locomotor region of the brainstem rather than decreased activity (Snijders *et al*., 2011). The increased activity in that study was taken to reflect a compensatory mechanism, with the mesencephalic locomotor region increasing its firing rate to offset the relative lack of cortically driven gait. The results of our study suggest that the mesencephalic locomotor region was less active during freezing as may be expected in the setting of overwhelming inhibition from the globus pallidus internus (Lewis and Barker, 2009). However the degree of activation within the left mesencephalic locomotor region was strongly correlated with the severity of clinical freezing of gait, suggesting that in patients with worse freezing of gait, the mesencephalic locomotor region may indeed be playing a compensatory role during freezing. The differing results of the two studies may be explained by the fact that tasks using motor imagery may be unable to accurately model complex motor tasks as evidenced by a study showing significant differences between characteristics of perceived and actual walking in patients with Parkinson's disease with freezing of gait (Cohen *et al*., 2011). Indeed, while the virtual reality task employed in this study does not accurately model gait in its entirety, it is an ecologically valid bipedal task shown to provoke freezing behaviour in a cohort of susceptible patients (Naismith and Lewis, 2010; Shine *et al*., 2012*a*). Therefore, the virtual reality task can be considered an effective task for robustly probing the neural correlates of freezing of gait in Parkinson's disease.

Conclusion

The findings presented here suggest that the combination of virtual reality and functional MRI has the potential to elucidate the neural correlates underlying the freezing phenomenon, which can ultimately manifest as freezing behaviour in a number of distinct activities aside from gait. Using functional imaging methods, we were able to provide evidence that freezing behaviour in Parkinson's disease is associated with increased basal ganglia inhibitory output, leading to a decrease in thalamic and brainstem information processing. To our knowledge, this is the first study to show BOLD response changes in a task that is both ecologically valid and related to actual clinical freezing of gait. Further studies will explore the specific roles of the multiple neural regions preceding and during an episode of freezing in order to better understand the specific neural correlates of the freezing phenomenon as they occur in real time.

Acknowledgements

We would like to thank Matthew Brett for his assistance with the region of interest analysis using MarsBar. We would also like to thank Dr Nathan Spreng for his help with the implementation of Caret software and Mr Josh Roberts and Prof Ulrich Schall for their critical review of the manuscript. We would like to thank Mr. Simon Wadsworth of Turambar Software for his assistance in developing the Virtual Reality paradigm. We would finally like to thank our patient volunteers for their participation in this study.

Funding

The study was funded in it's entirety by the Michael J. Fox Foundation (http://www.michaeljfox.com/foundation/grant-detail.php?grant_id=607).

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