

# Freezing of gait in Parkinson's disease is associated with functional decoupling between the cognitive control network and the basal ganglia

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Recent neuroimaging evidence has led to the proposal that freezing of gait in Parkinson's disease is due to dysfunctional interactions between frontoparietal cortical regions and subcortical structures, such as the striatum. However, to date, no study has employed task-based functional connectivity analyses to explore this hypothesis. In this study, we used a data-driven multivariate approach to explore the impaired communication between distributed neuronal networks in 10 patients with Parkinson's disease and freezing of gait, and 10 matched patients with no clinical history of freezing behaviour. Patients performed a virtual reality gait task on two separate occasions (once ON and once OFF their regular dopaminergic medication) while functional magnetic resonance imaging data were collected. Group-level independent component analysis was used to extract the subject-specific time courses associated with five well-known neuronal networks: the motor network, the right- and left cognitive control networks, the ventral attention network and the basal ganglia network. We subsequently analysed both the activation and connectivity of these neuronal networks between the two groups with respect to dopaminergic state and cognitive load while performing the virtual reality gait task. During task performance, all patients used the left cognitive control network and the ventral attention network and in addition, showed increased connectivity between the bilateral cognitive control networks. However, patients with freezing demonstrated functional decoupling between the basal ganglia network and the cognitive control network in each hemisphere. This decoupling was also associated with paroxysmal motor arrests. These results support the hypothesis that freezing behaviour in Parkinson's disease is because of impaired communication between complimentary yet competing neural networks.

**Keywords:** Parkinson's disease; freezing; functional magnetic resonance imaging; basal ganglia; cognitive control

**Abbreviation:** CCN = cognitive control network

## Introduction

Freezing of gait is a symptom of advanced Parkinson's disease in which an individual suffers from a paroxysmal breakdown in their normal footstep pattern while walking (Giladi *et al.*, 1992, 2000; Menon and Uddin, 2010). Similar freezing behaviour has been shown across a number of non-gait tasks (Nieuwboer *et al.*, 2009; Vercruyse *et al.*, 2012), suggesting that freezing of gait may exist as a motor manifestation of a global dysfunction in the concurrent processing of information across neuronal networks (Lewis and Barker, 2009; Nutt *et al.*, 2011; Shine *et al.*, 2011c, 2013c). In support of this concept, freezing behaviour has been shown to be strongly related to impairments in dual-task performance (Browner and Giladi, 2010; Spildooren *et al.*, 2010; Snijders *et al.*, 2010; Nutt *et al.*, 2011; Shine *et al.*, 2011c) and attentional set shifting (Amboni *et al.*, 2008; Naismith *et al.*, 2010; Friston, 2011; Shine *et al.*, 2013e), both of which depend on parallel processing across multiple levels of the CNS.

In keeping with the association between impaired executive functions and freezing of gait, neuroimaging studies have shown that freezing is related to dysfunction within frontoparietal regions of the cortex (Bartels and Leenders, 2008), known to subservise cognitive and executive functions (Wager *et al.*, 2004; Cole and Schneider, 2007). For example, although all patients with Parkinson's disease are able to recruit the dorsolateral prefrontal cortex and the posterior parietal cortex during the dual-processing of cognitive and motor tasks, patients with clinical freezing of gait show decreased activity in the pre-supplementary motor area and the anterior insula (Shine *et al.*, 2013d). This suggests a possible impairment in the ability to effectively 'shift' between competing attentional networks (Lewis and Barker, 2009; Menon and Uddin, 2010; Nutt *et al.*, 2011; Shine *et al.*, 2011c).

Alternatively, these functional abnormalities could reflect impaired interactions within habitual ('internal') drivers based in the basal ganglia leading to an over-reliance on goal-directed ('external') neural networks acting at a cortical level to complete normally automatic tasks, which they are not well suited to accomplish (Hallett, 2008; Browner and Giladi, 2010; Spildooren *et al.*, 2010; Nutt *et al.*, 2011; Shine *et al.*, 2011c). Indeed, recent neuroimaging studies have shown that episodes of freezing elicited during the performance of a virtual reality task are associated with activity in frontoparietal regions with concomitant impairments in important subcortical structures, such as the caudate nucleus, the globus pallidus, the subthalamic nucleus and the mesencephalic locomotor region (Shine *et al.*, 2013c, d). These results highlight the key role of subcortical activity in the pathophysiology of freezing of gait, which may reflect an inability to effectively 'update' motor sets during ongoing motor task performance (Chee *et al.*, 2009). Alternatively, freezing behaviour may also be because of increased inhibitory output from the subthalamic nucleus in the presence of cognitive and motor conflict (Cavanagh and Frank, 2013; Shine *et al.*, 2013c). Furthermore, it has been suggested that during freezing, the output structures of the basal ganglia may be involved in pathological oscillatory activity associated with decreased inhibitory tone from an underactive striatum (Lewis and Barker, 2009; Shine *et al.*, 2013c), leading to

overcompensation in the mesencephalic locomotor region (Bartels and Leenders, 2008; Snijders *et al.*, 2010).

However, it is not clear from these previous experiments whether the relative differences in blood oxygen level-dependent response observed in each region was related to differences in the functional connection strength between the regions *per se*. For example, two brain regions may be relatively dissociated based on the average blood oxygen level-dependent response during the performance of a task but there may be no discernible functional relationship between the two areas. One way to avoid this issue is through use of functional connectivity analyses, which allow for the measurement of 'functional coupling' between distinct neural regions (Friston, 2011). Although these analyses have generally been performed during the 'resting state', they can also be modified to explore the co-ordination between neuronal networks during the performance of behavioural tasks (Spregue *et al.*, 2010; Fornito *et al.*, 2012).

In this study, we sought to determine whether motor arrests elicited during the performance of a virtual reality task were associated with impaired task-based functional connectivity between the large-scale neuronal networks that are likely to be involved in the phenomenon of freezing. Our previous analyses have suggested that freezing would be associated with the executive networks becoming functionally decoupled from the basal ganglia nuclei, leading to impaired efficiency of neuronal information processing. Thus this analysis explored the motor and basal ganglia networks as well as the networks subserving executive control, such as the 'cognitive control network' (CCN), which includes the dorsolateral prefrontal cortex and the posterior parietal cortex (Wager *et al.*, 2004; Cole and Schneider, 2007); and the 'ventral attention network', which includes the anterior cingulate and anterior insula (Menon and Uddin, 2010).

To achieve this aim, we performed functional connectivity analyses on blood oxygen level-dependent data collected during the performance of a virtual reality task that is able to elicit freezing behaviour in Parkinson's disease (Shine *et al.*, 2013c). The task was performed on two separate occasions: once ON and once OFF regular dopaminergic medication, to determine whether a relative lack of dopamine exacerbated freezing behaviour along with underlying neuronal network impairments. In addition, we also manipulated cognitive load in the virtual reality environment in an attempt to determine whether there was an additive effect between medication state and cognitive load. Together, these experiments were designed to allow for the assessment of the degree to which impairments in the functional coupling between neuronal networks are associated with the pathophysiological mechanisms underlying freezing of gait.

## Materials and methods

### Patient details

Table 1 shows the demographic details of the patients in the study. All 20 patients were assessed twice (with an average of 4 weeks between sessions): once in their ON state and once in their clinically defined OFF state, having withdrawn from dopaminergic medication overnight (minimum time OFF medication = 18 h; average time OFF

**Table 1 Demographic, neuropsychiatric and virtual reality characteristics**

	Freezers	Non-freezers	P-value
<b>Demographics</b>			
Number	10	10	
Age	67.1 ± 6.4	66.3 ± 6.2	0.78
Disease duration, years <sup>a</sup>	7.3 ± 7.0	4.8 ± 2.8	0.32
Hoehn and Yahr, stage	2.3 ± 0.9	2.7 ± 0.6	0.11
MMSE	28.3 ± 0.8	28.6 ± 0.7	0.38
FOG-Q total <sup>a</sup>	11.6 ± 4.6	2.2 ± 2.4	0.00
FOG-Q question 3 <sup>a</sup>	2.3 ± 1.1	0.0 ± 0.0	0.00
UPDRS III, ON	26.2 ± 14.8	19.7 ± 10.4	0.40
UPDRS III, OFF	32.5 ± 18.4	23.9 ± 14.0	0.26
DDE, mg/day	869.2 ± 427	755.4 ± 501	0.59
<b>Virtual reality paradigm</b>			
Modal latency, ON	0.6 ± 0.2	0.5 ± 0.1	0.79
Modal latency, OFF	0.5 ± 0.2	0.5 ± 0.2	0.37
Motor arrests, ON	30.0 ± 15.9	12.7 ± 14.6	0.01
Motor arrests, OFF <sup>a</sup>	44.8 ± 45.2	14.8 ± 18.4	0.04
Motor arrests, high load <sup>a</sup>	41.4 ± 28.7	15.3 ± 13.6	0.01
Motor arrests, low load <sup>a</sup>	33.4 ± 25.4	12.2 ± 10.2	0.02

DDE = Dopamine dose equivalence; FOG-Q = Freezing of Gait Questionnaire; MMSE = Mini Mental State Examination; UPDRS = Unified Parkinson's Disease Rating Scale.

<sup>a</sup>A non-parametric test was used.

medication = 22.5 ± 3.1 h). Although some effects from dopamine agonist medications may still be evident, the protocol was similar between groups and any lingering dopaminergic effects would likely decrease potential differences between the two states, such that the findings obtained will represent a conservative estimate of dopaminergic effects. In addition, this procedure is commonly used in the cognitive literature, revealing robust effects (Cools *et al.*, 2001), and patients were randomly assigned to perform either their ON or OFF assessment first (Cools *et al.*, 2001; Frank *et al.*, 2004; Moustafa *et al.*, 2008).

All patients were screened before entry through their response 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), which has previously been shown to be a reliable screening tool for patients with freezing of gait (Giladi *et al.*, 2009). To confirm the presence of clinical freezing of gait, patients performed a brief series of timed up-and-go trials where they were required to make tight 180° turns to the left and right, immediately before scanning during the OFF state session. Patients were deemed to suffer from freezing of gait if they displayed one or more episodes of foot movement cessation during this brief assessment (Schaafsma *et al.*, 2003; Shine *et al.*, 2012). All patients in the freezer group showed worse freezing behaviour in the OFF state and no patient in the 'non-freezer' group displayed either self-reported or clinical freezing behaviour. Previously, 14 of the 20 patients reported here (10 non-freezers and four freezers) have been included in separate functional MRI studies exploring the freezing phenomenon (Shine *et al.*, 2013c, f), however this experiment used both the ON and OFF medication state and a novel analytic technique.

## Virtual reality gait paradigm

In each session, a single 10-min task was performed in the scanner, which consisted of a modified stop-signal task that was implemented

in a virtual reality environment (Naismith and Lewis, 2010). The patients were positioned in the magnetic resonance scanner so that they could clearly view a screen on which the virtual reality task was displayed while their feet rested on a pair of magnetic resonance-compatible foot pedals (Shine *et al.*, 2013c). They were able to navigate a first-person view of the corridor by the using the pedals that were fixed to a board at the base of the MRI scanner. As in previous experiments (Shine *et al.*, 2013c, d), 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. 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. Direct cues to stop walking during these low cognitive load blocks were signalled by a 'STOP' cue that appeared in red text.

Task difficulty was manipulated by introducing inter-leaved blocks of high cognitive load, which contained 'indirect' cues for walking and stopping. This counterbalancing resulted in an equal division throughout the experiment responding to high or low cognitive load cues for equal amounts of time during the 10-min trial. These indirect cues used colour-word pairings based upon a modified version of the Stroop task (Treisman and Fearnley, 1969), in which the direct 'WALK' and 'STOP' cues were replaced with the presentation of either congruent (e.g. 'RED' written in red) or incongruent (e.g. 'BLUE' written in red) colour word-pairings (i.e. 'indirect' cues). Before the experiment, patients were taught that a congruent colour-word pairing either represented a cue to 'WALK' or 'STOP'.

Conditions were randomly counterbalanced across patients, such that the congruent colour-word pairings represented 'WALK' for half of the group and 'STOP' for the remaining patients. Conditions were also randomly counterbalanced between sessions to ensure a lack of systematic bias associated with the performance of a specific rule in either the ON or OFF state. Before 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 10 blocks in 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.

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; Shine *et al.*, 2013d), we identified all occasions when a patient suffered a motor arrest, which was defined as a period in time when a patient suffered from a between-footstep latency longer than twice their modal footstep latency. Using this method, any epoch greater than a threshold of twice the modal footstep latency were defined as a motor arrest. This measure of freezing in the virtual reality paradigm has recently been correlated with the frequency and duration of actual clinical freezing of gait events suffered by patients while performing timed up-and-go walking tasks (Shine *et al.*, 2013b). As in previous studies, the cessation of the motor arrest was defined by the re-initiation of the normal walking pattern using the footpedals.

A mixed repeated-measures ANOVA was used to assess for differences in the number of motor arrests between the two groups with respect to medication state (Medication) and between the two different experimental blocks (Load), as well as for the interaction between the two elements of the experiment (Medication × Load). *Post hoc* *t*-tests were used for interpretation of the direction of significance at each level of the model. Where the data were deemed non-parametric, Kruskal-Wallis tests were used for group differences and Mann-Whitney U tests were used for *post hoc* comparisons.

To ensure that the presence of motor arrests was not due to global impairments on the virtual reality task, we calculated the number of 'effective stops', defined as instances in which patients performed two or fewer stops following a STOP cue. Depending on the individual cadence of each subject, WALK cues often appeared mid-step thus precluding direct measurements of response times to WALK cues. Thus an indirect measurement of response time was calculated by taking the average duration of the longest footstep that occurred within three steps of either a high or low cognitive cue presentation, which was taken to reflect the amount of time taken to effectively respond to a WALK cue. These outcomes measures were compared across group, medication state and cognitive load and were also correlated with the number of motor arrests across the virtual reality task. Where appropriate, non-parametric tests were used to evaluate statistical significance.

## Neuroimaging analysis

### Image acquisition

Imaging was conducted on a General Electric 3 T MRI (General Electric).  $T_2^*$ -weighted echo planar functional images were acquired in sequential order with repetition time = 3 s, echo time = 32 ms, flip angle =  $90^\circ$ , 32 axial slices covering the whole brain, field of view = 220 mm, and raw voxel size =  $3.9 \times 3.9 \times 4$  mm thick. High-resolution 3D  $T_1$ -weighted, anatomical images (voxel size  $0.4 \times 0.4 \times 0.9$  mm) were obtained for co-registration 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 preprocessing, according to a standard pipeline: (i) scans were slice-time corrected to the median (21st) slice in each repetition time; (ii) scans were then realigned to create a mean realigned image and measures of  $6^\circ$  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.

### Independent component analysis

Preprocessed images were then imported into an independent component analysis procedure using the GIFT toolbox (<http://mialab.mrn.org/software>) in SPM8. Briefly, independent component analysis is a data-driven approach that searches for maximally independent clusters of voxels within the brain that co-vary together in reliable temporal relationships. In this study, we used the InfoMax algorithm to extract 20 maximally independent components for the entire group of 20 patients with Parkinson's disease. The 20 extracted components were then spatially sorted at the group level using a set of predefined regions of interest, the co-ordinates of which reproduced hubs of well-known neural networks (Fig. 1). Co-ordinates for the masks were taken from previous imaging studies (Fox *et al.*, 2005; Spreng *et al.*, 2010) and were defined in MNI space (Table 2). Specifically, we used: a midline precentral gyrus mask (8 mm sphere centred around 0, -31, 67) to extract the motor network; two separate dorsolateral prefrontal cortex masks (10 mm spheres centred around -45, 11, 34 and 45, 11, 34) to extract a frontoparietal CCN for each hemisphere; a right anterior insula mask (8 mm sphere centred around 32, 20, -2) to extract the ventral attention network; and a right sided caudate

mask (8 mm sphere centred around 10, 14, 10) to extract the basal ganglia network.

### Task-based functional connectivity

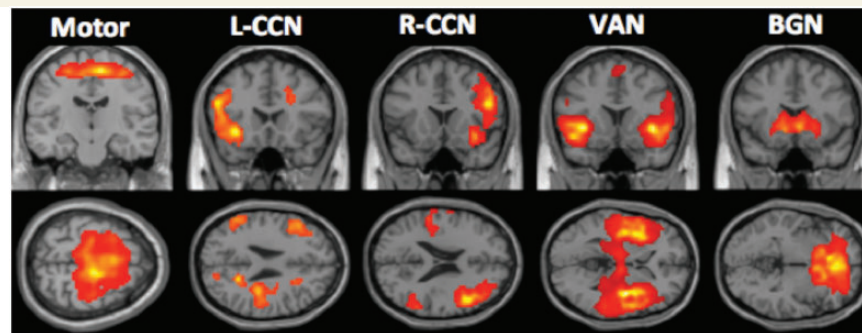
Each component extracted from the independent component analysis was also associated with a unique time course (with one numeric value per repetition time) that represented the average blood oxygen level-dependent signal across the entire component. Using the Functional Network Connectivity toolbox (<http://mialab.mrn.org/software>), the time courses for the five component networks of interest (motor network, left CCN, right CCN, ventral attention network and basal ganglia network) were subjected to a number of further preprocessing steps, including de-trending and interpolation, to remove spurious low frequency noise from the data (Friston, 2011). In addition, the time courses were also temporally filtered using a high-pass filter (0.009 Hz), further removing low-frequency noise from the data. The time course from each network was then extracted for each patient.

Using SPM8 software, task regressors modelling the onset and offset of high and low cognitive load blocks were convolved with the haemodynamic response function, creating a new variable that represented the expected blood oxygen level-dependent response in each experimental block. The five network time courses for each patient were then multiplied against these convolved task regressors, leading to a score that reflected the specific 'activity' in each network during blocks of both high and low cognitive load (Fig. 2). After this step, a series of Pearson's product-moment correlations were computed for each patient and were converted into a Z-score using Fisher's *r*-to-*Z* transformation.

To calculate network activity, the time course for each of the five networks was correlated against the convolved task regressor for each of the four experimental combinations (i.e. high and low cognitive load in each medication state). To calculate network connectivity, each of the network time courses was correlated with the other four networks in each of the four experimental combinations, allowing for an estimation of task-based functional connectivity across the different modes of the experiment.

To determine whether either of these measures changed with respect to freezing behaviour, we calculated a correlation between the frequency of motor arrests in each experimental block and the relevant network activity and network connectivity Z-score. To allow for calculations relevant to each outcome measure, the frequency of motor arrests was pooled across each experimental manipulation. The Dunn and Clark statistic (Dunn and Clark, 1969) was used to test for statistical significance between the two aspects of each mode of the experiment within each group. Finally, the Z-score associated with this statistic was compared between the two groups to determine whether the two groups showed significantly different network modulations with respect to the number of motor arrests.

In each analysis, the effect of medication state was calculated by contrasting the average Z-score representing the network association with both cognitive load states in the OFF state with the corresponding Z-scores from the ON state. To assess the effect of cognitive load, a similar comparison was made, however, the data were pooled with respect to cognitive load, rather than medication state. To assess for the presence of differences in the interaction between medication state and cognitive load, difference scores were calculated that represented the difference between high and low cognitive load in the OFF state with respect to the ON state. A series of *t*-tests were performed on these variables to determine whether activity within and/or between any of the networks was associated with a specific combination of the experimental variables. Subsequently, a series of independent-sample *t*-tests were used to assess potential group differences in any of the



**Figure 1** Spatial maps associated with each of the neuronal networks analysed in this study, which were extracted from an independent components analysis of task-based data in both the OFF and ON state. The intensity of the colour (red → yellow) denotes the degree of similarity between the voxels within each network. L-CCN = left CCN; R-CCN = right CCN; VAN = ventral attention network; BGN = basal ganglia network.

**Table 2** Brain areas associated with the components derived from the spatial sorting stage of the independent component analysis

Network	Neural region	x	y	z
Motor network	Precentral gyrus	0	-36	63
	Right SMA	3	-13	61
	Post Central Gyrus	0	-54	63
Left cognitive control network	Left PPC	-42	-58	37
	Left DLPFC	-48	11	10
	Left VLPFC	-39	44	-11
Right cognitive control network	Right PPC	51	-49	43
	Right DLPFC	48	14	25
	Right VLPFC	36	50	10
Ventral attention network	Right anterior insula	42	11	-5
	Left anterior insula	-42	11	-8
	Dorsal cingulate	0	50	19
Basal ganglia network	Left caudate	-15	23	4
	Right caudate	13	21	3
	Rostral cingulate	0	39	10

MNI co-ordinates for the peaks of maximum intensity in each component extracted from the independent component analysis spatial sorting stage. PPC = posterior parietal cortex; DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area.

network time courses (both within and between networks). Alpha inflation was controlled by performing a strict Bonferroni for each aspect of the analysis, such that the alpha level was  $P = 0.01$  ( $\alpha/5$  comparisons) for network activity analyses and  $P = 0.005$  ( $\alpha/10$  comparisons) for network connectivity analyses. Non-parametric tests were used where appropriate.

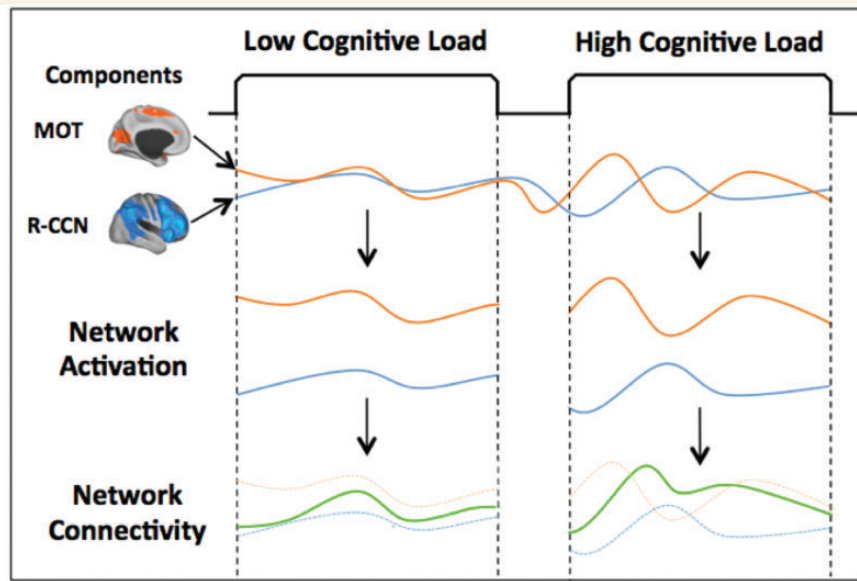
We performed a final analysis to determine whether abnormal network connectivity changes were specifically related to paroxysmal motor arrests in the virtual reality task. To this end, we calculated the temporal derivative of each component time course from each of the 10 patients with freezing of gait in the OFF state, allowing for a measure of the relative scan-to-scan blood oxygen level-dependent signal change in each network. We then multiplied these derivatives across the different network pairs, obtaining a metric that represented the degree of inter-network connectivity in each three-second epoch of the experiment. We were then able to extract the average connectivity score for each network pair for the following events on the virtual reality task: (i) normal walking, defined as

time-points on the task in which patients were able to navigate the environment in their normal modal footstep latency with no evidence of motor arrests within six seconds either side of the event; (ii) pre-arrest, calculated by subtracting the network connectivity derivative during the scan before an arrest from the derivative associated with the motor arrest itself; and (iii) post-arrest, defined as the derivative associated with the period immediately following an arrest. Following extraction of the average values associated with each event, we compared the values associated with each event using Mann-Whitney U-tests.

## Results

### Virtual reality task

Patients suffered from a total of 1023 motor arrests during the virtual reality task, with freezers 2.7 times more likely to suffer



**Figure 2** Graphical depiction of the experimental analysis. After extracting the time courses from each of the five network components, we then multiplied each time course with the convolved regressor representing either low or high cognitive load, leading to the creation of individual correlation coefficients representing the strength of network activation in each experimental block (orange and blue lines). To measure network connectivity, we then correlated each time course with one another, leading to a correlation coefficient representing the strength of association of each network pair in each block (green line). Finally, individual network activation and connectivity scores are correlated with the number of motor arrests in each block, leading to the calculation of network modulation.

from freezing events across the entire experiment [Group effect;  $F(1,18) = 4.42$ ,  $P < 0.05$ ; Fig. 3]. The Group  $\times$  Medication effect was not significant [ $F(1,18) = 1.00$ ,  $P > 0.05$ ], however, freezers were more likely to suffer from motor arrests during both the OFF state ( $t = 2.24$ ,  $P = 0.04$ ) and the ON state ( $t = 2.86$ ,  $P = 0.02$ ) than non-freezers. In addition, The Group  $\times$  Load effect was significant [ $F(1,18) = 7.86$ ,  $P < 0.01$ ], as freezers were more likely to suffer from motor arrests in both high cognitive load ( $t = 2.83$ ,  $P = 0.01$ ) and low cognitive load ( $t = 2.67$ ,  $P = 0.02$ ) blocks when compared with non-freezers. In keeping with previous studies (Shine et al., 2013d), freezers were also more likely to spend a greater proportion of time 'frozen' during the experiment, 'freezing' for an average of  $9.6 \pm 9\%$  compared to  $5.4 \pm 6\%$  in non-freezers ( $t = 2.20$ ,  $P < 0.05$ ).

Despite these differences, there were no significant differences in the modal footstep latency either between groups, between blocks or between medication states [ $F(1,18) = 0.347$ ,  $P < 0.05$ ], suggesting that the motor arrests were due to paroxysmal freezing events rather than general motor differences between the two groups and their medication states. There were no significant differences with respect to the number of effective responses to STOP signals between the two groups [ $F(3,16) = 2.44$ ,  $P = 0.08$ ], although there was a trend for increased ineffective stops in the freezing group. In addition, there were no significant differences in the average response times to cognitive cues in either group in both the ON and OFF states [ $F(3,16) = 0.23$ ,  $P = 0.88$ ]. Similarly neither group was more likely to suffer from motor arrests when responding to congruent versus incongruent cues ( $t = 1.7$ ,  $P = 0.10$ ). Finally, none of these measures were significantly

correlated with the number of motor arrests experienced during the virtual reality gait task ( $r < 0.445$ ,  $P > 0.05$ ).

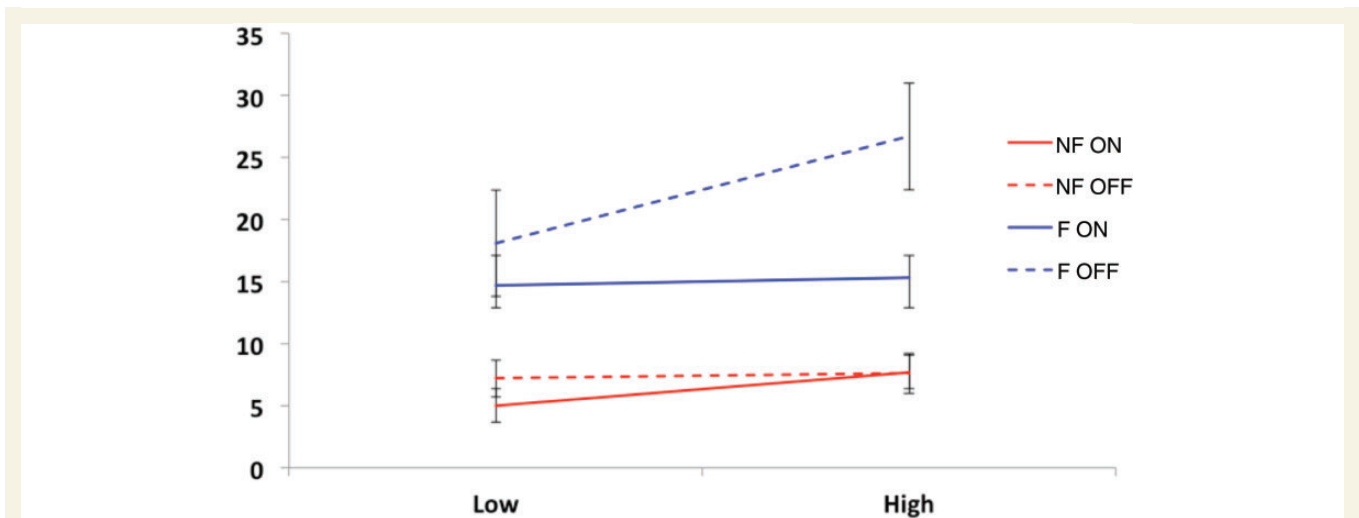
## Independent component analysis

Spatial maps for each of the selected components are presented in Fig. 1 and the voxel co-ordinates used to select each network map are presented in Table 2. There were no significant differences between the two groups when analysing the voxel patterns of the selected components (analysed at  $P < 0.05$  corrected for multiple comparisons using family-wise error; cluster size  $> 10$ ).

## Network activity and connectivity

While performing the virtual reality task, all patients regularly displayed activity within the left CCN ( $t = 3.39$ ,  $P = 0.003$ ) and the ventral attention network ( $t = 3.82$ ,  $P = 0.001$ ). In addition, all patients showed an increase in the connectivity between the left CCN and the right CCN ( $t = 5.43$ ,  $P < 0.001$ ). In the OFF state, all patients showed a decrease in the activity within the basal ganglia network ( $t = 2.95$ ,  $P = 0.009$ ), however, the increased connectivity between the left CCN and the right CCN remained intact ( $t = 5.08$ ,  $P < 0.001$ ).

In the presence of high cognitive load, there was an increased recruitment of the motor network ( $t = 3.69$ ,  $P < 0.01$ ), the left CCN ( $t = 4.76$ ,  $P < 0.001$ ) and the right CCN ( $t = 5.23$ ,  $P < 0.001$ ), along with an increased connectivity between the motor network and the left CCN ( $t = 3.52$ ,  $P < 0.01$ ). However, freezers were unable to sustain similar levels of activity in the motor network ( $t = 2.45$ ,  $P = 0.03$ ) or basal ganglia network



**Figure 3** Average number of motor arrests on the virtual reality task with respect to group, medication state and cognitive load. Patients with clinical freezing were likely to suffer from more motor arrests (displayed on the y-axis) in both the ON (filled line) and OFF state (dotted line). The combination of OFF medication and high cognitive load caused a significant increase in the number of motor arrests in freezers, but not in non-freezers [ $F(1,18) = 4.42, P < 0.05$ ].

( $t = 2.67, P = 0.02$ ) during the presence of increased cognitive load. A similar pattern of network activity was seen during the performance of the virtual reality task in the presence of high cognitive load in the OFF state, with an increase in motor network ( $t = 3.56, P < 0.01$ ), left CCN ( $t = 4.38, P < 0.001$ ) and the right CCN ( $t = 5.65, P < 0.001$ ), but a relative decrease in activity within the motor network ( $t = 2.24, P = 0.04$ ), basal ganglia network ( $t = 2.28, P = 0.03$ ) and ventral attention network ( $t = 2.11, P = 0.04$ ) in patients with freezing of gait.

## Relationship to freezing behaviour

In patients with freezing of gait, the number of motor arrests on the virtual reality task was associated with a decrease in the functional connectivity between the right CCN and the left CCN ( $ZI = 2.22, P = 0.02$ ) in the presence of high cognitive load (Fig. 4). In addition, the interaction between Medication  $\times$  Load was also associated with functional decoupling between the basal ganglia network and both the right CCN ( $ZI = 3.18, P < 0.01$ ) and the left CCN ( $ZI = 3.02, P < 0.01$ ) in patients with freezing (Fig. 5). No such statistically significant relationships were observed in patients without clinical freezing of gait (all  $ZI < 1.7, P > 0.05$ ).

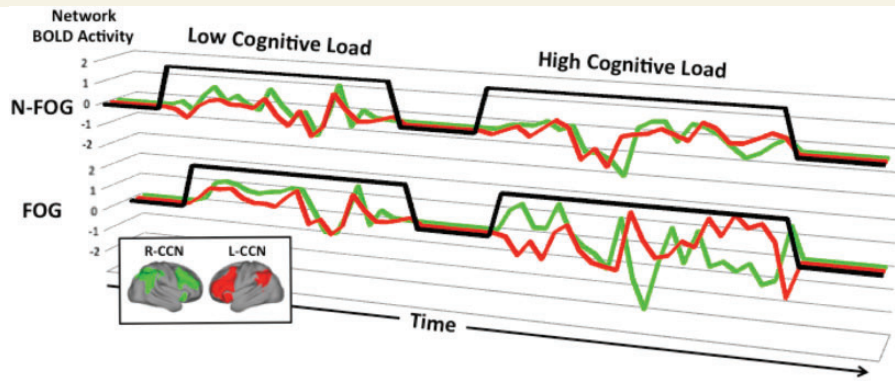
As shown in Fig. 6, there was a clear temporal pattern in the connectivity between the CCN and basal ganglia network when comparing normal motor output with the periods preceding and after a motor arrest. Specifically, there was a significant decrease in the connectivity between the right CCN and the basal ganglia network during the pre-arrest period when compared to epochs of normal walking ( $Z = -1.70, P = 0.04$ ). Furthermore, the connectivity between the two networks was re-established in the post-arrest epoch ( $Z = -2.25, P = 0.01$ ), which was not statistically different from the connectivity observed during normal walking ( $Z = 0.57, P = 0.72$ ). In addition, there was also a significant

increase in the connectivity between the right CCN and the ventral attention network in the post-arrest period when compared with the pre-arrest epoch ( $Z = -3.06, P < 0.001$ ).

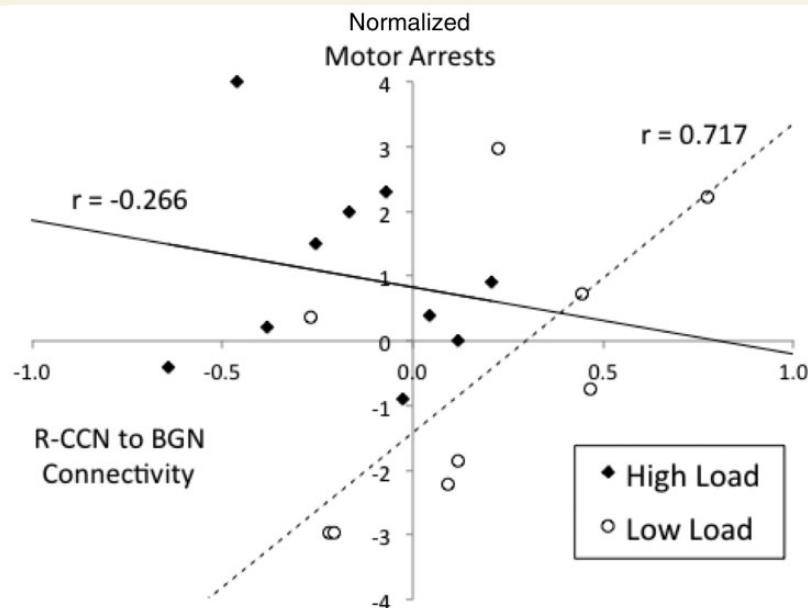
## Discussion

In this study, we used task-based functional connectivity and independent component analysis to show that freezing of gait in Parkinson's disease is associated with paroxysmal episodes of functional decoupling between neuronal networks. Specifically, the number of motor arrests was related to the degree of impairment of functional connectivity between the basal ganglia network and the bilateral CCN in patients with freezing of gait. Furthermore, the frequency of motor arrests in the virtual reality task was associated with impaired 'cross-talk' between the left and the right-lateralized CCNs. Finally, we also provided evidence to suggest that discrete motor arrests in the virtual reality task are related to functional decoupling between the CCN and the basal ganglia network (Fig. 6). As such, the results of this study confirm the notion that the pathophysiological mechanism underlying freezing of gait in Parkinson's disease reflects paroxysmal impairments in the spatiotemporal dynamics between frontostriatal neuronal networks (Lewis and Barker, 2009).

Consistent with previous neuroimaging studies in freezing of gait (Shine *et al.*, 2013c, d), this study has demonstrated that patients with Parkinson's disease display consistent activation across the CCN and the ventral attention network during the performance of the virtual reality gait task. Neural hubs within both of these networks are presumed to underlie the processing of goal-directed and task-related commands (Dosenbach *et al.*, 2006) and have previously been implicated in the pathophysiological mechanism of freezing of gait (Bartels and Leenders, 2008; Nutt *et al.*, 2011; Shine *et al.*, 2011c). In addition, all



**Figure 4** A comparison of the decreased connectivity between the right and left CCN (R-CCN and L-CCN, respectively) during the manipulation of cognitive load in a patient with freezing of gait (FOG) and a patient without freezing (N-FOG). The degree of impaired connectivity between these two networks was significantly correlated with the number of motor arrests in high versus low cognitive load blocks in the patients with freezing of gait and the difference between the two effects was statistically significant ( $ZI = 2.02$ ,  $P = 0.02$ ). BOLD = blood oxygen level-dependent.



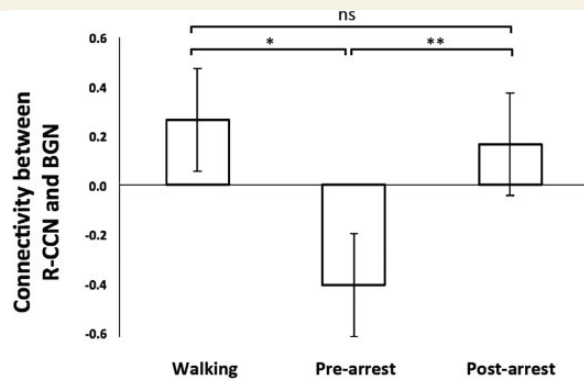
**Figure 5** Modulation of connectivity between basal ganglia network and right CCN during high load (OFF > ON;  $r = -0.266$ ,  $P = 0.46$ ) when compared with low load (OFF > ON;  $r = 0.717$ ,  $P = 0.02$ ). The x-axis represents the degree of functional connectivity between the basal ganglia network and the right CCN and the y-axis represents the frequency of motor arrests during the virtual reality task, normalized against the total number of events in each block to allow direct comparison. The difference between the two coefficients was significant ( $ZI = 3.02$ ,  $P < 0.01$ ). No such relationship was observed in patients without freezing of gait.

patients with Parkinson's disease in the present study showed a general increase in the functional connectivity between the left- and right-lateralized CCN during the task, suggesting that these two components were acting synergistically to effectively navigate the virtual reality environment. As predicted from previous studies (Shine *et al.*, 2013c, d), these results demonstrate that widespread neural regions are required to act together within larger neuronal networks in order to effectively perform the virtual reality task.

The manipulation of dopaminergic state and cognitive load was associated with specific alterations in the activity and connectivity

between the neuronal networks. For example, all patients were less able to recruit the basal ganglia network during the dopaminergic OFF state, perhaps reflecting a decrease in the coupling between the striatum and its cortical afferents (Cole *et al.*, 2013). In response to an increase in cognitive load, all patients were able to recruit activation in the motor network and the bilateral CCNs; however, freezers were unable to sustain activation in the motor network or the basal ganglia network during these periods, particularly in the dopaminergic OFF state. This specific pattern of hypo-activation across the motor network and basal ganglia





**Figure 6** The period preceding a motor arrest in the virtual reality task was associated with a significant decrease in the connectivity between the right CCN (R-CCN) and the basal ganglia network (BGN) when comparing normal walking with the epoch preceding a motor arrest (pre-arrest;  $P < 0.05$ ). This impairment in connectivity was subsequently restored in the epoch following a motor arrest (post-arrest;  $P < 0.08$ ), which was normalized to the levels of connectivity seen during normal walking ( $P = 0.68$ ). These results suggest that individual motor arrests on the virtual reality task are related to a functional decoupling within frontostriatal networks.

network may have predisposed susceptible patients to an increased frequency of motor arrests, which were substantially higher in the OFF state when performing the high cognitive load blocks of the experiment (Fig. 3). This raises the possibility that the decreased connectivity between these networks represents a predisposing factor for the increased freezing seen during the high cognitive load blocks in the OFF state, possibly reflecting impairments in the effective 'switching' between neuronal networks (Menon and Uddin, 2010; Shine *et al.*, 2013e).

The frequency of motor arrests was also strongly correlated with functional decoupling between key neuronal networks during the performance of the virtual reality task. In the presence of high cognitive load, the number of motor arrests was significantly correlated with the degree of impaired connectivity between the left and right CCN, possibly reflecting impaired 'cross-talk' between the two hemispheres (Fig. 4) (Lewis and Barker, 2009) which may be due in part to impaired efferent connectivity with the pedunculopontine nucleus, particularly in the right hemisphere (Fling *et al.*, 2013). During blocks of high cognitive load in the dopaminergic OFF state, the frequency of motor arrests suffered by patients with clinical freezing of gait was predictive of the degree of impaired connectivity between the basal ganglia network and both the left and the right CCN (Fig. 5).

Paroxysmal motor arrests on the virtual reality task were associated with impaired connectivity between the CCN and the basal ganglia network, which was re-established on the breaking of a motor arrest (Fig. 6). In addition, the breaking of a motor arrest was also associated with increased connectivity between the CCN and the ventral attention network. Together, these results suggest that freezing of gait is due to functional decoupling within the frontostriatal networks responsible for the mediation of goal-directed and flexible behaviours (Spreng *et al.*, 2010), an

interpretation which is consistent with recent behavioural evidence showing that freezing of gait is related to impairments in the processing of conflict-related signals (Vandenbosche *et al.*, 2011, 2012b). Indeed, a strong prediction from these lines of research is that the dissociation of frontoparietal cortical regions responsible for conscious goal-directed behaviour and the subcortical structures responsible for habitual behaviour would manifest peripherally as an episode of freezing (Vandenbosche *et al.*, 2012a).

The results of this study bring together a number of disparate findings across the unique (but not necessarily exclusive) hypotheses that have been used to explain the pathophysiology of freezing of gait (Nutt *et al.*, 2011; Shine *et al.*, 2011c). One major difficulty in aligning these models has been the elucidation of a mechanism that can link the provocation of freezing of gait (which is often associated with the completion of cortically mediated tasks, such as dual-tasking) with the manifestation of freezing of gait (which is likely to be because of the interruption of neuronal activity within the brainstem and spinal cord structures controlling gait) (Drew *et al.*, 2004; Lemon, 2008). The results of this study suggest that the functional decoupling of goal-directed frontostriatal systems is a likely mechanism responsible for the triggering of episodes of freezing of gait. This impaired coupling would lead to the loss of inhibitory influence over the output structures of the basal ganglia (Lewis and Barker, 2009; Shine *et al.*, 2013c), potentially leading to overwhelming inhibition in regions of the mesencephalic locomotor region that control locomotion, such as the glutamatergic nuclei of the pedunculopontine nucleus (Pahapill and Lozano, 2000). Interestingly, recent structural neuroimaging studies have shown a relative lack of white matter connectivity between the pedunculopontine nucleus and the cerebellum (Schweder *et al.*, 2010; Fling *et al.*, 2013), along with the thalamus and frontal cortex (Fling *et al.*, 2013), possibly placing the mesencephalic locomotor region (of which the pedunculopontine nucleus is a contributing region) at an increased risk of hyperpolarization by GABAergic input from the globus pallidus. This activity would therefore ultimately manifest as abnormal neuronal afferent signals travelling to the spinal cord, and poorly coordinated muscle firing patterns; 'trembling in place' (Jacobs *et al.*, 2009; Nutt *et al.*, 2011).

Another possible interpretation of the impaired intra-network connectivity in this study is that the freezing phenomenon is a manifestation of a global decrease in the information processing capacity of the brain. Theoretically, this effect would likely occur within neural circuits that perform a more domain-general function, such as switching activation between neural networks (Seeley *et al.*, 2007; Nelson *et al.*, 2010) or represent the attempted reduction of high-dimensional activity from the corticothalamic system by the basal ganglia nuclei (Bar-Gad *et al.*, 2003). In this manner, the functional decoupling between key members of the 'cognitive' frontostriatal loop in this experiment may reflect a breakdown in information processing within these circuits, which is supported by the recent finding of impaired executive network connectivity in patients with freezing of gait during the resting state (Tessitore *et al.*, 2012). Such an interpretation would be consistent with the results of a recent event-related functional MRI study, which showed that motor arrests on the virtual reality task were associated with increased blood oxygen level-dependent

response in the CCN with an associated decreased response in the bilateral head of the caudate and ultimately, increased inhibitory outflow from the basal ganglia (Shine *et al.*, 2013c). However, it is unclear from these analyses whether the decreased connectivity between these frontostriatal circuits arises at the cortical or the subcortical level.

Interestingly, key neural hubs within the ventral attention network, namely the anterior insula, have been previously implicated in the ability to effectively 'switch' activation between complementary yet competing neural networks (Menon and Uddin, 2010). However, if the ventral attention network was consistently recruited (as was the case in this study), the capacity to coordinate attentional resources required by evolving task demands may become impaired. In a healthy patient, this ventral attention network recruitment may not be associated with any adverse outcomes, whereas it is possible that the recruitment and associated 'burn-out' of the ventral attention network may play an important role in the pathophysiological mechanism of freezing of gait. Specifically, by forcing an increased reliance on the associative centres of the brain, such as the regions that comprise CCN (Cole and Schneider, 2007), but performing in a state in which the system is unable to 'switch' attentional processes towards these networks, the global neuronal functioning of a patient with freezing of gait would become impaired. This interpretation is consistent with modern models of basal ganglia function, which propose that the motor network uses striatal regions responsible for habitual functions, relying on the CCN and its interaction with more rostral striatal regions (such as the caudate and the ventral striatum) to accomplish goal-directed tasks (Redgrave *et al.*, 2010). Therefore, impaired ventral attention network function would place the basal ganglia in a state of information deficit that is exacerbated by a general lack of dopamine (Williams *et al.*, 2002; Dang *et al.*, 2012; Cole *et al.*, 2013). This would lead to decreased inhibition of basal ganglia output structures, an over-reliance on external 'drivers' (Hallett, 2008), and ultimately manifest as freezing behaviour (Lewis and Barker, 2009).

An important caveat to the findings of this study is that freezing events on the virtual reality task are not specific to those patients that have clinical freezing of gait. However, the measure of freezing used in this study is a sensitive measure that can delineate between patient groups, as evidenced by the statistically significant differences seen in the number of freezing events across the two patient cohorts (Fig. 3). In addition, the specific combination of increased cognitive load and the absence of dopaminergic medication led to a marked increase in the frequency of motor arrests, but only in the cohort of freezers. These results are strongly aligned with previous work that has shown that the frequency of motor arrests on the virtual reality paradigm is related to the severity of self-reported freezing of gait (Naismith and Lewis, 2010) and to the frequency and duration of clinically-observed freezing of gait triggered during the performance of timed up-and-go tasks (Shine *et al.*, 2013b). Although caution is required in interpreting the neural patterns associated with virtual reality freezing and real-life freezing of gait, suggesting that the results of this study advance our understanding of the mechanisms underlying freezing of gait. Future studies should attempt to explore the

kinematics associated with motor arrests on the virtual reality task and compare them directly with freezing events seen in both the upper limbs (Nieuwboer *et al.*, 2009; Vercruyse *et al.*, 2012) and gait (Morris *et al.*, 2012).

## Conclusion

The results of this study confirm that freezing of gait in Parkinson's disease is related to impaired functional communication between widespread neural networks. Specifically, we have shown that freezing behaviour on a virtual reality task is associated with functional decoupling between the right-lateralized CCN and the basal ganglia network. These data provide evidence that extends recent neuroimaging studies of freezing of gait in Parkinson's disease (Shine *et al.*, 2013c, d) and are consistent with the hypothesis that freezing of gait is because of abnormal communication between cortical and subcortical structures in the presence of increased cognitive load and low levels of dopamine (Lewis and Barker, 2009; Vandenbossche *et al.*, 2012a).

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