Alterations in white matter network topology contribute to freezing of gait in Parkinson's disease

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Abstract

Freezing of gait (FOG) is a common symptom in advanced Parkinson's disease (PD). Despite current advances, the neural mechanisms underpinning this disturbance remain poorly understood. To this end, we investigated the structural organisation of the white matter connectome in PD freezers and PD non-freezers. We hypothesized that freezers would show an altered network architecture, which could hinder the effective information processing that characterizes the disorder. Twenty-six freezers and twenty-four well-matched non-freezers were included in this study. Using diffusion tensor imaging, we investigated the modularity and integration of the regional connectome by calculating the module degree z score and the participation coefficient, respectively. Compared to non-freezers, freezers demonstrated lower participation coefficients in the right caudate, thalamus, and hippocampus, as well as within superior frontal and parietal cortical regions. Importantly, several of these nodes were found within the brain's 'rich club'. Furthermore, group differences in module degree z scores within cortical frontal and sensory processing areas were found. Together, our results suggest that changes in the structural network topology contribute to the manifestation of FOG in PD, specifically due to a lack of structural integration between key information processing hubs of the brain.

Keywords Parkinson's disease · Freezing of gait · Connectome · Diffusion imaging

Introduction

Freezing of gait (FOG) is a sudden and involuntary gait cessation that is common in idiopathic Parkinson's disease (PD) [1] and has a prominent impact on quality of life [2]. Freezing behaviour can be provoked by a range of triggers, including turning, dual tasking, and emotional stress [3]. Treatment options are limited, and although dopaminergic

medication can partially ameliorate freezing, patients are often forced to rely on behavioural strategies that temporarily enhance their gait pattern using goal-directed strategies [1]. Furthermore, patients with freezing often experience executive dysfunction, mood disorders, and perceptual problems [4–6]. These observations have led to the suggestion that FOG is not simply the result of dysfunctional locomotor output, but rather results from a diffuse, network-level dysfunction that ultimately manifests as a loss of top-down control over the brainstem structures that control gait [7].

A range of studies has been conducted to determine whether individuals with FOG demonstrate white matter abnormalities. For instance, widespread alterations in structural connections between cortical, subcortical, and brainstem regions have been reported in studies using diffusion tensor imaging (DTI), a technique that infers the integrity of inter-regional white matter. Compared to non-freezers, freezers have shown abnormalities in the corticopontine, pontine-cerebellar [8–11], and major cortico-cortical and frontostriatal tracts [10, 12]. Conversely, differences were not observed in a study investigating the frontostriatal

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hyper-direct pathway [13] or in a whole-brain analysis between freezers and non-freezers [14]. These results suggest that structural lesions in freezers might be subtle and dispersed, and hence raise the question of whether FOG actually stems from a focal anatomical lesion at all [7]. Indeed, a key caveat of the majority of studies to date is that they have used diffusion imaging in an attempt to identify lesions within specific regions or tracts. As such, they offer insights that are relatively limited to the field of interest and, therefore, miss more complex, distributed patterns that might exist in the data.

Given the multi-dimensional nature of FOG, the primary objective of this study was to investigate the structural brain network architecture in patients with FOG and this debilitating phenomenon. Specifically, we investigated whether white matter changes that contribute to freezing might emerge as alterations in structural network topology. The brain displays a modular structure, in which discrete communities ('modules') with densely interconnected nodes are only sparsely connected with nodes of other communities [15, 16]. These specialist modules allow for processing without unnecessary cross-talk [17]. Conversely, the integration of communities is crucial for incorporating complex information streams of different modalities, such as in cognitively challenging tasks (Fig. 1b) [15, 18].

Graph theory offers a robust mathematical framework for interrogating neural network topology, and can offer a detailed in vivo analysis of the brain at the level of circuits and modules [19]. Importantly, whole-brain graph theoretical embraces the inherent complexity of interacting sub-systems, rather than isolating a particular region within a circuit. Here, we used a combination of DTI and graph theoretical analyses to investigate the global and regional topology of the structural connectome in individuals with PD and FOG. Given the known impairments in multi-domain behaviour in patients with freezing, we predicted that freezers should exhibit impairments in inter-modular connectivity, especially in frontoparietal and subcortical networks [7].

Materials and methods

Fifty patients with mild-to-moderate idiopathic PD, recruited from the Parkinson's Disease Research Clinic at the Brain and Mind Centre, University of Sydney, were included in this study. Demographic and clinical details including age, gender, disease duration, levodopa equivalent daily dose, and motor severity were obtained and are listed in Table 1. Motor severity was measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III [20] and Hoehn and Yahr (H&Y) scale [21]. Patients with a H&Y score of >3 were excluded from the study. Cognitive screening was performed using

the Mini-Mental State Examination [22] and patients with a score of ≤ 25 on this test were also excluded from the study. Finally, Logical Memory [23], the Trail Making Test Part B – A (TMT_{B-A}) [24], and Digit Span Backward (DSB) [23] were used as measures of memory and executive functioning ability. Patients were identified as 'freezers' if they scored positively on the Freezing of Gait Questionnaire item 3 [25, 26] and as 'non-freezers' if they scored 0 on this item.

MRI acquisition

Neuroimaging was acquired on a 3-Tesla General Electric Discovery MR750 scanner (GE Medical Systems) using an eight-channel-phased array head coil. 3D T1-weighted, anatomical images (voxel size $1 \times 1 \times 1$ mm) were obtained for parcellation of cortical regions, using the following protocol: Repetition time 7.2 ms, echo time 2.7 ms, inversion time 450 ms, 196 transverse slices, 256×256 matrix; field of view 256×256 mm, and flip angle 12° . Diffusion-weighted images (DWI) were acquired in 61-gradient directions, using the following echoplanar imaging protocol: repetition time 7025 ms, echo time 80 ms, 55 transverse slices, 2.5 mm slice thickness, 256×256 matrix; field of view 240×240 mm. The effective diffusion weighting was $b = 1000$ s/mm². Four volumes with no diffusion weighting ($b = 0$ s/mm²) were acquired at the beginning of each diffusion sequence and used for robust individual registration between T1-weighted anatomical and the diffusion-weighted images.

Image pre-processing

Diffusion image pre-processing was performed using the FMRIB Software Library (FSL, <http://fsl.fmrib.ox.ac.uk>). Raw DWI were corrected for susceptibility, head motion, and eddy current distortions using FSL's tool *eddy* and skull stripped using *BET*. T1-weighted images were segmented into white and grey matter (cortical and subcortical structures) and cerebrospinal fluid using FreeSurfer (version 5.3; <http://surfer.nmr.mgh.harvard.edu>). The cortical surface was further parcellated into 219 cortical regions using the Lausanne anatomical atlas [27] distributed as part of the Connectome Mapping Toolkit [28] and validated for diffusion MRI analysis. Using FreeSurfer, 14 subcortical structures were segmented including the left and right thalamus, caudate, putamen, pallidum, amygdala, hippocampus, and nucleus accumbens area by an atlas based segmentation [29]. This atlas was chosen, because this scale has been shown to provide local interpretability whilst containing homogeneous clusters [27]. T1-weighted images were registered in DWI space to the b0 volume. Fibre reconstruction was performed using robust tensor fitting. The main diffusion direction of each voxel was estimated after decomposition of the tensor into eigenvectors and eigenvalues, and fractional anisotropy values, a measure of magnitude

Fig. 1 **a** Imaging processing flow. **b**. Representation of a brain network with a modular structure. Different graph metrics are highlighted

of directionality of diffusion in white matter fibres, were computed. White matter pathways were constructed using deterministic fibre tracking approach. The deterministic approach was chosen to control for the number of false positives, which are unfavourable when investigating network topology [30].

Using the fibre assignment by continuous tracking algorithm, streamlines were traced following the main diffusion direction starting from eight seeds evenly distributed in each white matter voxel and stopping when one of the following criteria was met: (1) fractional anisotropy < 0.1 ; (2) turn $> 45^\circ$; (3)

Table 1 Demographic and clinical data of patients with and without freezing of gait

	Freezers	Non-freezers	<i>p</i> -value
<i>n</i>	26	24	–
Age, years, mean ± SD	64.2 ± 9.4	66.9 ± 5.3	0.220
Disease duration, years, mean ± SD	5.2 ± 3.8	5.2 ± 3.0	0.970
LEDD, mg, mean (range)*	656.7 (0–1548)	526.6 (0–1200)	0.431
MDS-UPDRS III, mean ± SD	25.5 ± 13.0	23.3 ± 13.5	0.558
H&Y, mean (range)*	2.0 (1–2.5)	1.8 (1–2.5)	0.131
MMSE, mean (range) *	28.5 (26–30)	29.1 (26–30)	0.051
Logical Memory I, mean ± SD	36.1 ± 10.0	39.8 ± 10.3	0.201
Logical Memory II, mean ± SD	21.3 ± 7.8	22.5 ± 10.4	0.657
TMT _{B-A} , sec, mean (range) *	61.6 (17–216)	41.0 (–1–92)	0.063
Digit span backward, mean ± SD	6.38 ± 1.8	7.57 ± 3.3	0.118

LEDD levodopa equivalence daily dose, MDS-UPDRS III motor part of the Movement Disorder Society Unified Parkinsons Disease Rating Scale, H&Y Hoehn and Yahr motor scale, MMSE mini-mental state examination, TMT_{B-A} trail making test part B–A

*Mann-Whitney *U* test

the end of the brain mask was reached. Connectome maps were reconstructed using the Connectome Mapper [28]. By combining the parcellation map and the reconstructed fibres, a connectivity matrix was created for each subject, using the average fractional anisotropy of voxels of the reconstructed streamlines. The pipeline is illustrated in Fig. 1a. Finally, to account for spurious streamlines, values of tracts that were present in less than 50% of all participants were set to zero by applying a threshold on the individual connectivity matrices [31]. To verify the results which were not skewed by the choice of threshold, the analysis was also performed using thresholds of 40 and 60%.

Graph theoretical analyses

Graph metrics were calculated on the thresholded adjacency matrices using MATLAB scripts from the Brain Connectivity Toolbox [32]. First, we confirmed that the group mean structural connectome demonstrated a ‘small-world’ architecture, by comparing the ratio of the mean clustering coefficient (the average intensity of triangles around a node) to the shortest path length (a metric of information transmission) of the thresholded connectivity matrix. We next sought to identify significant differences in graph metrics between the two groups. To this end, network modularity was calculated using the Louvain modularity algorithm [32]. This algorithm iteratively assigns nodes to different communities, until the maximum possible modularity statistic *Q* is reached. In this way, the network is subdivided into non-overlapping groups of highly connected nodes that minimizes between module edges:

$$Q = \frac{1}{v} \sum_{ij} (w_{ij} - e_{ij}) \delta_{M_i M_j}. \quad (1)$$

Equation 1—Louvain modularity algorithm, where *v* is the total weight of the network (sum of all positive connections), *w_{ij}* is the weighted connection between regions *i* and *j*, *e_{ij}* is the strength of a connection divided by the total weight of the network, and $\delta_{M_i M_j}$ is set to 1 when regions are in the same community and 0 otherwise.

Due to the stochastic nature of the Louvain algorithm, the community assignment for each region was assessed 100 times on the group average connectome and a consensus partition was identified using a fine-tuning algorithm. To define an appropriate value for the resolution parameter (γ), we iterated the Louvain algorithm across a range of values (0.5–2.0 in steps of 0.1) for 100 iterations and then estimated the similarity of the resultant partitions using mutual information. A γ parameter of 1.0 provided the most robust estimates of topology across these iterations and, thus, was used for the main experiment.

To estimate the topology at the regional level, we calculated the module degree *z* score (*W_i*; a measure of intra-module connectivity; see Eq. 2) and participation coefficient (*B_i*; a measure of inter-module connectivity; see Eq. 3) for each node. Positive *W_i* values reflect nodes with more connections to other members of the same community (compared to the average number of connections) and vice versa. In contrast, the *B_i* values ranges between 0 and 1, with a value of 0, indicating that all connections are within its community, whereas a value of 1 indicates uniformly distributed connections across modules (<https://github.com/juliemaehall/topology>):

$$W_i = \frac{\kappa_i - \kappa_{s_i}'}{\sigma_{\kappa_{s_i}}}. \quad (2)$$

Equation 2—Module degree z score W_i , where κ_i is the strength of the connections of region i to other regions in its module s_i , κ'_{s_i} is the average of κ over all the regions in s_i , and $\sigma_{\kappa_{s_i}}$ is the standard deviation of κ in s_i :

$$B_i = 1 - \sum_{s=1}^{n_M} \left(\frac{\kappa_{is}}{\kappa_i} \right)^2. \quad (3)$$

Equation 3—Participation coefficient B_i , where κ_{is} is the strength of the positive connections of region i to regions in module s , and κ_i is the sum of strengths of all positive connections of region i . The participation coefficient of a region is, therefore, close to 1 if its connections are uniformly distributed among all the modules and 0 if all of its links are within its own module.

Rich-club analysis

We next identified the structural ‘rich club’ of the binarized group mean connectivity matrix of the entire sample. The ‘rich club’ of a network represents a set of high degree nodes (i.e. nodes with a large number of edges) that are more densely interconnected with other high degree nodes than would be expected by chance [33]. To estimate these regions, the degree of each node i was determined by taking the sum of the number of connections node i shared with k other nodes in the network. Then, a sub-network (the ‘ k core’) was obtained by removing all nodes that had connections $\leq k$. For each value of k , the rich-club coefficient Φ_k was then computed as the ratio of the number of connections between the nodes in the k core network and the sum of possible connections that would be present if the network was completely connected (see Eq. 4):

$$\Phi_k = \frac{2E_{>k}}{N_{>k}(N_{>k} - 1)}. \quad (4)$$

Since random networks also show an increasing function of Φ_k , we next normalized the rich-club coefficient in reference to a null model. To this end, we created 5000 random networks with a preserved degree distribution, and then, the average rich-club coefficient Φ_{rand} over the set of random networks was calculated for each level of k . We then divided Φ_k by Φ_{rand} , and to define the normalized rich-club coefficient (Φ_Z). Values of k with a $\Phi_Z > 1$ can thus be said to contain a stronger rich-club architecture than expected under the conditions of the null model [33]. The identity of rich-club nodes for the highest value of k with $\Phi_Z > 1$ can be found by identifying nodes that were present within the k core network for that value of k . The 85th percentile of nodes was selected as part of the rich club.

Statistical analyses

Data analyses for demographic and clinical variables were performed using IBM SPSS Version 19. Independent t tests and Mann–Whitney U tests were performed, depending on the distribution of the data. Missing values for LEDD ($n = 1$; 2% of the sample), Logical Memory ($n = 1$; 2% of the sample), TMT_{B–A} ($n = 2$; 4% of the sample), and DBS ($n = 1$, 2% of the sample) were replaced using the expectation minimization algorithm. The results are presented in Table 1. To assess statistical significance for the regional level metrics, a non-parametric permutation testing approach was used (5000 iterations) that effectively controls for multiple comparisons [34]. In addition, permutation testing with 5000 iterations was applied following a Spearman’s correlation analysis between the significant B_i and W_i values and TMT_{B–A} and DSB scores.

To determine whether there was overlap between the rich club and regions with altered topology in our two clinical groups, we compared the spatial overlap between the three variables. To analyse whether this overlap was statistically significant, a permutation test was performed in which we randomly permuted the rich-club identity of each region (5000 iterations) and used the overlap between the randomized vector and the significantly different W_i and B_i scores to populate two separate null distributions. We then compared the empirical overlap between rich club and topological outcome measures with the null distributions and rejected the null hypothesis of no overlap if the true overlap was less than the 97.5th percentile of null distribution (i.e., the top 2.5%).

The difference scores between the groups on the B_i and W_i values were compared across the three different thresholds, and moderate-to-very strong correlations were found, confirming the robustness of the findings (see Supplementary Materials).

Results

Demographics

Twenty-six patients were identified as freezers and twenty-four as non-freezers. There were no differences between the groups for age, disease duration, dopaminergic medication, disease severity as measured by the MDS-UPDRS part III and H&Y scale and the MMSE, Logical Memory, TMT_{B–A}, and DSB (see Table 1).

Graph metrics

A small-world organisation of the structural brain networks was confirmed in both patient groups [33]. Table 2

Table 2 Nodes with significantly different participation coefficients between groups

Node	Region	<i>x</i>	<i>y</i>	<i>z</i>	Freezers	Non-freezers	Rich club
Non-freezers > freezers							
Subcortical							
R caudate	Basal ganglia	15	10	11	0.690 ± 0.05	0.731 ± 0.05	✓
R hippocampus	Hippocampus	28	−22	−13	0.613 ± 0.09	0.668 ± 0.08	✓
R thalamus	Thalamus	13	−17	7	0.699 ± 0.07	0.752 ± 0.05	✓
Frontal							
lh-lateralorbitofrontal_4	Orbitofrontal cortex	−12	52	−19	0.562 ± 0.12	0.628 ± 0.10	–
rh-lateralorbitofrontal_4	Orbitofrontal cortex	16	52	−18	0.525 ± 0.13	0.612 ± 0.10	✓
lh-medialorbitofrontal_2	Orbitofrontal cortex	−5	33	−20	0.596 ± 0.11	0.676 ± 0.07	–
lh-superiorfrontal_5	Prefrontal cortex	−11	36	47	0.594 ± 0.10	0.653 ± 0.09	–
lh-superiorfrontal_7	Premotor cortex	−8	14	52	0.579 ± 0.16	0.660 ± 0.08	–
lh-superiorfrontal_8	Premotor cortex	−8	−2	63	0.524 ± 0.13	0.628 ± 0.10	–
lh-superiorfrontal_9	Premotor cortex	−17	−1	67	0.524 ± 0.10	0.608 ± 0.09	–
rh-superiorfrontal_3	Prefrontal cortex	11	40	40	0.580 ± 0.16	0.670 ± 0.11	–
rh-superiorfrontal_4	Prefrontal cortex	18	34	47	0.571 ± 0.17	0.674 ± 0.09	–
rh-superiorfrontal_5	Premotor cortex	12	18	52	0.583 ± 0.14	0.679 ± 0.09	–
rh-superiorfrontal_6	Premotor cortex	11	2	60	0.521 ± 0.15	0.611 ± 0.09	–
rh-paracentral_2	Primary motor cortex	10	−16	59	0.199 ± 0.18	0.325 ± 0.18	–
Parietal							
lh-inferiorparietal_4	Somatosensory association cortex	−36	−71	42	0.304 ± 0.16	0.423 ± 0.18	–
lh-postcentral_2	Primary somatosensory cortex	−26	−31	65	0.596 ± 0.11	0.676 ± 0.10	–
lh-postcentral_3	Primary somatosensory cortex	−40	−30	57	0.479 ± 0.15	0.565 ± 0.16	–
lh-superiorparietal_2	Somatosensory association cortex	−33	−43	55	0.239 ± 0.16	0.373 ± 0.17	–
lh-superiorparietal_4	Somatosensory association cortex	−20	−62	61	0.574 ± 0.14	0.681 ± 0.08	✓
lh-superiorparietal_7	Visual association cortex	−13	−87	34	0.548 ± 0.15	0.640 ± 0.10	✓
Cingulate							
lh-posteriorcingulate_1	Posterior cingulate gyrus	−4	−11	35	0.409 ± 0.16	0.512 ± 0.18	–
rh-caudalanteriorcingulate_1	Anterior cingulate gyrus	9	36	5	0.497 ± 0.17	0.602 ± 0.18	–
Non-freezers < freezers							
rh-caudalmiddlefrontal_1	Prefrontal cortex	36	2	47	0.333 ± 0.17	0.235 ± 0.16	–

lh Left hemisphere, *rh* right hemisphere

and Fig. 2a demonstrate the 23 nodes that had significantly lower B_i values in freezers compared to non-freezers (nodes coloured in green in Fig. 2a). Three of these more segregated nodes encompassed subcortical nuclei, including the right caudate, thalamus, and hippocampus. In the left hemisphere, we found six nodes in the frontal cortex, six nodes in the parietal cortex, and one node in the posterior cingulate gyrus. In the right hemisphere, six nodes in the frontal cortex and one node in the anterior cingulate gyrus showed significantly lower values in freezers compared to non-freezers. Conversely, the right caudal middle frontal gyrus showed a significantly higher B_i value in freezers. Nine nodes in distributed cortical regions with lower W_i scores (nodes coloured in green in Fig. 2b) and six cortical nodes with higher z scores (nodes coloured in orange in Fig. 2b) were found in PD freezers compared to non-freezers (see Table 3).

Of the regions that showed significantly different B_i values, two nodes in the superior parietal cortex negatively correlated with the TMT_{B-A} scores ('lh-superiorparietal_2': $r = -0.32$, $p < 0.05$; 'lh-superiorparietal_4': $r = -0.34$, $p < 0.05$), whilst the right hippocampus and node 'rh-superiorfrontal_4' showed a positive correlation with the DSB ($r = 0.35$, $p < 0.01$ and $r = 0.27$, $p < 0.05$, respectively). One node with a significantly different W_i value showed a positive correlation ('lh-superiorfrontal_4': $r = 0.30$, $p < 0.05$) with the TMT_{B-A} . Finally, node 'rh-superiorfrontal_8' showed a negative correlation with the DSB ($r = 0.17$, $p < 0.05$), whilst node 'rh-rostralmiddlefrontal_4' showed a negative correlation with this test performance ($r = -0.27$, $p < 0.05$).

A rich-club network encompassing 35 nodes was identified. Of the 24 nodes that had a significantly different B_i value between groups, six nodes were identified as part of the rich-club, which was deemed significant ($p < 0.05$; see

Fig. 2 **a** Nodes with a significantly different participation coefficient in freezers compared to non-freezers. **b** Nodes with a significantly different module degree z score in freezers compared to non-freezers

Table 2, Fig. 3 and Supplementary materials). Of the 15 nodes with different W_i values between groups, two nodes were considered within the rich-club network, but this overlap was not significant ($p > 0.05$).

Discussion

Here, we used graph theoretical methods to assess the structural network topology of PD patients with FOG. This approach allowed us to investigate both integrative as well as specialised properties of individual nodes within the brain's structural connectivity network in a data-driven manner, thus obviating any a priori assumptions about selected regions. In doing so, we demonstrated that freezers had a significantly lower participation coefficient in 23 of the 233 nodes compared to non-freezers. Specifically, these more segregated nodes included the right subcortical caudate, thalamus, and hippocampus, as well as nodes within bilateral frontal and

parietal regions. Moreover, the six of these nodes were also part of the rich-club network that forms the backbone of the structural connectome by reducing path length (as opposed to multiple short-path connections) and hence permits faster and less noisy signal transmission [18, 33, 35].

Therefore, in keeping with other biological models [36, 37], we hypothesize that the symptoms of FOG may in part arise due to a lack of structural integration between key information processing hubs of the brain including motor, cognitive and limbic structures. A decreased ability to recruit alternative routes for parallel information processing [38] would lead to a lack of resilience when there are functional network challenges (such as cognitive dual-task performance) and also offer an explanation for the known characteristic set-shifting deficits in individuals with FOG [4]. The motor manifestation of FOG could thus arise due to a flow-on effect, whereby an inefficient network architecture would hamper the effective communication between major cortical and subcortical integration centres [7].

Table 3 Nodes with significantly different module degree z-scores between groups

Node	Region	<i>x</i>	<i>y</i>	<i>z</i>	Freezers	Non-freezers
Non-freezers > freezers						
Frontal						
lh-medialorbitofrontal_1	Orbitofrontal cortex	−7	52	−11	−0.482 ± 0.70	0.189 ± 0.95
lh-parstriangularis_1	Prefrontal cortex	−43	33	2	0.371 ± 0.74	0.847 ± 0.88
rh-parsorbitalis_1	Prefrontal cortex	43	43	−10	0.324 ± 0.80	0.904 ± 0.66
rh-superiorfrontal_8	Prefrontal cortex	22	10	58	−0.574 ± 0.49	−0.181 ± 0.51
Parietal						
lh-postcentral_5	Primary sensory cortex	−55	−15	43	−0.686 ± 0.48	−0.367 ± 0.52
rh-postcentral_5	Primary sensory cortex	28	−32	69	0.249 ± 0.72	0.826 ± 0.91
Occipital						
lh-lateraloccipital_5	Visual association cortex	−34	−83	−10	−0.222 ± 0.80	0.534 ± 0.78
Cingulate						
lh-rostralanteriorcingulate_1	Anterior cingulate	−7	37	2	0.566 ± 1.00	1.234 ± 0.83
rh-rostralanteriorcingulate_1	Anterior cingulate	14	−33	52	0.713 ± 0.93	1.397 ± 0.50
Non-freezers < freezers						
Frontal						
lh-superiorfrontal_4	Prefrontal cortex	−8	32	37	−0.556 ± 0.87	−1.082 ± 0.57
rh-rostralmiddlefrontal_4	Prefrontal cortex	34	52	10	−0.837 ± 0.54	−1.187 ± 0.55
Parietal						
lh-postcentral_7	Retrosubicular area	−52	−11	19	−0.354 ± 0.75	−0.724 ± 0.52
rh-superiorparietal_1	Somatosensory association cortex	33	−43	54	0.550 ± 0.85	0.095 ± 0.79
rh-precuneus_1	Visual association cortex	23	−65	21	0.282 ± 0.76	−0.183 ± 0.71
Temporal						
lh-inferiortemporal_1	Inferior temporal gyrus	−41	−3	−38	−0.100 ± 0.61	−0.518 ± 0.68

lh left hemisphere, *rh* right hemisphere

Fig. 3 Representation of the rich-club network

Nodes with high participating coefficients have previously been characterized as ‘connector hubs’ [39], as they tend to interconnect otherwise segregated communities. In

the brain, nodes with high participation are thought to be crucial for incorporating complex information streams of different modalities. Affected participation scores, especially

across these connector hubs, may cause disruptions extending across cognitive, motor, and limbic domains [18]. Nodes with high participation coefficients exhibit more activity when coordinated activity occurs across communities, such as during cognitive task performance [15]. These hubs provide an integrative network function to an even greater extent than rich-club nodes [40]; and importantly, ten regions affected in freezers were amongst the nodes with the highest participation scores. Hence, they likely play a crucial role in disrupted information processing in these patients.

The caudate nucleus and thalamus have previously been implicated in the freezing pathophysiology with studies showing reduced grey matter volume [41] and hypo-activity within subcortical structures [42]. Importantly, the thalamic nuclei receive input from and project to diffuse areas in the cortex, basal ganglia, and cerebellum which play a role in modulating activity in the rest of the brain. Rather than simply being a relay station, the thalamic nuclei are a major hub for controlling the information flow across cortical and subcortical regions [43]. The caudate nucleus also receives inputs from various prefrontal regions [44] and plays a major part in task-switching behaviour, which can be understood in terms of activating different modules for specialised function. Despite not reaching significance, the left thalamus and caudate also showed lower participation coefficients in freezers ($p = 0.07$ and $p = 0.08$, respectively), and hence, there was no strong lateralization effect observed. Thus, the lower participation scores of these nodes may contribute to the pathophysiology of FOG through either ineffective integration of motor, sensory, and limbic activity during gait or inefficient shifting between functionally distinct but complementary neural pathways [7].

The previous findings of neuromodulatory systems have demonstrated the existence of an inverted U-shaped curve on executive functioning [36], and recent conceptual work has suggested that this relationship may also be present in network topology [15]. Consistent with the well-established association between FOG and impaired executive function [45–47], our findings showed less integrated nodes in the caudate, bilateral dorsolateral prefrontal (DLPFC), and anterior cingulate cortex. Moreover, participation coefficients of nodes within the DLPFC, superior parietal cortex, and hippocampus were associated with a performance on tasks investigating set-shifting and working memory. Thus, is it possible that changes in integration scores in areas associated with cognitive performance affect effective information transfer across the network, and might explain these phenotypic changes. However, the within the prefrontal cortex, one node showed a higher participation coefficient, perhaps reflecting a rerouting of the common path in this region.

Lower participation coefficients were also found across frontoparietal structures, including the premotor, primary motor cortex, and somatosensory association cortices,

Automated movements are performed by activity in segregated modules [15, 17] and these movements are affected by PD pathology [48]. As such, PD patients rely more on effective communication in superior frontoparietal regions, since combining different sources of information between these regions is fundamental for successful completion of an accurate and context-appropriate movement [49]. When a region becomes too specialised or segregated, it loses its flexibility that is necessary to navigate through changing circumstances, which may underpin the difficulties which freezers experience navigating complex environments.

A number of fMRI studies using region-of-interest analyses comparing PD freezers to non-freezers have shown alterations in similar regions as reported in the current study. Specifically, a functional decoupling between the bilateral cognitive control network and the basal ganglia during freezing episodes has been reported during motor arrests provoked by a virtual reality paradigm [50]. Furthermore, using this paradigm, freezing episodes were associated with alterations in BOLD response within frontoparietal sensorimotor regions, basal ganglia, thalamus, and in the mesencephalic locomotor region [42]. Altered resting-state functional connectivity within the cognitive control network, visual networks, and locomotor regions has further been shown to be associated with FOG severity [13, 51]. However, future research avenues should explore alterations in functional network topology associated with freezing of gait.

The current study also compared within-module connectivity across groups. Segregation into isolated modules allows for specialised processing of an action and increases efficiency, flexibility, and robustness to perturbation [35]. Abnormal within-module scores can affect these characteristics by increasing effective metabolic costs [35]. Compared to non-freezers, freezers showed lower module degree z scores in nodes within the prefrontal cortex (pars orbitalis, pars triangularis, and orbitofrontal and rostral anterior cingulate), primary sensory, primary motor, and visual association cortex. Perhaps surprisingly, higher module degree z scores were observed in patients with FOG in prefrontal cortices (DLPFC and the frontal eye fields), and various sensory information processing areas such as the somatosensory association, visual association, and inferior temporal regions. Interestingly, higher module degree z scores are considered favourable for behaviours that require specific, unimodal function, such as certain sensory processing systems [52]. As such, freezers may need to rely more heavily on exogenous stimuli to gather information to guide their actions, perhaps, due to a loss of automaticity [53]. Indeed, the previous studies have shown a proprioceptive deficit in PD patients with [54] and without freezing [49] along with a greater dependence on visual information [55]. Therefore, it could be speculated that a reweighting of sensory systems occurs in PD patients with freezing. Specifically, there may

be an increased emphasis placed on discrete modality specific pathways that process afferent information; however, if the system is unable to effectively integrate this information, the dynamic evolution of the gait pattern may suffer.

Limitations and future directions

The current study has several limitations. First, we grouped the participants based on a subjective question of the FOGQ. Currently, there is no gold standard to define FOG, and whilst objective measures are preferable, FOG can be difficult to elicit in a clinical or experimental environment and might remain unnoticed [56]. Another possible weakness of this study's methodology is that the Louvain algorithm does not allow for overlapping modules, as a node is only assigned to one community. Furthermore, although DTI is an established method for measuring white matter integrity and has led to great insights in PD [57, 58], it suffers from inherent limitations. Specifically, diffusion imaging measures the motion of water molecules along a tract and thus only allows for indirect validation of streamlines. The deterministic diffusion tensor fitting approach used in this study requires sufficient directional information at each voxel and is incapable of resolving crossing or 'kissing' fibres. However, the deterministic diffusion tensor fitting approach used in this study requires sufficient directional information at each voxel and is incapable of resolving crossing or 'kissing' fibres. At an ambiguous directional point in a voxel, fractional anisotropy values might drop leading to a premature termination of the reconstruction of a tract. This could be especially problematic in structures with complex fibre architecture such as subcortical nuclei. Future research should use more sophisticated methods, such as constrained spherical deconvolution, that are better equipped to deal with complex fibre configurations. Finally, this study used single shell DTI data, without EPI distortion corrections, which could have impacted the registration accuracy between the DTI and T1 images, creating suboptimal connectomes. Hence, these results should be interpreted with caution and replication studies using multi-shell sequences are necessary to fully understand the changes in network topology associated with FOG.

Conclusion

This is the first study to use graph theory to demonstrate subtle alterations in network topology in PD patients with FOG compared to those without this symptom. Specifically, we showed that freezers have lower participation scores in subcortical regions as well as higher order and integrative cortical cortices. We argue that this increase in segregation hinders efficient communication between major cortical

and subcortical centres, resulting in ineffective integration of motor, sensory, and limbic activity, as well as inefficient shifting between specialised modules that could disrupt gait in PD. Decreased intra-module connectivity might reflect a less cost-effective processing of information, whereas an increase in these scores in the sensory cortex of freezers suggests a possible compensatory strategy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All persons gave their informed consent prior to their inclusion in registries. The registries were approved by the Human Research Ethics Committee of the University of Sydney. Patients were included after informed written consent had been obtained, as set forth by the Declaration of Helsinki (WMA, 1964–2014).

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