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Altered organization of the dorsal attention network is associated with freezing of gait in Parkinson's disease

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ABSTRACT

Introduction: Deficits in executive function and attention have been associated with freezing of gait (FOG) in patients with Parkinson's disease (PD). However, the exact changes in the ventral and dorsal attentional networks that may contribute to FOG are unknown. Our aim was to examine the changes in connectivity of the attentional networks in patients with PD and their role in FOG.
Methods: Resting-state fMRI was obtained in 20 healthy controls (age: 69.7 ± 1.3yrs), 11 patients without FOG (age: 74.1 ± 1.2yrs), and 26 patients with FOG (age: 72.3 ± 1.3yrs). Graph theory analysis was used to examine differences in previously defined attention networks between groups.
Results: We found differences between the groups in the dorsal attentional network (Global Efficiency: $p = 0.007$, Local Efficiency: $p = 0.017$, Between Centrality: $p = 0.010$). Global efficiency was lower in patients with FOG compared to healthy controls ($p = 0.003$) and patients without FOG ($p = 0.025$). Local efficiency was higher in patients with FOG compared to healthy controls ($p = 0.014$) but not compared to patients without FOG ($p = 0.109$). In contrast, no differences were found in the ventral attentional network between the groups (Global Efficiency: $p = 0.258$, Local Efficiency: $p = 0.114$, Between Centrality: $p = 0.130$).
Conclusions: Altered organization of the dorsal attention network in patients with FOG may explain the higher risk for FOG during complex walking situations. In contrast, the lack of changes in the ventral attention network may partially explain the effectiveness of external cues on gait in patients with PD. Our findings support the idea that attentional networks play an important role in FOG.

1. Introduction

Freezing of gait (FOG) is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk. It has been associated with falls and loss of independence and therefore is considered one of the most debilitating motor symptoms in patients with Parkinson's disease (PD) [1]. One explanation for the appearance of FOG is that the difficulty of patients with PD in automatically performing movements results in an increased reliance on attention to execute movements [2]. At the same time, cognitive deficits, mainly those associated with attention, have been reported in PD [3]. Therefore, some suggest that when patients with PD attempt to compensate for reduced movement automaticity by using attention, overloading of the cognitive system may lead to FOG [1]. As previously shown, complex walking situations such as dual tasking require higher levels of attention which may increase the risk for FOG [4,5]. In contrast, external cues that also increase attentional demands are commonly used to alleviate FOG [6].

Two main attentional networks are thought to contribute to movement execution: the dorsal and ventral attentional networks [7]. Their role in FOG has not yet been carefully examined. The dorsal attentional network putatively mediates the top-down guided voluntary allocation of attention to specific tasks and as such has been related to the executive processes of movement. It comprises of the intra-parietal sulcus

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and the frontal eye fields of each hemisphere. Both intra-parietal sulcus and frontal eye fields maintain spatial priority maps for covert spatial attention, saccade planning, and visual working memory [8]. The ventral attentional network is presumably involved in detecting unattended or unexpected stimuli and triggering shifts of attention. It encompasses the temporo-parietal junction and the ventral frontal cortex [7].

Resting state fMRI (rsfMRI) has been used to show that during rest, the cerebral cortex enters into a mode of ultra-slow fluctuations organized in clear and consistent networks [9]. Specifically, sets of cortical regions tend to demonstrate correlated modulations of activity that occur as consistent patterns, reflecting the tendency of these networks to co-activate during task performance [10]. However, in contrast to task-related fMRI, rsfMRI substantially reduces the potential influences of compliance and task performance. Studies have shown that the dorsal and ventral networks have distinct correlation patterns [11]. A quantitative meta-analysis that included 28 rsfMRI studies in PD patients revealed consistent evidence of changes in intra-parietal sulcus and temporo-parietal junction connectivity, brain areas that are both part of the attentional networks [9]. While FOG has been attributed to exaggerated deficits in automaticity and attention, changes in functional connectivity of the attentional networks in PD with and without FOG have not yet been examined.

Graph theory provides a theoretical framework in which the topology of complex networks can be examined. A graph (network) consists of a set of nodes and a set of connections between these nodes that can be characterized by measures of local organization, global organization, and centrality [12]. The local organization of a network is assessed by a clustering coefficient in which higher clustering is associated with the robustness of a network that is resilient against random network damage. Global organization is defined by the average shortest path length between nodes and it is associated with global efficiency. Centrality is a measure that refers to the relative importance of a node within the network. As such, graph theory allows us to quantify network properties in health and disease at different levels [12].

Brain networks in humans are organized according to a highly efficient topology that combines a high level of local organization with a high level of global efficiency; this type of organization is considered a small-world organization [12]. Several studies have demonstrated that the overall functional network organization in PD is disrupted when compared to healthy controls [13]. Moreover, changes in global and local network efficiency were related to PD motor subtypes [14] and it was shown that levodopa tends to normalize the disrupted network topology [15]. However, these network properties have not been tested specifically in patients with and without FOG.

Therefore, we sought to better understand the contradicting effects of increased attention on FOG. To address this aim, we used rsfMRI and graph theory to examine alterations in the dorsal and ventral attention networks in PD patients with and without FOG. We hypothesized that local efficiency and global efficiency would be altered in patients with FOG compared to patients without FOG and compared to healthy controls.

2. Methods

2.1. Participants

This study was a sub-study of the V-TIME project [16]. The sub-study included patients with PD and healthy controls from the Tel-Aviv Medical Center in Israel. Thirty-seven subjects with PD and 20 healthy controls participated. Inclusion criteria were (1) idiopathic PD, (2) 60–90 years old, (3) Hoehn and Yahr stage II-III, (4) able to walk at least 5 min unassisted, and (5) taking anti-Parkinsonian medication. Participants were excluded if they had: contra-indications for MRI testing, psychiatric co-morbidity, clinically significant cognitive impairment (Mini Mental State Exam < 24), a history of a neurological disorder other than PD, orthopedic problems or unstable medical condition [16]. The study was approved by the local ethical committee at Tel-Aviv Medical Center and was performed according to the principles of the Declaration of Helsinki.

2.2. Cognitive and motor tests

The Montreal cognitive assessment (MOCA) and Color Trails Test were used for the assessment of cognitive function. The Unified PD Rating Scale (UPDRS) was used to assess disease severity. Patients also completed the new FOG Questionnaire (NFOG-Q) to evaluate the appearance and severity of FOG. Patients were categorized with FOG (n = 26) if they scored 1 on item 1 of the NFOG-Q or without FOG (n = 11) if they scored 0 on this item [17].

2.3. Image acquisition

Imaging was performed on a GE 3T Signa HDxt scanner (GE Signa EXCITE, Milwaukee, WI) with a resonant gradient echoplanar imaging system, using a standard 8-channel head coil. Each subject received an anatomical scan (spoiled gradient echo sequence: field of view 250 × 250 mm; matrix size 256 × 256 mm; voxel size 0.98 × 0.98 mm; repetition time = 59 ms; echo time = 3.6 ms) and 266 functional scans (single-shot gradient echoplanar imaging sequence: echo time/repetition time = 35/1,680 ms; 30 axial slices; voxel size = 3.1 × 3.1 × 3.5 mm; no gap; scanning time was approximately 7.5 min; 266 images). During scanning, all subjects were asked to keep their eyes open and to avoid repetitive thoughts.

2.4. Image processing and first level analysis

Data were preprocessed and analyzed using CONN functional connectivity toolbox version 17.f [18]. Images were spatially realigned, slice-time corrected, normalized to Montreal Neurological Institute (MNI) space using unified segmentation, and smoothed with an isotropic 8-mm full width at half maximum gaussian kernel. Several additional preprocessing steps were utilized to reduce spurious variance unlikely to reflect neuronal activity. These steps included: (1) a temporal band-pass filter (0.008 Hz < f < 0.09 Hz), (2) regression of six parameters obtained by rigid body head motion correction, (3) removal of confounding effects from the BOLD time series of white matter and CSF, each characterized by 5 dimensions, using the implemented aCompCor-strategy [19] in the CONN toolbox. The toolbox regresses out from the BOLD time series (for each ROI and for each voxel) all of these effects before computing the connectivity measures in the first level analysis. Seed-to-voxel connectivity maps were created for each subject and for each source ROI, and ROI-to-ROI connectivity matrices were computed for each subject and for each source ROI (connectivity values between the source ROI and every ROI that was defined). Bivariate correlation was used as a measure of 'total' functional connectivity between two areas in the first level analysis.

2.5. Graph construction

At the second level analysis graph theory was performed for the seed regions of the two main attentional networks, dorsal attention and ventral attention networks, using the CONN toolbox [18]. Nine ROIs for the dorsal-attention network and eleven ROIs for the ventral-attention network were drawn from a set of 264 ROIs that were defined through several meta-analyses of task fMRI data and with the functional connectivity mapping technique applied to Ref. [20]. All ROIs were modeled as 10 mm diameter spheres centered upon ROI coordinates. Three contrasts between the groups were tested, healthy controls vs. patients without FOG, healthy controls vs. patients with FOG, and patients without FOG vs. patients with FOG.

2.6. Graph theory measures

Standard graph-theory measures were used to compare the organization of the two attention networks across groups while controlling for age, gender, levodopa equivalent doses (LEDD), and disease duration, using the CONN functional connectivity toolbox. The connectivity threshold was defined based on the cost value of 0.15. The second level results were threshold using FDR corrected, $p < 0.05$. Formally, a graph is defined as a set of nodes that referred to specific regions of the brain connected by a set of edges [21]. The measures of interest were global efficiency, local efficiency, and betweenness-centrality, all measures of network topology related to theoretical information transfer within a network [22]. These measures are similar to other small-world measures in graph theory, but more directly related to information processing within a network [21,22]. These measures were investigated at the network-level and at the ROI-level in order to explore the ROIs that play major role within a specific network.

Global efficiency was defined as the average inverse shortest path length from one node to all other nodes in the network. The shortest path length is defined as the fewest number of connections between two nodes. Thus, a network with high global efficiency would be one in which nodes are highly integrated so the path length between nodes is consistently short. Global efficiency measures how integrated the entire network is; that is the efficiency of information transfer throughout the entire network. Local efficiency is defined as the average global efficiency within a local sub-network consisting only of the neighbors of a given index node. It can be understood as a measure of the fault tolerance of the network, indicating how well each subgraph exchanges information when the index node is eliminated. Betweenness-centrality is a measure of accessibility that is the number of times a node is crossed by shortest paths in the graph. As such, nodes with the largest betweenness-centrality can be identified as 'hubs' in the network [23].

2.7. Statistics

Means and standard errors were calculated for all dependent variables. Differences in participant characteristics and graph theory measures (e.g., global efficiency) between the three groups were analyzed using One-way ANOVA. The graph theory measurements were extracted from the CONN analysis after controlling for age, gender, LEDD, and disease duration. Post hoc test p-values were Bonferroni corrected for multiple comparisons. The association between graph theory measures and FOG severity, estimated by the NFOG-Q, was explored using Pearson correlation coefficients. Statistical significance was assumed when the p-value was less than or equal to 0.05. Statistical analysis was performed using SPSS for Windows version 22.

3. Results

3.1. Participant characteristics

Participant characteristics are presented in Table 1. Groups were similar in age, gender, and education. Patients with PD had significantly lower scores on the MOCA ($F = 14.0$, $p < 0.001$) compared to healthy controls. As expected, patients with FOG had longer disease duration, higher LEDD, and worse motor symptoms than patients without FOG.

3.2. Changes in dorsal and ventral attentional networks

Groups were similar in all graph theory measurements of the ventral attentional network (Global Efficiency: $F_{(2,49)} = 1.39$, $p = 0.258$, Local Efficiency: $F_{(2,49)} = 2.27$, $p = 0.114$, Between Centrality: $F_{(2,49)} = 2.13$, $p = 0.130$). In contrast, significant differences between the groups were observed in the dorsal attentional network (Global Efficiency: $F_{(2,49)} = 5.45$, $p = 0.007$, Local Efficiency: $F_{(2,49)} = 4.41$, $p = 0.017$, Between Centrality: $F_{(2,49)} = 5.01$, $p = 0.010$) (Fig. 1). Global efficiency was lower in patients with freezing of gait compared to healthy controls ($p = 0.003$) and compared to patients without FOG ($p = 0.025$). At the ROI-level, the healthy controls showed higher global efficiency than patients without FOG in three nodes: (1) left middle frontal gyrus (MFG) (FDRcorr $p = 0.012$), (2) left middle temporal gyrus (MTG) (FDRcorr $p = 0.003$), and (3) right MTG (FDRcorr $p = 0.006$). Patients without FOG presented higher global efficiency than healthy controls in the right superior parietal lobe (SPL) (FDRcorr $p = 0.031$) (Fig. 2A). In addition, healthy controls demonstrated higher global efficiency than patients with FOG in left and right MFG (FDRcorr $p < 0.005$) and left and right MTG (FDRcorr $p = 0.026$), while patients with FOG showed higher global efficiency in left and right SPL (FDRcorr $p < 0.040$) (Fig. 2A). Direct comparison between patients with and without FOG revealed higher global efficiency of the right middle frontal gyrus in patients without FOG (FDRcorr $p = 0.013$) (Fig. 2A).

Local efficiency was higher in patients with FOG compared to healthy controls ($p = 0.014$) but similar between patients with FOG and without FOG ($p = 0.109$). Higher local efficiency in patients with FOG was found in the right superior parietal lobe (FDRcorr $p = 0.036$) (Fig. 2B). Betweenness centrality was lower in patients with FOG, compared to healthy controls, ($p = 0.007$) but similar between patients with and without FOG ($p = 0.372$). Lower betweenness centrality in patients with FOG was observed in three nodes: (1) left middle frontal gyrus (FDRcorr $p = 0.010$), (2) right middle frontal gyrus (FDRcorr $p = 0.010$), and (3) left middle temporal gyrus (FDRcorr $p = 0.022$) (Fig. 2C).

3.3. Correlations between graph theory measures and FOG severity

The NFOG-Q score in the group of patients with FOG ranged

Table 1
Participant characteristics.

Domain	Healthy controls	FOG-	FOG+	Test statistics & df	p-values
Age (years)	69.6 ± 1.3	74.3 ± 2.3	73.9 ± 1.6	$F_{(2,49)} = 2.42$	0.099
Education (years)	14.5 ± 0.5	14.3 ± 1.6	14.4 ± 0.6	$F_{(2,49)} = 0.02$	0.984
MOCA	27.4 ± 0.5	21.9 ± 1.1*	23.0 ± 0.8*	$F_{(2,49)} = 13.99$	< 0.001
CTT-A (sec)	59.3 ± 5.0	126.7 ± 30.7*	100.9 ± 11.1*	$F_{(2,49)} = 5.61$	0.006
Gender (M/F)	10/10	7/4	15/11	$\chi^2_2 = 0.69$	0.405
Disease duration (years)	NA	4.1 ± 0.9	11.7 ± 1.2**	$F_{(2,49)} = 44.70$	< 0.001
UPDRS motor	NA	21.0 ± 3.6	33.58 ± 2.62**	$F_{(2,49)} = 55.50$	< 0.001
LEDD (mg)	NA	524 ± 93	1425 ± 256**	$F_{(2,49)} = 17.13$	< 0.001

FOG = Freezing of gait, MOCA = Montreal cognitive assessment, CTT = Color trail test, df = degrees of freedom, *significant differently from Healthy Controls, **significantly different from patients without FOG.

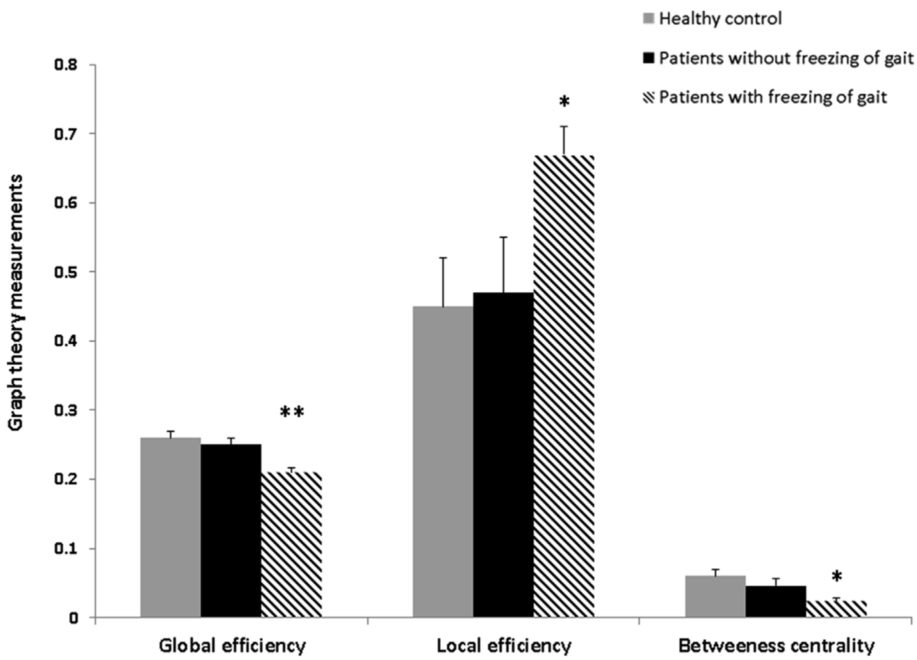

Fig. 1. Graph theory measures (covariate corrected) of the dorsal attention network in the three groups of participants. Patients with FOG showed significant lower global efficiency than patients without FOG and healthy controls and significantly higher local efficiency than healthy controls.
**significantly different from healthy controls and patients without FOG, *significantly different from healthy controls.

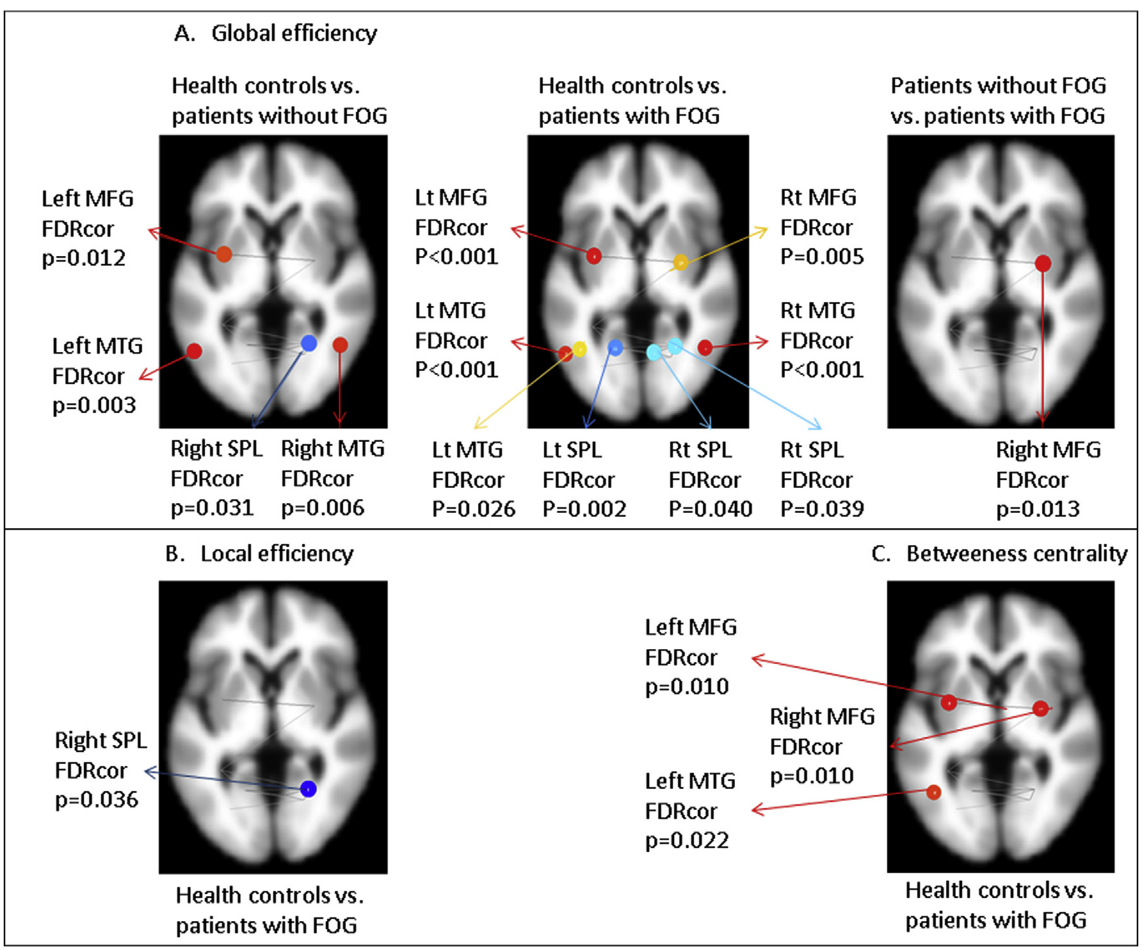

Fig. 2. Differences in the graph theory measures of the dorsal attention network at the ROI-level. (A) global efficiency between healthy controls and patients without FOG, healthy control and patients with FOG, and patients without FOG and patients with FOG, (B) local efficiency between healthy controls and patients with FOG, and (C) betweenness centrality between healthy controls and patients with FOG. The red and yellow circles represent positive differences (red greater differences than orange and yellow), whereas blue circles represent negative differences. The lines represent the functional connectivity with other ROIs within the network. MFG = Middle frontal gyrus, MTG = Middle temporal gyrus, SPL = superior parietal lobe. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

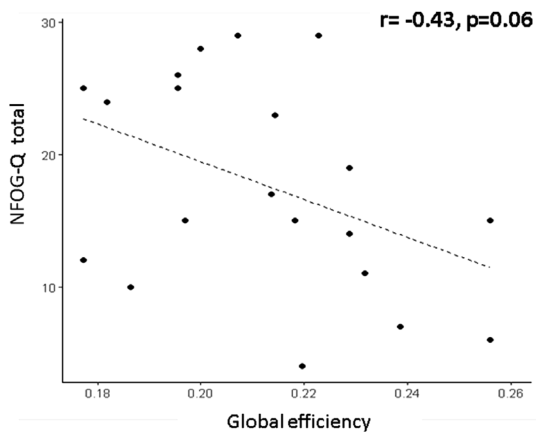

Fig. 3. Correlation between NFOG questionnaire score and global efficiency of dorsal attention network among patients with FOG.

between 4 and 29 (average 18 ± 1.7). A trend toward a significant correlation was found between NFOG-Q score and global efficiency of dorsal attention network ($r = -0.43$, $p = 0.06$) (Fig. 3). No correlation was found at the ROI-level and no correlations were observed between NFOG-Q and local efficiency or betweenness centrality.

4. Discussion

FOG has been associated with an increased reliance on cognitive resources to compensate for reduced automaticity. Our results show altered connectivity in the dorsal attention network and no differences in connectivity in the ventral attention network in patients with FOG. More specifically, patients with FOG showed lower global efficiency, higher local efficiency, and lower betweenness centrality of the dorsal attention network than the healthy controls. Patients with FOG also demonstrated lower global efficiency of the dorsal attention network compared with patients without FOG. No differences between healthy controls and patients without FOG were observed.

The dorsal attentional network mediates the top-down guided voluntary allocation of attention and plays an important role in the implementation of cognitive strategies required for gait [24]. The comparison between patients with and without FOG revealed lower global efficiency in patients with FOG, resulting from the right middle frontal gyrus. Accumulating findings propose that right-hemisphere circuitry seems to be more affected in patients with FOG [25]. Given the association between FOG and visuospatial abnormalities, we speculate that the right hemispheric lateralization could be related to the right hemispheric predominance of visuospatial skills shown in the brain. In addition, it has been suggested that the right middle frontal gyrus may be the seed that links the ventral and dorsal networks by acting as a “circuit-breaker”, interrupting ongoing processes in the dorsal network, and reorienting a person's attention to an external stimulus [25]. As such, changes in right middle frontal gyrus connectivity may indicate that occurrence of FOG may be attributed to impaired ability to switch from one attentional network to another during walking in every-day life situations. Altered middle frontal gyrus connectivity in patients with FOG is consistent with findings reported by Tessitore et al.; they showed reduced functional connectivity of the right middle frontal gyrus in patients with FOG compared to patients without FOG [25].

A large body of evidence demonstrates that external stimuli, such as visual or auditory cues, alleviate FOG in patients with PD [26]. External cues have been defined as external temporal or spatial stimuli which facilitate the initiation and continuation of repetitive sequential movements such as gait [26]. Several explanations have been put forward to explain the effectiveness of external cues: (1) external information in the form of cues activates cortical, parieto-premotor pathways that bypass the basal ganglia allowing temporary access to motor programs governing movements, (2) external cues may decrease the need to internally plan and prepare movements, reducing cognitive load, and (3) cues may act to focus attention during the performance of more complex tasks and thus aid in gait [27]. However, the underlining neural mechanisms to support these explanations are missing. It has been proposed that bottom-up external sensory-driven attention is elicited via the ventral dorsal attention network [7,11]. Given the role of the ventral attention network in detecting unattended or unexpected stimuli and triggering shifts of attention, one can speculate that the ventral attention network plays a role when external cues are presented. As such, the reduced involvement of the ventral attention network observed in our study may provide possible explanation for the effectiveness of external cue in patients with PD.

Three graph theory measurements were assessed to reflect the robustness and vulnerability of the two attentional networks [22]. Global and local efficiency are measures of the network performance based on the structure of the network by the connections of the network. Global efficiency measures the ability of a network to transmit information at the global level, whereas local efficiency represents this at the local level [22]. Interestingly, our findings demonstrate that the global and local efficiency of the dorsal attention network changed in the opposite directions with FOG. Global efficiency decreased with FOG, while local efficiency increased with FOG. Decreased global efficiency indicates a reduced capacity of information transfer across the entire network and therefore may explain higher efficiency in older adults. This finding is in line with several studies reporting decreased global efficiency in the entire brain in early and mid-stage PD patients [28,29]. In contrast, the increased local efficiency in patients with FOG compared to healthy controls indicates a possible compensatory reorganization in the local dorsal attention network. These changes in graph theory measures suggest that the dorsal attention network is transformed from a small world organization characterized by high local and high global efficiency to regular organization characterized by low global and high local efficiency.

The main limitations of this study are that it was focused on two attentional networks during resting state while it is most likely that changes in other networks such as the visual network may also occurred. In addition, the only significant correlation with clinical measures was between scores on the NFOG-Q and the global efficiency of the dorsal attention network.

In summary, our findings support the hypothesis that attentional dysfunction, mainly associated with the topology of the dorsal attention network during resting state, may contribute to the mechanisms related to FOG in patients with PD. Our findings show that disparate involvement of the two main attentional networks may be a component of the neural mechanism in the occurrence of FOG. Moreover, we speculate that these differences may explain the effectiveness of external cues. To further elucidate the role of attentional networks in the pathogenesis of FOG and better understand the role of the ventral attentional network during cueing, future studies should examine functional connectivity during the performance of specific attentional tasks that relate to top-down and bottom-up processes. In addition, changes in the relationship with other neural networks, such as the default mode network and visual network should be explored. Moreover, alterations in the attentional networks have been attributed to hallucinations [30]. Therefore, future studies should examine possible association between these changes in the attentional networks and hallucinations.

Authors' roles

I.M., N.G., J.M.H., and A.M. were responsible for the conception, study design, review, and critique. I.M. and Y.J. were responsible for execution and analysis of data. I.M. was responsible for the drafting of the manuscript and figures.

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