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Keywords: Parkinson's disease (PD), freezing of gait (FoG), electroencephalography (EEG), functional connectivity, Attention Network Test (ANT), executive control.

Abstract

Objective

To explore changes over time in the network specificities underpinning a visual attentional task in patients with Parkinson's disease and freezing of gait (the PD+FoG group), patients with Parkinson's disease but no FoG (PD-FoG), and healthy controls (HCs).

Methods

High-resolution electroencephalography (EEG) data were acquired for 15 PD+FoG patients, 14 PD-FoG patients, and 18 HCs performing the Attention Network Test. After source localization, functional connectivity was assessed and compared by applying the dynamic phase-locking value method.

Results

The PD+FoG patients showed an impairment in executive control. Furthermore, the PD+FoG patients showed abnormally high theta band connectivity (relative to HCs, and 400 to 600 ms after target presentation) in a network connecting the orbitofrontal and occipitotemporal regions.

Conclusions

In PD+FoG, the greater functional connectivity between the visual network and the regions to which executive function has been attributed might indicate greater reliance on environmental features when seeking to overcome the impairment in executive control.

Significance

FoG in PD involves cognitive, attentional and executive dysfunctions. Our observation of abnormally high connectivity in PD+FoG patients argues in favor of the interference model of FoG.

Highlights

- High-resolution electroencephalography was used to explore changes over time of the networks underpinning a visual attention task in patients with Parkinson's disease and freezing of gait.
- During the visual attention task, patients with Parkinson's disease and freezing of gait showed impairments in executive control.
- The elevated theta band connectivity observed in patients with Parkinson's disease and freezing of gait during the attentional task argues in favor of the interference model.

1. Introduction

1.1. Freezing of Gait: Clinical Features and Physiopathological Models

Freezing of gait (FoG) is a frequent, disabling symptom of Parkinson's disease (PD). FoG is defined as "a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk" (Giladi and Nieuwboer, 2008, Nutt et al, 2011). The phenomenon is related to the disease duration (with a prevalence ranging from 50-80% in late-stage PD) but can sometimes present at earlier stages (Amboni et al., 2015; Forsaa et al., 2015; Perez-Lloret et al., 2014). FoG can lead to falls and loss of autonomy (Espay et al., 2012; Fietzek et al., 2013; Giladi and Nieuwboer, 2008). Given that the clinical response of FoG to levodopa is variable, there is an urgent need for other treatment options (Espay et al., 2012; Fietzek et al., 2013; Nonnekes et al., 2015; Smulders et al., 2016). One can hypothesize that the development of new treatments for FoG will be facilitated by a better understanding of the underlying mechanism and the application of pathophysiological models like the interference model and the cognitive model. The interference model was developed by Lewis and Barker on the basis of "cross-talk" phenomena (Lewis and Barker, 2009). The small neural reserve in patients with PD with FoG (PD+FoG) is sufficient for limited tasks but jams the system in more complex situations (such as dual tasks) during which motor, cognitive and limbic networks compete; this causes sudden motor inhibition and FoG (Lewis and Barker, 2009). The cognitive burden of dual tasks involving gait can also be evidenced in healthy people because it prompts one task to be prioritized over the other and this causes the participants to underperform (Bayot et al. 2018). For both healthy people and PD patients, most activities of daily living are dual tasks. However, the cost of dual tasks is greater for PD+FoG patients - especially in the "off-drug" state (Bekkers et al., 2018, Matar et al. 2019). Although executive function and attention are the most frequently altered cognitive domains in PD (regardless of whether or not FoG is present) (Dujardin et al., 2015; Muslimovic et al., 2005), it was shown that PD+FoG patients perform worse for specific cognitive variables (e.g. flexibility). The cognitive model therefore completes the interference model of PD+FoG by adding the concept of a failure in cognitive control. In contrast, PD patients who do not experience FoG (henceforth "PD-FoG patients") compensate for their loss automaticity by exerting stronger cognitive control (Vandenbossche et al., 2012). The cognitive model is based on the lower neuropsychological scores observed in PD+FoG patients with regard to executive functions, set-shifting, and executive control (Amboni et al., 2008; Naismith et al., 2010; Stefanova et al., 2014), although these impairments might also be related to the disease duration (Morris et al., 2020). Executive control can be explored by performing a validated attentional task, such as the Attention Network Test (ANT) (Fan et al., 2009, 2002). The ANT tests the three components of the attentional model developed by Posner and Petersen (Posner and Petersen, 1990). We will from now on refer to this model in order to study executive control in PD+FoG patients in both the "off-drug" and "'on-drug" states (Vandenbossche et al., 2011).

1.2. Connectivity Failure in PD-FoG Patients

Studies of functional connectivity (measured with functional MRI (fMRI), magnetoencephalography (MEG), or high-resolution electroencephalography (HR-EEG)) allow researchers to explore the brain's functional networks. Most connectivity studies of PD patients have focused on motor networks (Bharti et al., 2019). However, Tessitore et al.'s fMRI study showed that resting-state connectivity between the visual network and the dorsal attention network was abnormally low in PD+FoG patients – suggesting the failure of a compensatory mechanism involving visual attention (Tessitore

et al., 2012). Furthermore, a fMRI study of connectivity during a walking simulation in PD+FoG patients highlighted the presence of specific network patterns associated with FoG severity and compensating situations. The severity of freezing was linked to the dorsal attention network, which connected limbic network nodes instead of cerebellar nodes in a compensatory walking situation; these findings leant support to the cross-talk hypothesis mentioned above (Ehgoetz Martens et al., 2018). Indeed, these findings were replicated by Shine et al., who showed that FoG severity was correlated with greater frontoparietal activation during the episode (Shine et al. 2013b). An fMRI study also evidenced mediofrontal cortical overactivation in PD+FoG patients during dual-task paradigms (Shine et al. 2013a). There are few published MEG- or EEG-based connectivity studies, and very few of these looked at PD patients. Some researchers have used EEG to detect the occurrence of freezing (Handojoseno et al., 2012, Handojoseno et al., 2013) or to highlight an abnormal EEG pattern with increased frontocentral theta-band coupling during freezing episodes (Shine et al., 2014). During execution of the ANT by PD patients, greater activation of the dorsal attention network is associated with an executive control effect; this might reflect the need for more attentional resources in PD (relative to healthy controls (HCs)) for a given task (Boord et al., 2017). To the best of our knowledge, however, there are no published EEG/MEG data on the nature of abnormalities in functional connectivity in PD+FoG patients performing an attentional task.

1.3. Objective

The objective of the present study was to determine whether functional connectivity in PD+FoG patients is impaired during a visual attentional task, relative to PD-FoG patients and healthy controls (HCs). We focused on executive control by using the ANT, the performance of which is specifically impaired in PD+FoG patients. Hence, we expected to observe impairments in the executive and attention networks in PD+FoG patients, relative to the two other study groups.

2. Methods

2.1. Population

We included a total of 47 adults (aged 18 or over): PD+FoG patients (n=15), PD-FoG patients (n=15), and HCs (n=18), all of whom provided their written, informed consent to participation. All the PD patients were being followed up in the Department of Neurology at Lille University Medical Center (Lille, France). People with a neurological disease (other than PD, for patients) were excluded. Furthermore, people with a Montreal Cognitive Assessment (MoCA) score below 24 (Nasreddine et al., 2005), those taking benzodiazepines or neuroleptics, and those with an uncorrected visual impairment were also excluded. The study was approved by the local institutional review board (*CPP Nord-Ouest*, Lille, France; reference: 2015-A00013-46). The following data were recorded for all participants: age, sex, current medication, medical history, and MoCA score. For patients with PD, we also recorded the following data (in the “on-drug” state, for motor scores): the levodopa equivalent daily dose (LEDD) (Tomlinson et al., 2010), the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) (Movement Disorder Society Task Force for Rating Scales for Parkinson’s Disease, 2003, Goetz et al., 2008) score (especially part III, for motor severity), the Hoehn and Yahr scale score (Goetz et al., 2004), the disease duration, and Freezing of Gait Questionnaire (FoG-Q) (Giladi et al., 2009, 2001) score for FoG severity. PD patients were classified as PD+FoG or PD-FoG on the basis of medical reports from the attending physicians (all experts in movement disorders), the third item of the FoG-Q, and the results of a freezing trajectory with half-turns

(Snijders et al., 2012). We also computed the axial subscore (the sum of several items from the MDS-UPDRS part III: speech, facial expression, neck rigidity, arising from a chair, gait, postural stability, and posture (Moreau et al., 2013)) and identified fallers on the basis of a UPDRS item 2.13 (falling unrelated to freezing) ≥1 or a UPDRS item 2.14 (freezing when walking) ≥3. Moreover, certain cognitive abilities were assessed in the PD patients: visuospatial functions via the Benton Judgement of Line Orientation Test (BJLOT) (Benton et al., 1978; Gullett et al., 2013), processing speed via the Symbol Digit Modalities Test (SDMT) (Smith, 1982, 1973), inhibitory control via the inhibition trial in the Color-Word Interference Test (CWIT) from the Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001; Stroop, 1935), and flexibility via the switching trial in the D-KEFS CWIT (Delis et al., 2001). The results of the cognitive tests were expressed as z-scores, in order to take into account differences in age and educational level (abnormal z-score: <-1.5). Lastly, the patients' limbic parameters were characterized: anxiety via the Parkinson Anxiety Scale (PAS; lower threshold: 14) (Leentjens et al., 2014), apathy via the Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006) if available (lower threshold: -21) or if not via the UPDRS item 1.4 (score ≥ 1), and depression via the Hamilton Depression Rating Scale (HAM-D; lower threshold: 11) (Hamilton, 1960) or the UPDRS item 1.3 (score ≥ 1). The two patient groups were matched for age, sex, global cognitive decline (according to the MoCA) and motor severity (according to the MDS-UPDRS-III). The patients were also matched for age and sex with the HC group.

2.2. Task

Participants performed a modified version of the ANT in the seated position (Figure 1). They looked at a computer screen and answered via a keyboard. Participants were asked to indicate the direction of a target (i.e., a central arrow pointing either left or right on the screen) as quickly as possible and without making mistakes by pressing the "A" key on the keyboard for a left-pointing arrow or the "P" key for a right-pointing arrow. Each target was flanked with distractor arrows (i.e. flankers). The flankers pointed in the same direction as the target in the congruent (C) condition or in the opposite direction in the incongruent (I) condition (for a more detailed paradigm, see (Braquet et al., 2020)). The present study focused on executive control, and so only C and I conditions were compared; the difference between the median reaction time (RT) in each condition is a marker of the effect of executive control (Fan et al., 2002). In fact, executive control is an attentional component responsible for inhibitory control, conflict resolution, and error detection. All patients were in the "on-drug" state during the experimental session.

For each trial, the RT (in ms) and response accuracy were recorded. The 20 first trials (giving over 300 trials in total) served as training trials and were excluded from the analyses. Trials with an RT below 100 ms were considered to be anticipated starts and so were rejected. Trials with erroneous responses were also excluded. The median RT and error rate were assessed in each target condition for each participant. The differences in RT and response accuracy between target conditions were then analyzed.

2.3. Recording and Preprocessing

High-resolution (128-electrode) scalp EEG data (Waveguard, ANT Neuro) were acquired for all participants during the ANT. The electrodes were positioned according to the 10-05 system, and the EEG signal was recorded with ASA software (ANT Neuro), a sampling frequency of 512 Hz, and impedances below 20 kΩ. Preprocessing was performed with the EEGLAB toolbox in MATLAB (Delorme and Makeig, 2004). The signal was down-sampled at 256 Hz, and filters were applied to set

the bandwidth to [0.5-100 Hz]. A 50 Hz notch filter was used to remove line noise. Flat signal electrodes and aberrant signal electrodes were semi-automatically removed and then spherically interpolated; trials requiring the interpolation of more than 10% of the electrodes were rejected. Transient, large-amplitude artefacts were removed using the artifact subspace reconstruction method (Chang et al., 2018; Mullen et al., 2015). An average reference was applied. Stationary artefacts were removed using an independent component analysis and the Infomax algorithm (Delorme et al., 2012)), followed by the semi-automatic rejection of components with artefacts via the ICLabel toolbox (a highly-trained component classifier (Pion-Tonachini et al., 2019)). The final manual screen targeted non-neurologic signal sources (such as muscle, eye and heart movements). Trials with more than 20 artefacts were rejected. The remaining signal was segmented into target-locked epochs (one per ANT trial) starting 1500 ms before the target's appearance and ending 1700 ms afterwards. All epochs were classified as C or I target conditions. Lastly, each epoch was inspected visually, and those with any remaining artefacts were rejected manually.

2.4. Source Localization and Functional Connectivity

Epochs were used as inputs for the source localization step, using the Brainstorm toolbox in MATLAB (Tadel et al., 2011). The inverse problem was resolved by using the boundary element method (Gramfort et al., 2011; Kybic et al., 2005) for head modelling, applying weighted minimal norm estimation (Baillet et al., 2001; Hämäläinen and Ilmoniemi, 1994), and then projecting the source signal onto the 68 regions of interest (ROIs) from the Desikan-Killiany atlas (Desikan et al., 2006).

Functional connectivity matrices in three frequency bands (theta (4-8 Hz), alpha (8-12 Hz) and beta (12-30 Hz)) were built for each condition and each participant. The dynamic phase locking value method was used (Lachaux et al., 1999) to measure phase relationships between oscillatory signals, such as EEG signals. In the present case, dynamic phase locking enabled us to determine functional connectivity between ROIs; the resulting three-dimensional matrix give a connectivity value for each pair of ROIs at every time point. For visualization, a threshold was applied to the matrices using the efficacy cost optimization (ECO) method - a more physiological approach to thresholding than a simple cut-off (Fallani et al., 2017). Thereafter, matrices were averaged over 100 ms intervals, giving six 100 ms time-interval matrices from 0 ms (target appearance) to 600 ms (the median RT in HCs). The interval matrices were averaged by group within each condition (C and I) and shown as graphs via the EEGNET toolbox in MATLAB (Hassan et al., 2015).

2.5. Statistical Analyses

The groups were compared with regard to demographic and clinical variables and ANT scores. All statistical tests were performed with SPSS software (version 16.0). The normality and homoscedasticity of residuals were assessed visually and by means of the Shapiro-Wilk and Levene tests. Qualitative variables were compared in a chi-squared test. Quantitative variables with a normal distribution and homoscedasticity of residuals were compared in (i) a one-way analysis of variance (ANOVA), with group as a between-subjects factor, and (ii) either a Student's t-test or a non-parametric Mann-Whitney U test in PD patients. In order to evaluate executive control in the ANT, the median RTs were compared in a repeated-measures 2x3 ANOVA, with the group as the between-subjects factor and the target condition as the within-subject factor. Bonferroni's correction was applied for post-hoc analyses.

Functional connectivity matrices were compared using the Network Based Statistic Toolbox (NBST), a MATLAB toolbox developed specifically for network comparisons (Zalesky et al., 2010). Raw matrices (without any thresholding) were used, after having been averaged within 100-ms intervals between 0 ms and 600 ms, and assessed by group within each target condition. The NBST minimizes the family-wise error rate when comparing all connections in a graph, which results in multiple comparisons. In a first step, all the connections (connectivity values) were compared in a test with a manually chosen threshold for its statistic. This yielded a set of above-threshold links, which were then organized into identified graph structures called components. Here, we set the first statistical threshold to $p<0.001$. In a second step, the components were compared by group and by target condition, using an ANOVA with permutation testing. The threshold for statistical significance was set to $p<0.05$. Again, Bonferroni's correction was applied for post-hoc analyses.

Lastly, for networks that were differently connected in PD+FoG patients vs. PD-FoG patients or HCs, we calculated Pearson's or Spearman's coefficient for the correlations between the functional connectivity measure at each edge and the clinical data (disease duration, LEDD, cognitive and motor scores, and neuropsychiatric symptoms), depending whether the assumption of bivariate normality was met or not.

3. Results

3.1. Population

Participants from all three groups were matched for age, sex, and overall cognitive performance. The PD+FoG and PD-FoG groups did not significantly differ in terms of disease duration, LEDD, and disease severity (motor functions, visuospatial functions, processing speed, inhibition control in the D-KEFS CWIT, flexibility, and neuropsychiatric symptoms) (Table 1). However, the proportion of patients with falls was higher in the PD+FoG group than in the PD-FoG group.

3.2. The Executive Control Effect

The mean ± standard deviation (SD) RT during the ANT (Table 1) was significantly longer in PD+FoG patients than in HCs (C: 620 ± 55 vs. 5623 ± 65 ms, respectively; I: 685 ± 85 vs. 601 ± 64 ms, respectively; $p=0.011$) (Figure 2). The PD+FoG patients had worse executive control than PD-FoG patients and HCs (65 ± 43, 41 ± 21, and 38 ± 16, respectively; $p=0.023$). Relative to HCs, PD patients showed a significantly greater decrease in response accuracy when confronted with I targets ($p=0.01$).

3.3. Network Dynamics during the Visual Attentional Task

In a visual inspection, the theta-band network dynamics were clearly apparent for HCs, with a reinforcement of posterior connections at 100-200 ms and an even greater reinforcement of anterior connections after 400 ms. In the PD groups, the network dynamics in the theta band were much less clear (Figure 3). Network dynamics in the alpha and beta bands were not apparent in any of the groups.

3.4. Comparisons of Network Dynamics

Functional connectivity matrices were compared by group and by target condition. In the theta band, the NBST revealed a between-group difference during the 300-400 ms interval in a frontotemporal network ($p=0.019$). Post-hoc analysis revealed that connectivity was greater in the PD-FoG patients

than in HCs (5 connections, p=0.03 after correction). In the 400-500 ms interval, a between-group difference was also observed in a left frontotemporo-occipital network (p=0.013). Post-hoc analysis revealed that connectivity was greater in the PD+FoG group than in HCs (4 connections, p=0.033 after correction). In the 500-600 ms interval, a between-group difference was found in a large network with left predominance (p=0.006). Post-hoc analysis revealed that connectivity was greater for PD+FoG patients than for HCs in two distinct networks: a ventral frontotemporo-occipital network (5 connections, p=0.016 after correction) and an interhemispheric parietotemporo-frontal network (5 connections, p=0.016 after correction). The significant network differences in the 400-500 ms interval and the frontotemporo-occipital network difference in the 500-600 ms interval had similar patterns, i.e. greater connectivity for PD+FoG patients than for HCs (Figure 4).

In the alpha band, we observed a between-group difference during the 300-400 ms interval only in an interhemispheric parieto-frontal and parieto-temporal network (7 connections, p=0.023). Post-hoc analysis revealed that connectivity in this network was greater in PD-FoG patients than in HCs (7 connections, p=0.012 after correction). In the beta band, there were no significant intergroup differences. There were no differences between target conditions in any of the three frequency bands, and no group-target condition interactions were observed. There were no significant differences in alpha, beta or theta functional connectivity between PD+FoG and PD-FoG patients.

3.5. Clinical Correlations

In the 400-500 ms and 500-600 ms intervals, the strength of the theta band connectivity between the right cuneus and the banks of the left superior temporal sulcus was significantly correlated with the MoCA score in the PD+FoG group (400-500 ms: r = 0.57, p=0.027; 500-600 ms: r = 0.541, p=0.037). Although none of the other correlations achieved statistical significance, we observed a non-significant trend for the relationship between greater theta band connectivity and worst executive control.

4. Discussion

We found differences in network organization between PD+FoG patients and HCs during a visual attentional task that require executive control. Unexpectedly, we did not observe such differences between PD+FoG and PD-FoG patients. The networks involved in this visual attentional task in PD+FoG patients differed from those observed in PD-FoG patients and HCs. This finding suggest the existence of specific features in PD+FoG that were not different of PD-FoG because the sample size was too low. The greater theta band connectivity during an attentional task in PD+FoG patients argues in favor of the interference model and might explain the patients' dependency on external visual information. Indeed, the ANT task involved first just after target presentation networks in the theta band involving nodes in posterior regions and during decision making, at round 400-600 ms after target presentation, networks implying nodes in the frontal lobes in all participants whatever the condition. We observed differences between the PD+FoG group and the other groups. With regard to behavioral parameters, PD+FoG showed impairments in executive control during the ANT visual attention task. This finding is in line with the literature data (Vandenbossche et al., 2011). The cortical network was similar in PD+FoG and PD-FoG patients, although PD+FoG patients showed an increase (relative to matched HCs) in theta band functional connectivity within the frontotemporal-occipital networks, with left predominance. The differences appeared quite late (after 400 ms) in the time interval between target presentation and the motor response. The network with increased

functional connectivity in PD+FoG patients at 400-500 ms and 500-600 ms included a number of ROIs involved in visual and attentional networks.

Comparisons between our present results and the literature data are problematic. fMRI studies have provided information about the various networks' functions. The network that differed when comparing PD+FoG patients and HCs included the cuneus and inferior temporal regions (such as the fusiform area) that are part of the visual network. The cuneus is involved in processing visual information in general and during a visual attention task (like that presented by Yang et al. (Yang et al., 2015) in particular. The above-mentioned inferior temporal regions (the fusiform and middle temporal gyri) have been associated with the ventral visual pathway - also referred to as the "what" pathway - involved in the identification of the shape and nature of visual information (Kravitz et al., 2013). An abnormally high level of connectivity within this pathway during a visual attention task might reflect the operation of a mechanism for overcoming interpretation difficulties in PD+FoG patients. Interestingly, these visual nodes are known to be connected to the orbitofrontal cortex (Bettcher et al., 2016; Wallis, 2007). The orbitofrontal cortex is a key region in executive functions, behavior, and decision-making. Abnormally high connectivity between this node and the visual network at the very end of the cognitive process (i.e. just before the motor response) in PD+FoG patients might reflect an attempt to compensate for changes in the decision-making process during a visual attention task. In contrast, Fan et al.'s fMRI study described a different network related to the executive control component of ANT (Fan et al., 2005). The network involved fusiform, anterior cingulate, posterior cingulate, left lateral temporal and left lateral frontal regions (Fan et al., 2005). The network that discriminated between PD+FoG patients and HCs in the present study contained the fusiform regions. This results suggest that the dysfunction in executive control in PD+FoG might generate a compensatory mechanism that is strongly connected to the visual network. Indeed, PD patients use environmental cues to facilitate their mobility in everyday life, namely when the situation contains conflicting information. Patients with PD+FoG are known to rely on visual information more heavily than healthy people do (Huh et al., 2016). Environmental cueing is an effective way of improving gait in PD patients and is now part of many rehabilitation programs (Delval et al., 2014; Nieuwboer et al., 2007). Greater dependence on the environment might explain the improvement of gait by cueing and also its worsening during a dual task (Yogev et al., 2005). Greater connectivity between nodes in the executive control network or the executive function cortex with a network that processes environmental information (the visual network, in the present study) might reflect a greater dependence on the environment in PD+FoG patients for a given task.

The above-mentioned hypotheses have some weaknesses, nevertheless. Some nodes involved in the network that discriminated between PD+FoG patients and HCs in the present study have also been found in attention networks by fMRI studies. The orbitofrontal node and the node corresponding to the banks of the superior temporal sulcus node in the discriminant network can also stand for the ventral frontal region and the temporoparietal junction found in the ventral attention network (also referred to as the "bottom-up" attention network) (Corbetta and Shulman, 2002; Fox et al., 2006; Vossel et al., 2014). One can hypothesize that stronger connections between the stimulus-driven attention network and the visual network in PD+FoG patients reflect greater attentional demands during a visual attention task. However, the attentional task should mostly involve the dorsal ("top-down") attention network as long as the task is goal-driven (following instructions) and not stimulus-driven. The activation of the ventral network during the ANT task in PD+FoG patients appears to be a compensatory mechanism for task performance. The ventral attention network is usually described

as being located mainly in the right hemisphere, whereas the discriminant network in the present study was located mainly in the left hemisphere. The right temporoparietal junction is believed to have an important role in detecting "mismatch" between pre-established models and the processed environmental stimuli. Conversely, the left temporoparietal junction is also consistently involved regardless of the presence of mismatches or matches between models and stimuli (DiQuattro and Geng, 2011; Doricchi et al., 2010).

Limitations: Firstly, we measured functional connectivity in PD patients in the "on-drug" state. The literature data suggest that levodopa can induce changes in connectivity and can partly reverse abnormalities in resting-state connectivity (Schneider and Alcalay, 2020). It must be borne in mind that the networks described here are abnormal features that persist after treatment with levodopa, rather that strictly physiological abnormalities. Some pathological changes might have been underestimated, which could explain why we did not observe a difference between PD+FoG and PD-FoG patients. However, the ANT requires a motor response and could not be performed in the "off-drug" state. To minimize this bias, PD+FoG and PD-FoG patients were matched for LEDD. Secondly, EEG provides low spatial resolution; even after source localization, the nodes' location remains somewhat imprecise. This is why only cortical sources were studied, given that EEG's spatial resolution is much higher for cortical sources than for subcortical sources. Lastly, the sample size was small. To confirm our present findings, further research should assess a larger number of patients.

5. Conclusion

Theta band functional connectivity between nodes involved in executive functions (including executive control and visual network nodes) was greater in PD+FoG patients than in HCs. Use of the standardized ANT revealed a specific deficiency in executive control in PD+FoG patients. However, there were no apparent network differences between PD+FoG and PD-FoG patients. We hypothesize that network abnormalities in PD+FoG correspond to a mechanism that compensates for the patients' greater dependence on the environment. Our results emphasized the need to combine motor, sensorimotor and cognitive rehabilitation in PD+FoG patients.

Authors' Roles

1) Research project: A. Conception, B. Organization, C. Execution;

2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;

3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Morgane Gérard: 1A/B/C, 2A/B, 3A; Madli Bayot: 1A/B/C, 2A/B, 3B; Philippe Derambure: 2C, 3B; Kathy Dujardin: 2C, 3B; Luc Defebvre: 2C, 3B; Nacim Betrouni: 2A/C, 3B; Arnaud Delval: 1A, 2C, 3B.

Conflict of Interest

None.

Funding

Madli Bayot has received a Marie Sklodowska-Curie grant (reference: 721577) under the European Union's Horizon 2020 research and innovation program. Morgane Gérard received a research internship grant from the University of Lille.

Financial Disclosures of all Authors (for the preceding 12 months)

None of the authors has conflicts of interest directly related to the present study.

M. Gerard received a grant from Lille University for a research year.

M. Bayot received a Marie Sklodowska-Curie fellowship (reference: 721577) as part of the European Union's Horizon 2020 research and innovation program.

L. Defebvre has received consultancy fees from Abbvie and Orkyn and has received speaker's fees from UCB and Abbvie.

N. Betrouni is a staff researcher at the Institut National de la Santé et de la Recherche Médicale. He has received a grant from PROCOPE Campus France and has received consultancy fees from LLL France.

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Table and Figure Legends

Table 1. Demographic and clinical characteristics of the three study groups. Data are quoted as the mean ± standard deviation or the median [interquartile range].

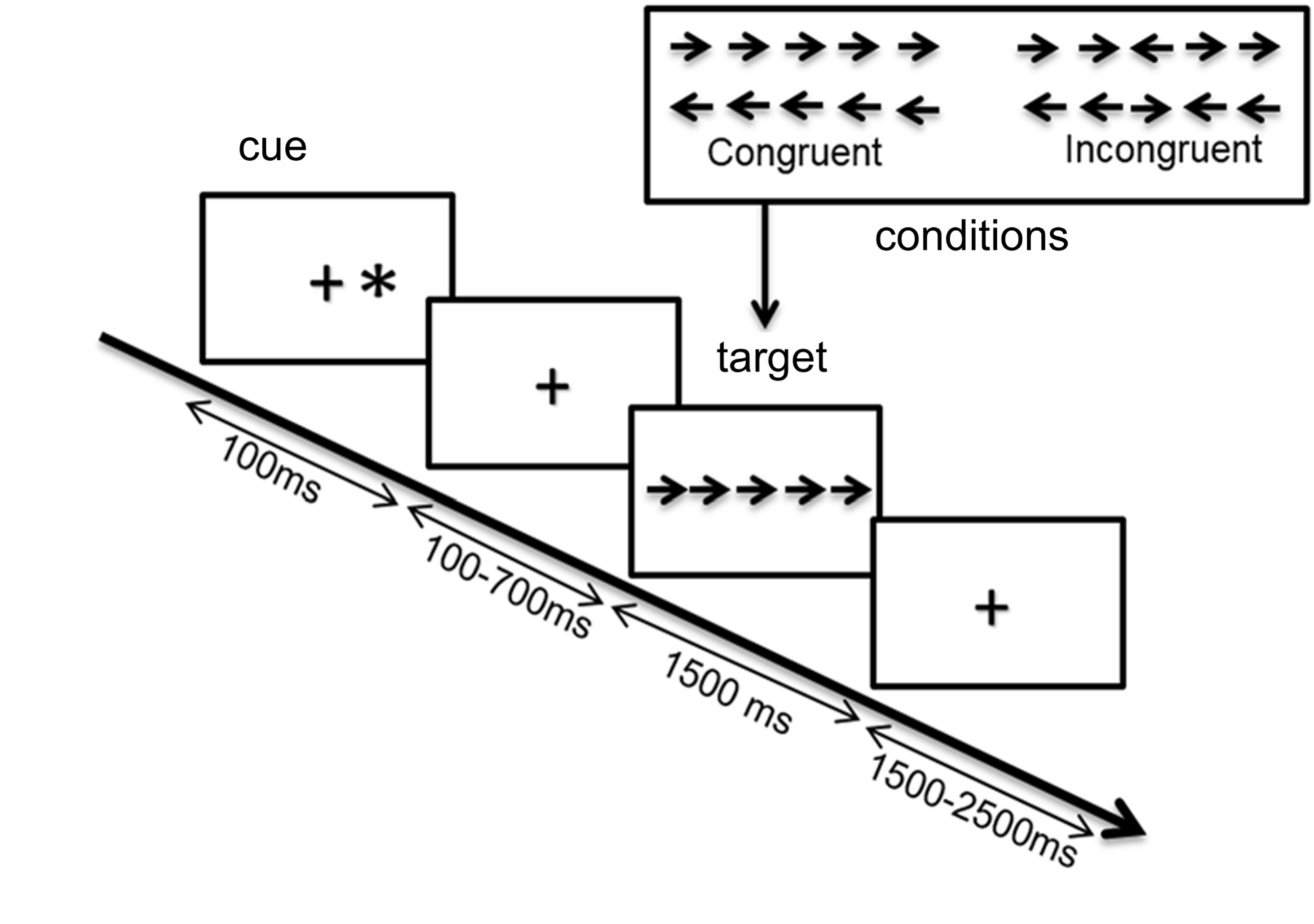
Notes. F/M = females/males; LEDD = levodopa equivalent daily dose; MoCA = Montreal Cognitive Assessment; ΔRT = difference in RTs; ΔAccuracy = difference in response accuracies; BJLOT = Benton Judgement of Line Orientation Test; SDMT = Symbol Digit Modalities Test; D-KEFS CWIT = Color-Word Interference Test from the Delis-Kaplan Executive Function System; MDS-UPDRS III – on-drug = Movement Disorders Society-Unified Parkinson Disease Rating Scale, part III, assessed in the "on-drug" state; H&Y – on-drug = Hoehn and Yahr scale assessed in the "on-drug" state; FoG-Q = Freezing of Gait Questionnaire; PAS = Parkinson Anxiety Scale; PD+FoG = PD patients with FoG; PD-FoG = PD patients without FoG; HCs = healthy controls.

Figure 1. The modified Attention Network Test.

Figure 2. The executive control effect during the ANT: Mean [95% confidence interval] RT by group (ms). DRT = delta (difference) in the response time for each participant (the median RT in the incongruent (I) target condition less the median RT in the congruent © target condition); * = $p<0.05$; PD+FoG = PD patients with FoG; PD-FoG = PD patients without FoG; HCs = healthy controls.

Figure 3. Network dynamics in theta band: graphical visualization of dynamic functional connectivity during the ANT, in 100-ms intervals; C = congruent condition; I = incongruent condition; R = right; L = left; Ant = anterior; Post = posterior; PD+FoG = PD patients with FoG; PD-FoG = PD patients without FoG; HCs = healthy controls.

Figure 4. Functional networks with stronger theta band connectivity in PD+FoG patients than in HCs in the 400-500 ms ($p=0.033$) and 500-600 ms ($p=0.016$) time intervals. 1 = the right medial orbitofrontal cortex; 2 = the right cuneus; 3 = the banks of the left superior temporal sulcus; 4 = the left fusiform gyrus; 5 = the left middle temporal gyrus; 6 = the left and right entorhinal cortex; in blue: visual network nodes; in light green: nodes associated with the executive control network in fMRI studies; in dark green: nodes associated with executive functions; In red: nodes in the ventral attention network; PD+FoG = PD patients with FoG; PD-FoG = PD patients without FoG; HCs = healthy controls.


Congruent
Incongruent
conditions
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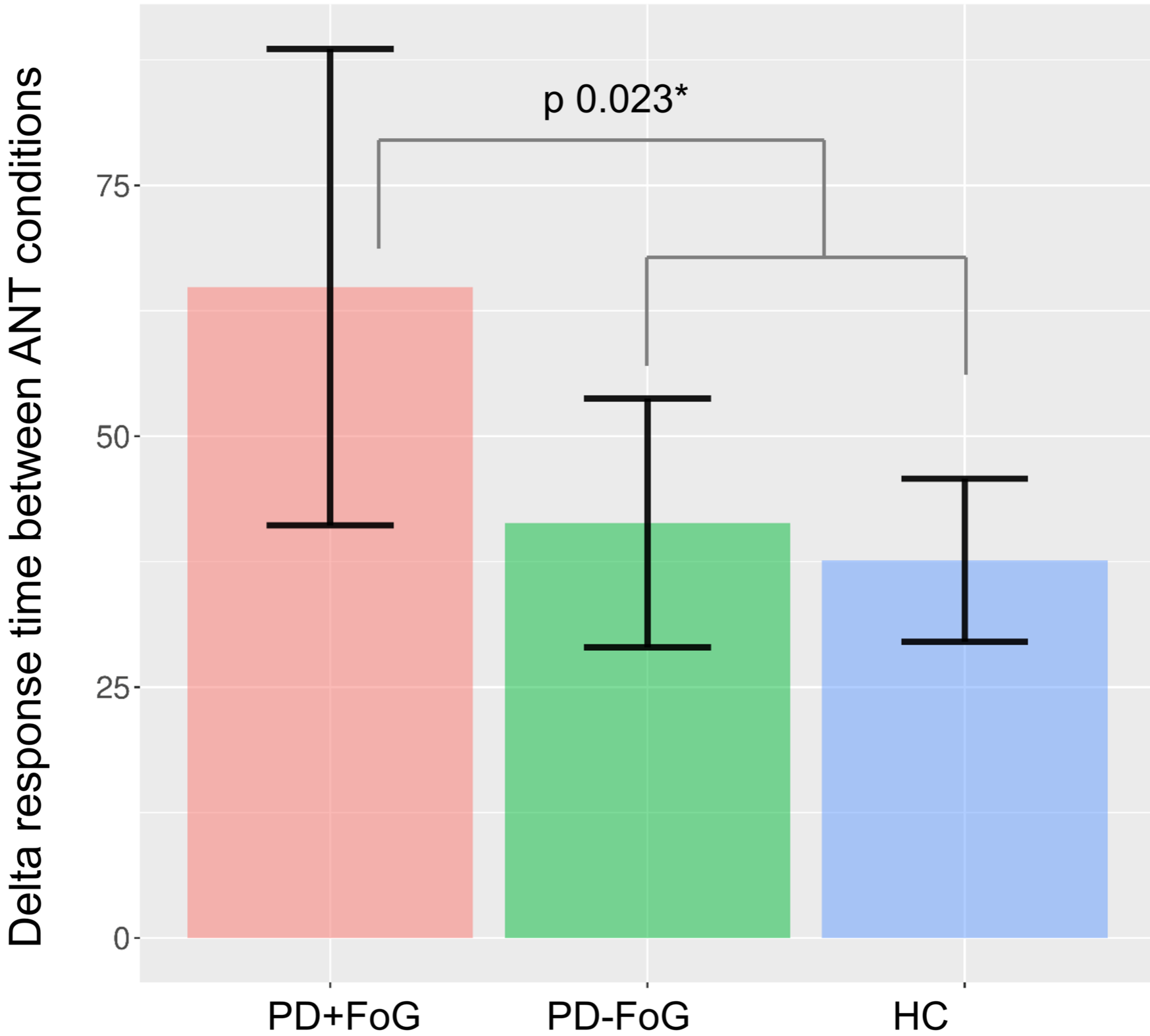
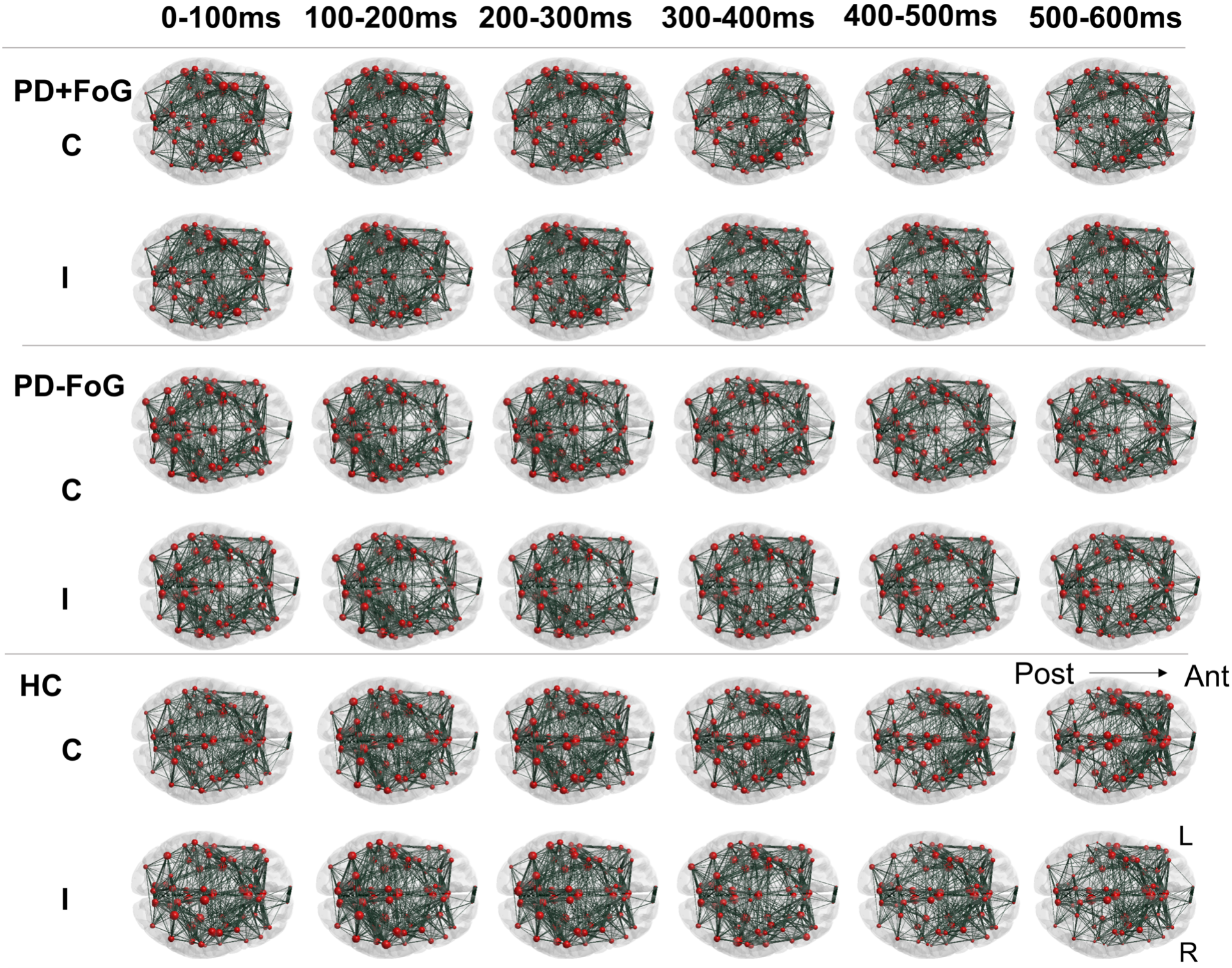
100ms
100-700ms
1500 ms
1500-2500ms


Delta response time between ANT conditions
p 0.023*
75
50
25
0
PD+FoG
PD-FoG
HC


0-100ms
100-200ms
200-300ms
300-400ms
400-500ms
500-600ms
PD+FoG
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PD-FoG
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I
HC
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Ant
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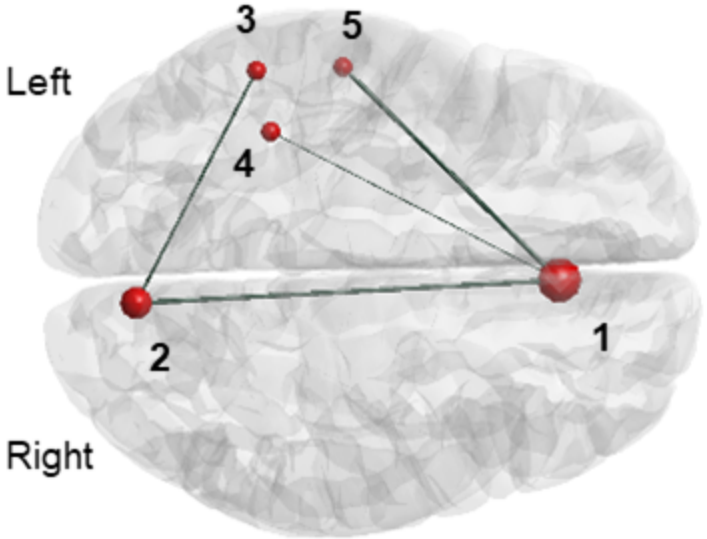
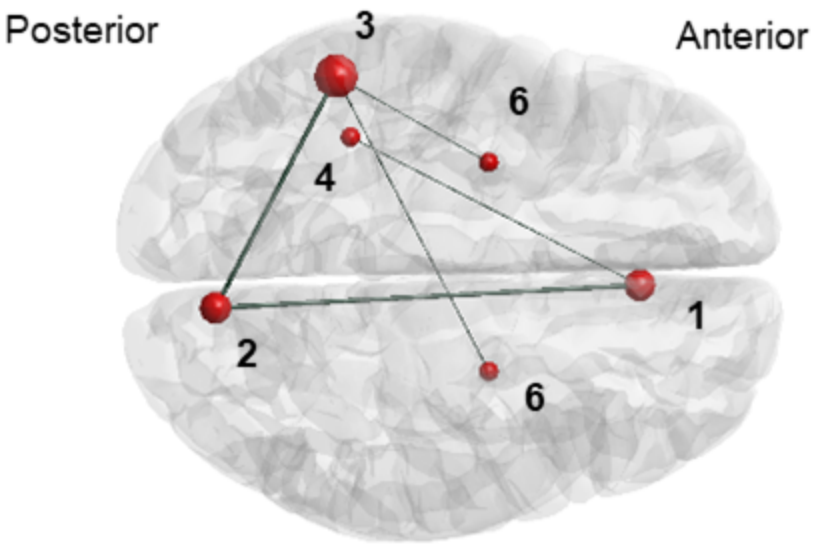


[400 - 500ms]

PD+FoG > HC p 0.033



[500 - 600ms]

PD+FoG > HC p 0.016

Category	Variable	PD+FoG (n=15)	PD-FoG (n=14)	HC (n=18)	Statistic	p-value
Demographic data	Age (years)	63 ± 8	61 ± 9	60 ± 7	F(2, 44) = 0.342	0.712
	Sex (F/M)	4/11	7/7	8/10	$X^2(2, N = 47) = 1.833$	0.4
History of the disease	Disease duration (years)	9 ± 4	9 ± 4	/	U = 105	1
	LEDD (mg L-Dopa)	1082 ± 582	1126 ± 333	/	t(27) = -0.249	0.805
Cognitive functions	MoCA (/30)	27 [24 – 27.75]	26.5 [25 – 28.75]	28 [26 – 29]	F(2,43) = 2.284	0.114
	Executive control effect - ΔRT (ms)	65 ± 43 C: 620 ± 56 I: 685 ± 85	41 ± 21 C: 609 ± 69 I: 650 ± 67	38 ± 16 C: 563 ± 65 I: 600± 63	Group effect: F(2,44) = 4.942 Target effect: F(1,44) = 129.612 Group x Target interaction: F(2,44) = 4.125	Group effect: 0.012 (PD+FoG > HC) Target effect: < 0.001 (C < I) Group x Target interaction: 0.023
	Executive control effect – ΔAccuracy (%)	2.43 ± 3.59 C: 99.57 ± 0.65 I: 97.14 ± 3.73	2.66 ± 4.52 C: 99.13 ± 1.18 I: 96.47 ± 4.98	0.46 ± 0.88 C: 99.84 ± 0.38 I: 99.39 ± 0.88	Group effect on ΔAcc: H(2) = 9.266 Target effect: $X^2(1) = 29.121$	Group effect on ΔAcc: 0.01 (PD > HC) Target effect: < 0.001 (C > I)
	BJLOT (z-score)	0.056 ± 1.41	0.556 ± 1.119	/	t(20) = -0.885	0.387
	SDMT (z-score)	-1.049 ± 0.968	-0.779 ± 0.968	/	t(20) = -0.644	0.527
	D-KEFS CWIT - Inhibition (z-score)	0.111 ± 1.313	0.037 ± 0.632	/	t(19) = 0.156	0.878
	D-KEFS CWIT - Switching (z-score)	0.083 ± 0.986	0.183 ± 0.835	/	t(19) = -0.245	0.809
Motor functions	MDS-UPDRS III – Med ON (/132)	22 [16 – 32]	18 [15.25 – 26]	/	U = 129	0.304
	H&Y – Med ON (/5)	2.5 [2 – 3]	2 [2 – 2]	/	U = 135	0.059
	Axial subscore (/28)	4 [3 – 6]	3.5 [1 – 5]	/	U = 127.5	0.179

	Faller (Y/N)	10/5	1/13	/	$X^2(1, N = 29) = 10.898$	< 0.001
	FoG-Q (/24)	11 [8.5 – 14.5]	/	/	/	/
Neuropsychiatric symptoms	PAS (/48)	10 [4 – 14.75]	1 [1 – 6]	/	U = 95.5	0.043
	Apathy (Y/N)	2/13	4/10	/	$X^2(1, N = 29) = 1.025$	0.311
	Depression (Y/N)	6/9	3/11	/	$X^2(1, N = 29) = 1.167$	0.28