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DUAL-TASK-RELATED NEURAL CONNECTIVITY CHANGES IN PATIENTS WITH PARKINSON' DISEASE

G. VERVOORT,[a]* E. HEREMANS,[a] A. BENGEVOORD,[a] C. STROUWEN,[a] E. NACKAERTS,[a] W. VANDENBERGHE[b] AND A. NIEUWBOER[a]

[a] *KU Leuven, Department of Rehabilitation Sciences, Leuven, Belgium*

[b] *University Hospitals Leuven, Department of Neurology, Leuven, Belgium*

Abstract—*Background and objectives:* Dual-task (DT) gait impairment in people with Parkinson's disease (PD) and specifically in those with freezing of gait (FOG), reflects attentional dependency of movement. This study aimed to elucidate resting-state brain connectivity alterations related to DT gait abnormalities in PD with and without FOG. *Methods:* PD patients ($n = 73$) and healthy age-matched controls ($n = 20$) underwent DT gait analysis and resting-state functional Magnetic Resonance Imaging (rs-MRI) while 'off' medication. Patients were classified as freezer ($n = 13$) or non-freezer ($n = 60$). Functional connectivity (FC) alterations between PD and controls and between patient subgroups were assessed in regions of interest (ROIs) within the fronto-parietal and motor network. *Results:* PD had longer stance times, shorter swing times and more step length asymmetry during DT gait and needed more time and steps during DT turning compared to controls. Additionally, freezers showed similar impairments and longer double support times compared to non-freezers during DT gait. PD demonstrated hyper-connectivity between the inferior parietal lobule and premotor cortex (PMC) and between the cerebellum and the PMC and M1. FOG-specific hypo-connectivity within the striatum and between the caudate and superior temporal lobe and hyper-connectivity between the dorsal putamen and precuneus was correlated with worse DT performance. *Conclusion:* PD showed FC alterations in DT-related networks, which were not correlated to DT performance. However, FOG-specific FC alterations in DT-related regions involving the precuneus and striatum were correlated to worse DT performance, suggesting that the balance between cognitive and motor networks is altered.

Key words: Parkinson's disease, freezing of gait, resting-state fMRI, dual-tasking.

INTRODUCTION

Dopaminergic denervation in the basal ganglia is responsible for reduced movement automaticity in patients with Parkinson's disease (PD) and increased reliance on attention to execute movements (Wu and Hallett, 2005). Movement automaticity is often assessed using dual-task (DT) paradigms. Dual-tasking can be defined as the simultaneous execution of two tasks which have distinct goals and often involve motor and/or cognitive task sets (McIsaac et al., 2015). Although several studies have shown DT interference on gait in PD (Hausdorff et al., 2003; Rochester et al., 2004, 2014; Yogev et al., 2005; Lord et al., 2011), the effect sizes are variable and strongly rely on the nature of the task, cohort selection and medication state. Several studies have established that dual-tasking aggravates freezing of gait (FOG) Camicioli et al., 1998; Hackney and Earhart, 2010; Spildooren et al., 2010. FOG is defined as a brief, episodic absence or marked reduction of forward progression of the feet despite the intention to walk (Nutt et al., 2011). It is associated with reduced functional mobility, increased fall risk and reduced quality of life (Bloem et al., 2004; Rahman et al., 2008a; Kerr et al., 2010). Nutt et al. (2011), proposed that an exaggerated loss of automaticity and/or frontal executive dysfunction may partially explain FOG (Nutt et al., 2011), which also provides a possible rationale for its strong link with dual-tasking.

Several theoretical frameworks have been put forward to explain DT deterioration (Meyer and Kieras, 1997; Ruthruff et al., 2003; Tombu and Jolicoeur, 2003; Wickens, 2008), but studies investigating its neural mechanisms in PD are scarce. Wu et al. (2008) showed greater activation in the prefrontal cortex, middle frontal gyrus (MFG), parietal cortex, temporal lobe and cerebellum in PD compared to controls while performing a tapping task

*Corresponding author. Address: Department of Rehabilitation Sciences, Tervuursevest 101/1501, 3001 Leuven, Belgium. Tel: +32-16/37-65-75.
E-mail addresses: griet.vervoort@faber.kuleuven.be (G. Vervoort), elke.heremans@faber.kuleuven.be (E. Heremans), aniek.bengevoord@faber.kuleuven.be (A. Bengevoord), carolien.strouwen@faber.kuleuven.be (C. Strouwen), evelien.nackaerts@faber.kuleuven.be (E. Nackaerts), wim.vandenberghe@uzleuven.be (W. Vandenberghe), alice.nieuwboer@faber.kuleuven.be (A. Nieuwboer).

Abbreviations: CV, coefficient of variability; D, dominant; DT, dual task; FAB, Frontal Assessment Battery; FC, functional connectivity; FD, framewise displacement; FDR, false discovery rate; FOG, freezing of gait; GP, globus pallidus; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's disease rating scale; MFG, middle frontal gyrus; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; MoCA, Montreal Cognitive Assessment; ND, non-dominant; NFOG-Q, new freezing of gait questionnaire; PD, Parkinson's disease; PMC, premotor cortex; PPN, pedunculopontine nucleus; ROI, region of interest; rs-fMRI, resting-state functional Magnetic Resonance Imaging; SMA, supplementary motor area; SNc, substantia nigra pars compacta; ST, single task; TMT, Trail-Making Test; TR, repetition time.

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together with letter counting (Wu and Hallett, 2008). In addition, increased brain activity registered in the cerebellum, the dorsolateral prefrontal cortex and precuneus was interpreted to have a supervisory role in DT integration both in PD and healthy subjects (Wu et al., 2008, 2013). As for FOG, a recent functional Magnetic Resonance Imaging (fMRI) study showed decreased activation in prefrontal areas, the pre-supplementary motor area (pre-SMA) and posterior parietal cortex in freezers compared to non-freezers during a DT foot pedaling task performed in supine position in the scanner (Shine et al., 2013a). In addition, a Diffusion Tensor Imaging (DTI) study demonstrated that reduced structural connectivity of the right pedunculopontine nucleus (PPN) in freezers was strongly related to DT gait interference outcomes (Peterson et al., 2015).

While these studies provided essential information to unravel the neural correlates underlying DT performance, translation to gait is not straightforward due to movement restrictions inherent to a scanner environment(Hanakawa, 2006). While proxy-measures such as mental imagery of gait have proven useful to investigate single-task (ST) walking Snijders et al., 2011; Crémers et al., 2012; Peterson et al., 2014, they are less suitable for DT conditions. To overcome the problem of performance dependence (Tessitore et al., 2014), resting-state fMRI (rs-fMRI) measures brain networks which remain temporally correlated during rest, providing a global window into functional connectivity (FC) changes. Therefore, this study used rs-fMRI to investigate FC changes underlying DT gait in PD and more specifically in an exploratory fashion in those with FOG. So far, only two rs-fMRI studies highlighted decreased connectivity in the visual and right fronto-parietal network and between the mesencephalic locomotor region and SMA in freezers compared to non-freezers, without modeling direct correlations with gait outcomes (Tessitore et al., 2012; Fling et al., 2014). For this purpose, we analyzed connectivity between regions of interest (ROIs) within the motor and fronto-parietal network, known to be implicated in DT and FOG (Wu and Hallett, 2008; Shine et al., 2013b,c) and performed a correlation analysis with DT gait outcomes obtained from 3D gait analysis in PD and age-matched controls. Based on the work of Wu and colleagues (Wu and Hallett, 2008; Wu et al., 2014, 2015), we expected that reduced DT gait performance in PD patients compared to controls would correlate with hyper-connectivity in cognitive control areas. In addition, we hypothesized that DT gait impairment would be more pronounced in freezers compared to non-freezers and that this impairment would correlate to more widespread FC alterations in cognitive and motor control areas (Tessitore et al., 2012), including the prefrontal cortex, precuneus and cerebellum.

EXPERIMENTAL PROCEDURES

Participants

Seventy-three PD patients and 20 healthy age-matched controls were recruited. Patients were included if they were diagnosed with PD according to the UK Brain Bank criteria and were able to walk independently for at least 10 min. Exclusion criteria were: a Mini-Mental State Examination (MMSE) score < 24; presence of a Deep Brain Stimulator (DBS); neurological or motor comorbidities. The new freezing of gait questionnaire (NFOG-Q) was used to classify patients as freezers (NFOG-Q > 1) (FOG: $n = 13$) or non-freezers (NFOG: $n = 60$) and was administered at the beginning of the behavioral test session. In addition, presence of FOG was determined by the physician in all but one patient, who reported to have FOG after watching the video of the NFOG-Q. Disease severity was assessed by means of the Movement Disorder Society-Unified Parkinson's disease rating scale (MDS-UPDRS) part III 'off' medication and disease duration was calculated from the moment of first motor symptom onset. All tests were performed 'off' medication, i.e. at least 12 h after the last intake of medication (short and long working action) intake. All subjects gave written informed consent and the study was approved by the ethics committee of the University Hospitals Leuven according to the declaration of Helsinki.

Gait analysis

Gait was assessed using the VICON 3D motion analysis system (©Vicon Motion Systems Ltd., UK). Subjects were instructed to continuously walk back and forth over a 6-m trajectory in the gait laboratory. They had to walk in a straight line in the part of the laboratory where the camera view was optimal and turn at the outer parts of the field of view. This was repeated until at least 30 steps were recorded (i.e. approximately 10 trials). Only straight line walking in the middle of the walkway was included in the analyses. In addition, patients were asked to turn in the center of the walkway for six trials. Sixteen reflective markers were placed on anatomical landmarks of the lower limb and pelvis according to the Plugin Gait model and were recorded at a sample frequency of 100 Hz. Marker trajectories were processed using Nexus software (version 1.8.5) to calculate the position and timing of the heel strikes and toe-offs of each step. This information was used to calculate spatiotemporal gait kinematics (Pijnappels et al., 2001). Outcome measures for gait at self-preferred speed were: step time (s), % stance time, % swing time, % double support time, step length (mm), step width (mm) and gait speed (m/s). The average and variability were calculated for the disease dominant (D) and non-dominant (ND) leg for all parameters. Variability was expressed as the coefficient of variability (CV) and asymmetry was calculated between the D and ND leg for patients and between right and left leg for controls for all parameters except step width and gait speed. Stance time, swing time and double support time were expressed as a percentage of the total gait cycle. To maximize the DT impact, gait tests were performed while 'off' medication at self-preferred gait speed and during 360° turning (Spildooren et al., 2010; Snijders, 2012). All subjects performed 360° turns to the left and right side (Spildooren et al., 2010). Outcome measures were step number, turn duration (s) and cadence (steps/min).