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Citation: Vitorio, Rodrigo, Stuart, Sam and Mancini, Martina (2020) Executive control of walking in people with Parkinson's disease with freezing of gait. Neurorehabilitation and Neural Repair, 34 (12). pp. 1138-1149. ISSN 1545-9683

Published by: SAGE

URL: https://doi.org/10.1177/1545968320969940 <https://doi.org/10.1177/1545968320969940>

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Executive control of walking in people with Parkinson's disease with freezing of gait

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Abstract: 249 words

Body of the manuscript: 3825 words

Table: 3

Figure: 3

ABSTRACT

Background: Walking abnormalities in people with Parkinson's disease (PD) are characterized by a shift in locomotor control from healthy automaticity to compensatory prefrontal executive control. Indirect measures of automaticity of walking (e.g., step-to-step variability and dual-task cost) suggest that freezing of gait (FoG) may be associated with reduced automaticity of walking. However, the influence of FoG status on actual prefrontal cortex (PFC) activity during walking remains unclear. **Objective**: To investigate the influence of FoG status on automaticity of walking in people with PD. **Methods**: Forty-seven people with PD were distributed into two groups based on FoG status, which was assessed by the New Freezing of Gait Questionnaire: PD-FoG (n=23; UPDRS-III=35) and PD+FoG (n=24; UPDRS-III=43.1). Participants walked over a 9m straight path (with a 180° turn at each end) for 80s. Two conditions were tested Off medication: single- and dual-task walking (i.e., with a concomitant cognitive task). A portable functional near-infrared spectroscopy system recorded PFC activity while walking (including turns). Wearable inertial sensors were used to calculate spatiotemporal gait parameters. **Results**: PD+FoG had greater PFC activation during both single and dual-task walking than PD-FoG ($p=0.031$). There were no differences in gait between PD-FoG and PD+FoG. Both groups decreased gait speed ($p=0.029$) and stride length ($p<0.001$) during dual-task walking compared to single-task walking. **Conclusions**: These findings suggest that PD+FoG have reduced automaticity of walking, even in absence of FoG episodes. PFC activity while walking seems to be more sensitive than gait measures in identifying reduction in automaticity of walking in PD+FoG.

Keywords: Locomotion, fNIRS, dual-tasking

INTRODUCTION

Freezing of gait (FoG) is one of the most debilitating walking impairment in 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".[1] It occurs in up to 63% of individuals with PD, with increasing frequency in more advanced stages of the disease.[2,3]. FoG episodes often result in falls, disability, reduced functional independence and poor quality of life.[1,4,5] FoG is often difficult to treat[1,6] and the development of enhanced interventions requires a better understanding of the neural basis of FoG.

Although the underlying pathophysiology of FoG is not fully understood,[7] it is thought to be associated with reduced automaticity in the control of walking.[8-10] A hallmark of healthy walking is automaticity, defined as the ability of the nervous system to successfully control movement with minimal use of executive-attentional resources.[11] It has been proposed that many walking abnormalities in people with PD are characterized by a shift in locomotor control from healthy automaticity to compensatory prefrontal executive control.[12-17] Behavioral studies demonstrate that people with FoG have increased gait variability (i.e., surrogate measure of gait automaticity where higher variability equates to reduced automaticity) compared to people without FoG. In addition, gait impairments, such as reduced gait speed, are more pronounced in people with FoG when walking during dual-task conditions compared to people without FoG.[8,16,18,19] These behavioral findings suggest that automaticity of walking is poorer in PD with FoG compared to PD without FoG. However, these are indirect measures of automaticity of walking and, therefore, more direct neurophysiological measures are needed for a better understanding of the control mechanisms of walking in people with FoG.

Neuroimaging studies suggest that two distinct supraspinal locomotor networks are involved in the control of walking.[20-22] The automatic locomotor network is mainly active during steady state walking and it involves direct projections from the primary motor cortex to the central pattern generator circuits.[20,21] The executive locomotor network is active for complex walking requiring planning and modulation of locomotion.[20-22] In the executive network, locomotor signals originate in the supplementary motor area and the prefrontal cortex (PFC) and are transmitted through the basal ganglia (i.e., striatum, pallidum and subthalamic and mesencephalic locomotor region) before reaching the medullary and pontine reticular formations and the spinal cord.[20,21] A feedback loop runs from the spinal cord to the cerebellum and thereby via the thalamus to the cortex in both networks.[20,21] In PD, the executive locomotor network is activated as a compensatory mechanism even during single-task walking.[21,22] Using this model as a background framework, direct measures of automaticity and executive control can be obtained by recording cortical activity during actual walking. For example, functional near-infrared spectroscopy (fNIRS) systems can be used to record changes in cortical oxy- (HbO_2) and deoxygenated hemoglobin (HHb) concentrations, which infer cortical activity.

Measures of PFC activity obtained using fNIRS are reliable[23] and can differentiate healthy older adults and clinical populations, such as people with PD.[13,23,24] Existing studies focusing on FoG mainly characterize the executive control of turning.[25-27] People with PD with FoG have increased PFC activity while turning in place in comparison to non-freezers.[26] Increased PFC activity has also been reported immediately before and during FoG episodes when turning 180° during walking.[27] In addition, higher PFC activity while turning in place is associated with worse FoG severity and poorer turning performance.[26] Such findings suggest greater prefrontal executive control of turning in people with FoG. However, the influence of

FoG status on automaticity of walking is still unclear. Based on evidence from gait studies and the increased PFC activity reported for those with FoG in turning studies, we would expect that during walking PFC activity would be greater in people with PD who report FoG compared to non-freezers, even in absence of an actual episode of FoG. Such increased PFC activity would indicate a reduction in automaticity of walking even in absence of an actual FoG episode, and could partly explain the additional gait impairments noticed in people with FoG compared to people without FoG with similar disease severity.

In the current study, we recorded PFC activity and spatiotemporal gait parameters during single and dual-task walking to investigate the influence of FoG status on automaticity of walking in people with PD. As we hypothesized that people with FoG have reduced automaticity of walking in comparison to people without FoG, we expected to observe increased PFC activity and step-to-step variability in people with FoG. We also expected greater deterioration of gait measures under dual-task walking in people with FoG compared to non-freezers. Additionally, this study explored the relationship between PFC activity while walking and spatiotemporal gait parameters and FoG severity.

METHODS

Participants

Participants were recruited from local Neurology clinics via referrals from movement disorder specialist neurologists. Forty-seven people with idiopathic PD were included in the study. Participants were included if they were aged 55-90 years, had a diagnosis of idiopathic PD according to the UK Brain Bank Criteria, were taking anti-parkinsonian medication, and were

able to give informed consent to participate, and able to cooperate with the testing. Exclusion criteria included: inability to stand or walk for 2 min at a time, factors affecting gait (e.g., musculoskeletal disorders, hip replacement, uncorrected vision or vestibular problems, etc.) and inability to follow instructions. Participants were grouped according to their perceived FoG status, which was assessed by the New Freezing of Gait Questionnaire[28] (NFoGQ): freezers (NFoGQ ≥ 1; PD+FoG) and non-freezers (NFoGQ = 0; PD-FoG). Study procedures were approved by the Oregon Health and Science University Institutional Review Board (eIRB #9903 and #17805), with written informed consent obtained prior to participation.

Experimental procedures and equipment

All participants were tested in their ‘‘Off” medication state, at least 12 h after the last administration of their usual anti-parkinsonian medications. Participant characteristics of age, sex, disease duration, height, and weight were recorded. Disease severity was measured using the Movement Disorders Society (MDS-revised) Unified Parkinson’s disease Rating Scale[29] (MDS-UPDRS). PD stage was assessed by the Hoehn and Yahr Rating Scale[30] (H&Y). Cognitive function was assessed with the following tests: the Montreal Cognitive Assessment[31] (MoCA), the Frontal Assessment Battery[32] (FAB), the Royall Clock Drawing Tasks[33] (CLOX 1 and 2), and the Trail Making Test (TMT).

Participants walked, at self-selected comfortable pace, back and forth over a 9m straight path, with a 180° turn at each end. Two conditions were tested in a randomized order: single and dual-task walking. Each condition included an initial 20 s of quiet standing (baseline period) followed by 80 s of walking (task period). Participants performed a single trial for each walking

condition. The dual-task condition consisted of executing the walking task while performing a concurrent cognitive task (auditory Modified AX-Continuous Performance Task),[34] which required participants to press a handheld button after a two-paired letters sequence. The sequence consisted of a cue letter ‘‘A” and a probe letter ‘‘I” presented sequentially so that the target trail was ‘‘AI” and participants were asked to respond as fast as possible after the probe letter. No information about task priority was assigned to participants not to influence the task execution. A research assistant stood by and walked with the participants to avoid eventual falls and ensure their safety. The Modified AX-Continuous Performance Task was also applied while participants were seated in a chair (before the walking part). No FoG episode occurred during the protocol.

A portable 8-channel fNIRS system (OctaMon, Artinis Medical Systems, Elst, The Netherlands) recorded changes in HbO_2 and HHb bilaterally in the PFC at a sampling rate of 50 Hz. The fNIRS device consisted of two light detectors and eight light emitters (continuous wave diodes with wavelengths of 760 and 850 nm). Three regular channels (interoptode distance of 35 mm) and one short-separation channel (interoptode distance 15 mm) were used for each hemisphere. Optodes were placed on participants forehead using a headband with predetermined locations (according to the international 10-20 EEG system). A digitizer (Polhemus Patriot 3D digitizer, Colchester, VT, USA) was used to provide 3-dimensional coordinates of anatomical references (Cz, nasion, inion and left and right preauricular points) and positions of optodes.

Eight inertial measurement units (Opal, APDM, Portland, OR, USA) were used to quantify spatiotemporal gait parameters at a sampling rate of 128 Hz. They were located at the sternum and pelvis levels, on the wrists, shanks and both feet of participants. Each inertial sensor consisted of tri-axial accelerometers, gyroscopes, and magnetometers, and were securely fixed to

the participant's body with Velcro straps. The inertial sensors and fNIRS system were synchronized through the Artinis PortaSync.

Data analysis

Processing of fNIRS signals followed current recommendations.[22,35] Data from the digitizer was entered into the software package NIRS-SPM (http://www.nitrc.org/projects/nirs_spm),[36] which was implemented within MATLAB 2017a (The Mathworks Inc., Natick, MA, USA). The spatial registration routine was used to find the correspondence between the scalp location where the fNIRS measurement was performed and its underlying cortical surface where the source signal was located.[37] Cortical regions assessed included the Brodmann areas 9 and 10.

The fNIRS data were preprocessed within custom-made MATLAB algorithms, which consisted of several steps. The initial steps involved functions available in HOMER2 (https://homer-fnirs.org/), and specifically: 1) raw intensity data were converted into optical density, 2) artifacts were removed/attenuated by wavelet filtering;[38] 3) optical density data were converted into HbO_2 and HHb concentrations; 4) remaining artifacts were removed/attenuated by applying the correlation-based signal improvement method.[39] The data were then baseline corrected by subtracting the mean of the baseline period (standing) from the entire trial. The following step involved removing superficial hemodynamic response from regular channels.[23,40] Briefly, scaling factors were determined by detecting the peaks (positive and negative) of the heart rate within the regular and short-separation channel signals, then dividing them to produce the scaling factors for each pair of channels. These were then used to remove the noise detected

within the short-separation reference channels within the regular channels. A low-pass filter with a cut-off frequency of 0.14 Hz removed any remaining high-frequency noise and the six channels were median averaged. Finally, relative changes in HbO_2 and HHb concentrations were calculated for both early (median of the first half of the task = initial 40 s) and late (median of the second half of the task = final 40 s) phases of the task, considering straight walk and turns together. The division of the fNIRS signal into early and late phases was motivated by previous studies showing phase-specific PFC activation patterns while walking.[35,41-43]

Spatiotemporal gait measures were calculated from the inertial sensors using the Mobility Lab software, V2 (APDM, Portland, OR, USA).[44] All recorded steps corresponding to walking were included in the analysis. The following gait measures were calculated: gait speed, stride length, foot strike angle and step time variability (coefficient of variation). The accuracy of the Modified AX-Continuous Performance Task was calculated for both seated and walking (i.e., dual-task walking) conditions.

Statistical Analysis

Independent t-tests and Mann-Whitney tests were used to compare demographic and clinical/cognitive variables between groups. Linear mixed-effects models were fit, using the Restricted Maximum Likelihood Estimation (REML), to investigate whether outcomes differed between groups and conditions, while controlling (model #2) or not (model #1) for between-group differences on demographic and clinical/cognitive variables (i.e., MDS-UPDRS-III, H&Y, disease duration, MoCA and TMT-B). The use of covariates in the model allowed us to better isolate the factor of interest (i.e., FoG status) in the analysis. Moreover, comparison between

results of the two models would provide evidence on whether or not the covariates influence potential changes on PFC activity and gait in PD-FoG and PD+FoG. REML estimation were used to avoid bias due to our small sample size.[45] Each model was adjusted for group (PD-FoG versus PD+FoG), task (single versus dual-task), and the group*task interaction (to test whether groups had different linear trend between tasks). Each model included a random intercept for each participant to account for the repeated measurements within each participant. The association between PFC activity while walking (HbO_2) and gait measures was explored, separately per group, using Spearman and Pearson correlation coefficients (according to data type and distribution). For PD+FoG, we also analyzed the association between PFC activity while walking and FoG severity (NFoGQ). The statistical analysis was conducted using Matlab R2019b (The Mathworks Inc., Natick, MA, USA) and SPSS v25 (IBM Inc., IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Participant characteristics

All demographic characteristics and clinical scale scores are reported in Table 1. There were no differences between groups for age, gender, height, weight, FAB, TMT_A, TMT_B-A, CLOX1 and CLOX2. PD+FoG had more severe motor symptoms (MDS-UPDRS-III) and advanced stage (H&Y), longer disease duration and worse cognition (MoCA and TMT_B) than PD-FoG.

<Insert Table 1 here>

PFC activity

Freezers showed greater PFC activity than nonfreezers when controlling for severity of disease and cognitive status (i.e., MDS-UPDRS-III, H&Y, disease duration, MoCA and TMT-B). Results of the two linear mixed-effects models for relative HbO_2 and HHb are reported in Table 2. No significant results were observed for fNIRS outcomes in model #1, which did not control for covariates. While controlling for covariates (model #2), PD+FoG showed higher HbO_2 in the late phase of walking compared to PD-FoG ($p = 0.031$; see Figure 1), regardless of walking condition. In addition, HbO_2 and HHb, both in the early and late phases, were similar between single- and dual-task. Lastly, no significant group*task interactions were found in model #2.

<Insert Table 2 and Figure 1 here>

Gait

Freezers and nonfreezers showed very similar gait characteristics, when results were controlled for severity of disease and cognitive status (i.e., MDS-UPDRS-III, H&Y, disease duration, MoCA and TMT-B). Results of the two linear mixed-effects models for spatiotemporal gait parameters are reported in Table 3. Model #1 revealed a group main effect for step time variability only ($p = 0.044$). PD+FoG showed greater step time variability than PD-FoG (Figure 2). However, such difference was no longer significant in model #2, which revealed no significant group main effect (Table 3). Both models revealed task main effects for gait speed (model #1: $p = 0.026$; model #2: $p = 0.029$), stride length (model #1: $p < 0.001$; model #2: $p < 0.001$) and foot strike angle (model #1: $p = 0.012$; model #2: $p = 0.013$). In fact, both groups had

slower gait speed, shorter stride length and lower foot strike angle in the dual-task compared to single task (Figure 2). No significant group*task interactions were observed for gait outcomes.

<Insert Table 3 and Figure 2 here>

Concurrent cognitive task

Freezers and nonfreezers showed similar performance on the cognitive dual task. Due to technical issues with the equipment (e.g., signals from button and inertial sensor not synchronized), the accuracy of the concurrent cognitive task was not evaluated in all participants. The accuracy is reported for 17 PD-FoG (mean ± standard error of the mean; seated: 0.91 ± 0.04; walking: 0.80 ± 0.07) and 15 PD+FoG (seated: 0.86 ± 0.07; walking: 0.79 ± 0.08). Both statistical models revealed no significant main effect or group*task interaction ($p>0.05$).

Correlations

During dual-task walking, greater $HbO_{2\ late}$ was associated with less severe FoG ($r = -0.526$, $p = 0.011$) and greater $HbO_{2\ early}$ was associated with lower step time variability ($r = -0.463$, $p = 0.023$) in PD+FoG; see Figure 3. For PD+FoG, no significant correlations were observed for HbO_2 during single-task walking. No significant correlations were observed for PD-FoG ($p > 0.05$).

<Insert Figure 3 here>

DISCUSSION

To the best of our knowledge, this is the first study applying fNIRS to examine the influence of FoG status on PFC activity during single and dual-task walking in people with PD. To better isolate the influence of FoG status itself rather than disease progression, we controlled the analysis for between-group differences on demographic and clinical/cognitive variables. Our main results, when controlling for covariates, were: 1) PD+FoG had greater PFC activity while walking (i.e., higher $HbO_{2\ late}$ levels) than PD-FoG, regardless of walking condition; 2) Spatiotemporal gait measures were similar in PD+FoG compared to PD-FoG, and both groups showed worse performance in dual-task compared to single-task; 3) higher PFC activity while walking was associated with less severe FoG and less variable gait, only in the PD+FoG group. These findings suggest that greater contribution of the executive locomotor network is required in PD+FoG due to impaired movement automaticity. Thus, our hypothesis of more pronounced reduction in automaticity of walking in PD+FoG was confirmed by PFC activity (measured by fNIRS) outcomes, but not by gait measures.

NIR light illuminates reduction in automaticity of walking in freezers

This study suggests that PFC activity, measured through mobile fNIRS, can identify reduction in automaticity of walking in PD+FoG. Overall, our findings corroborate previous studies showing that automaticity of walking is reduced in people with PD and even more in those with FoG.[1,16] The observed deterioration of gait parameters under the dual-task condition in both groups suggests that walking is not an automatic task for people with PD,[11,16] regardless of FoG status. Moreover, the increased PFC activity ($HbO_{2\ late}$ level) observed in PD+FoG

suggests further reduced automaticity of walking in this group, which is in line with existing fNIRS studies on turning.[26,27] PD+FoG required the allocation of additional prefrontal executive resources for the control of walking, which is likely a compensatory mechanism to maintain gait performance comparable to non-freezers.

In fact, in keeping with these findings, spatiotemporal gait parameters were unable to differentiate PD+FoG and PD-FoG, while controlling for covariates, even under the dual-task condition. Thus, fNIRS outcomes may be more sensitive than gait outcomes in identifying reduction in automaticity of walking in PD+FoG. Since PFC activation is argued to be part of a compensatory mechanism to maintain a certain level of task performance,[22] it is also possible that changes in PFC activity precede further gait impairments in people with FoG. Such interpretation is supported by the literature. Changes in cortical activity have been proposed as a preclinical sign of (future) gait impairments and falls in healthy middle-aged adults[46] and high-functioning older adults.[47] Longitudinal studies are needed to confirm (or not) if this line of interpretation applies to people with FoG.

Although near-infrared light seems appropriate to illuminate reduction in movement automaticity in PD+FoG, careful definition of outcomes is required. The fact that between-group difference for HbO_2 was only observed in the late phase of the task might relate to a sustained pattern of PFC activation throughout the task by PD+FoG. Several previous studies have reported PFC activation in the initial part of walking corresponding to gait initiation and acceleration phase.[41-43,48] In healthy individuals, the initial increased PFC activity tend to be attenuated during later periods of walking, suggesting a more automatic control.[41-43,48] On the hand, PFC activation has been shown to be sustained throughout the walking task in clinical populations, such as post-stroke patients.[41] Thus, it is possible to interpret that PD+FoG had a

more sustained PFC activation pattern throughout the task compared to PD-FoG. Alternatively, one may also speculate that a potential fatigability component of our task played a role. PD+FoG usually report increased perceived fatigue[49] and, therefore, they are more susceptible to fatigue during a motor task. Fatigue negatively impacts performance in locomotor tasks[50] and therefore may require more higher level attention to control locomotion. It is possible that PD+FoG increased PFC activity (relative to PD-FoG) to deal with the increasing fatigue level. Since this explanation is speculative, we encourage future studies designed (e.g., including fatigue outcomes or protocol to induce fatigue) to further explore the influence of fatigue on PFC activity in PD+FoG.

Both groups prioritized the concurrent cognitive task

Our findings demonstrated that while accuracy in the concurrent cognitive task was similar between seated and dual-task conditions for both groups, gait parameters deteriorated during dual-task walking. Thus, participants prioritized the concurrent cognitive task in detriment of gait performance, even not having received a specific instruction to do so. Such prioritization may have occurred due to a low hazard estimation by patients,[51] as they were in a controlled environment and had a research assistant ensuring their safety. However, the adoption of the so called "posture-second" strategy may go at the expense of maintaining balance during daily activities in the real world.[52] Since PFC activity was also similar between single and dual-task walking, it is possible that participants allocated most of the available prefrontal cognitive resources for the performance of the cognitive task in the dual-task condition. As a consequence, gait deteriorated for not having the required level of prefrontal cognitive resources.

PFC activity during dual-task walking is associated with FoG severity and gait variability in PD+FoG

In PD+FoG, we observed negative correlations between relative HbO_2 during dual-task walking and NFoGQ score and step time variability. Specifically, freezers with greater PFC activity during dual-task walking had less severe FoG (perceived, self-reported) and lower step time variability. These findings suggest that those with less severe FoG may have more prefrontal resources available or a relatively more effective compensatory prefrontal executive control of gait (compared to those with more severe FoG). In addition, we observed no significant correlations involving PFC activity during single-task walking. This finding combined with the significant correlations involving PFC activity during dual-task walking reinforces the important role of the PFC in the control of locomotion during more demanding tasks.

Clinical implications

Findings suggest that PFC should be targeted for the development of enhanced interventions aiming to improve gait in PD+FoG. Cortical non-invasive brain stimulation offers a potential method to achieve this end.[7] In fact, there is preliminary evidence that transcranial magnetic and direct current stimulation applied over the PFC improved turning[53] and clinical symptoms of FoG.[54]

Key study strength and limitation

A key strength of this study is the robust data analysis methods for fNIRS processing, especially the use of short-separation channels to remove the superficial hemodynamic response from the fNIRS signal. This approach reduces the likelihood of false positive results[55,56] and, therefore, is recommended.[22,35] On the other hand, our study is limited by assessing the PFC only. Since PD leads to a broad cortical dysfunction,[57] future studies should assess multiple cortical areas while walking for a more complete understanding of PD- and FoG-related cortical control mechanisms.

CONCLUSION

In conclusion, people with PD who report FoG have reduced automaticity of walking, based on PFC activity, in comparison to people without FoG, even when they have no actual FoG episodes. Higher PFC activity in people with FoG may be compensatory to maintain gait similar to people without FoG. PFC activity while walking seems to be more sensitive than spatiotemporal gait parameters in identifying changes in automaticity in people with PD who report FoG.

Acknowledgements

The authors thank all participants for generously donating their time to participate. We also thank Georgeann Booth and Makena Strand for helping with data collection and study coordination, and Dr. Fay B Horak for helpful discussion.

Funding

This work has been supported by grants from the National Institute of Health via Career Development Award 5R00HD078492-04 (PI Mancini) and a PCO Pilot Grant Award (PI Mancini).

Conflict of interest

Nothing to report

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Table 1. Participants' characteristics

Variable	PD-FoG	PD+FoG	pValue
NFoGQ	0 ± 0	12.2 ± 5.8	**<0.001**
Gender (male / female)	18 / 5	16 / 8	0.380
MDS-UPDRS-III (score)	35.0 ± 10.3	42.4 ± 13.2	**0.038***
H&Y (I / II / III)	1 / 19 / 3	0 / 16 / 8	**0.09†**
Disease duration (years)	7.2 ± 5.2	10.1 ± 6.1	**0.072†**
MoCA (score)	27.2 ± 3.7	26.0 ± 3.1	**0.020***
FAB (score)	14.6 ± 3.1	14.6 ± 3.0	0.940
TMT_A (s)	36.5 ± 15.6	51.9 ± 57.7	0.395
TMT_B (s)	83.5 ± 38.5	116.5 ± 56.1	**0.035***
TMT B-A (s)	46.9 ± 30.4	64.5 ± 44.9	0.125
CLOX1 (score)	12.1 ± 2.0	12.2 ± 1.4	0.761
CLOX2 (score)	13.9 ± 0.9	13.3 ± 1.6	0.208
Age (years)	70.8 ± 7.6	70.3 ± 4.7	0.756
Height (cm)	169.6 ± 12.8	167.9 ± 13.2	0.461
Weight (kg)	84.4 ± 21.9	78.8 ± 14.8	0.580

CLOX: Royall Clock Drawing Tasks; FAB: Frontal Assessment Battery; H&Y: Hoehn and Yahr Rating Scale; MDS-UPDRS: Movement Disorders Society - Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; NFoGQ: New Freezing of Gait Questionnaire; PD-FoG: people with Parkinson's disease without freezing of gait; PD+FoG: people with Parkinson's disease with freezing of gait; TMT: Trail Making Test.

Table 2. Results of the statistical models applied for fNIRS outcomes, while controlling (model #2) or not (model #1) for covariates, which included MDS-UPDRS-III, H&Y stage, disease duration, MoCA and TMT-B.

Variable	Estimate	SE	pValue	Lower 95% CI	Upper 95% CI
Model 1					
Group effects					
$HbO_{2\ early}$	-0.078	0.108	0.472	-0.294	0.137
$HHb_{\ early}$	0.060	0.060	0.321	-0.059	0.179
$HbO_{2\ late}$	-0.239	0.140	0.092	-0.518	0.040
$HHb_{\ late}$	0.116	0.082	0.157	-0.046	0.279
Task effects					
$HbO_{2\ early}$	-0.108	0.094	0.251	-0.294	0.078
$HHb_{\ early}$	0.064	0.048	0.185	-0.031	0.160
$HbO_{2\ late}$	-0.143	0.114	0.215	-0.370	0.084
$HHb_{\ late}$	0.100	0.064	0.125	-0.028	0.228
Group*task					
$HbO_{2\ early}$	0.054	0.059	0.364	-0.064	0.173
$HHb_{\ early}$	-0.035	0.031	0.258	-0.096	0.026
$HbO_{2\ late}$	0.082	0.073	0.259	-0.062	0.227
$HHb_{\ late}$	-0.045	0.041	0.275	-0.127	0.036
Model 2					
Group effects					
$HbO_{2\ early}$	-0.107	0.111	0.338	-0.328	0.114
$HHb_{\ early}$	0.073	0.062	0.243	-0.051	0.197
$HbO_{2\ late}$	**-0.314**	**0.143**	**0.031**	**-0.598**	**-0.029**
$HHb_{\ late}$	0.146	0.084	0.086	-0.021	0.314
Task effects					
$HbO_{2\ early}$	-0.105	0.094	0.269	-0.292	0.082
$HHb_{\ early}$	0.063	0.048	0.195	-0.033	0.159
$HbO_{2\ late}$	-0.135	0.115	0.242	-0.598	-0.029
$HHb_{\ late}$	0.097	0.064	0.137	-0.031	0.225
Group*task					
$HbO_{2\ early}$	0.053	0.06	0.381	-0.066	0.172
$HHb_{\ early}$	-0.034	0.031	0.267	-0.095	0.027
$HbO_{2\ late}$	0.079	0.073	0.283	-0.066	0.225
$HHb_{\ late}$	0.044	0.041	0.291	-0.125	0.038

CI: confidence interval; HbO_2: oxygenated hemoglobin; HHb: deoxygenated hemoglobin; SE: standard error.

Table 3. Results of the statistical models applied for gait outcomes, while controlling (model #2) or not (model #1) for covariates, which included MDS-UPDRS-III, H&Y stage, disease duration, MoCA and TMT-B.

Variable	Estimate	SE	pValue	Lower 95% CI	Upper 95% CI
Model 1					
Group effects					
Speed	0.011	0.062	0.862	-0.112	0.133
Foot strike angle	-0.330	1.568	0.833	-3.447	2.785
Stride length	0.039	0.057	0.498	-0.075	0.154
Step time variability	**-1.609**	**0.787**	**0.044**	**-3.173**	**-0.045**
Task effects					
Speed	**-0.063**	**0.028**	**0.026**	**-0.119**	**-0.008**
Foot strike angle	**-1.553**	**0.609**	**0.012**	**-2.764**	**-0.343**
Stride length	**-0.077**	**0.021**	**<0.001**	**-0.119**	**-0.034**
Step time variability	-0.394	0.455	0.389	-1.298	0.510
Group*task					
Speed	0.014	0.018	0.436	-0.021	0.049
Foot strike angle	0.250	0.388	0.521	-0.521	1.021
Stride length	0.019	0.014	0.173	-0.008	0.046
Step time variability	0.401	0.290	0.170	-0.174	0.976
Model 2					
Group effects					
Speed	-0.075	0.055	0.173	-0.183	0.034
Foot strike angle	-1.434	1.622	0.379	-4.66	1.792
Stride length	-0.044	0.049	0.368	-0.141	0.053
Step time variability	-0.803	0.722	0.269	-2.238	0.632
Task effects					
Speed	**-0.062**	**0.028**	**0.029**	**-0.118**	**-0.007**
Foot strike angle	**-1.548**	**0.612**	**0.013**	**-2.764**	**-0.332**
Stride length	**-0.075**	**0.021**	**<0.001**	**-0.118**	**-0.033**
Step time variability	-0.392	0.455	0.391	-1.300	0.513
Group*task					
Speed	0.013	0.018	0.452	-0.022	0.049
Foot strike angle	0.247	0.389	0.527	-0.526	1.020
Stride length	0.018	0.014	0.191	-0.009	0.045
Step time variability	0.400	0.290	0.170	-0.176	0.977

CI: confidence interval; SE: standard error.

Fig.1

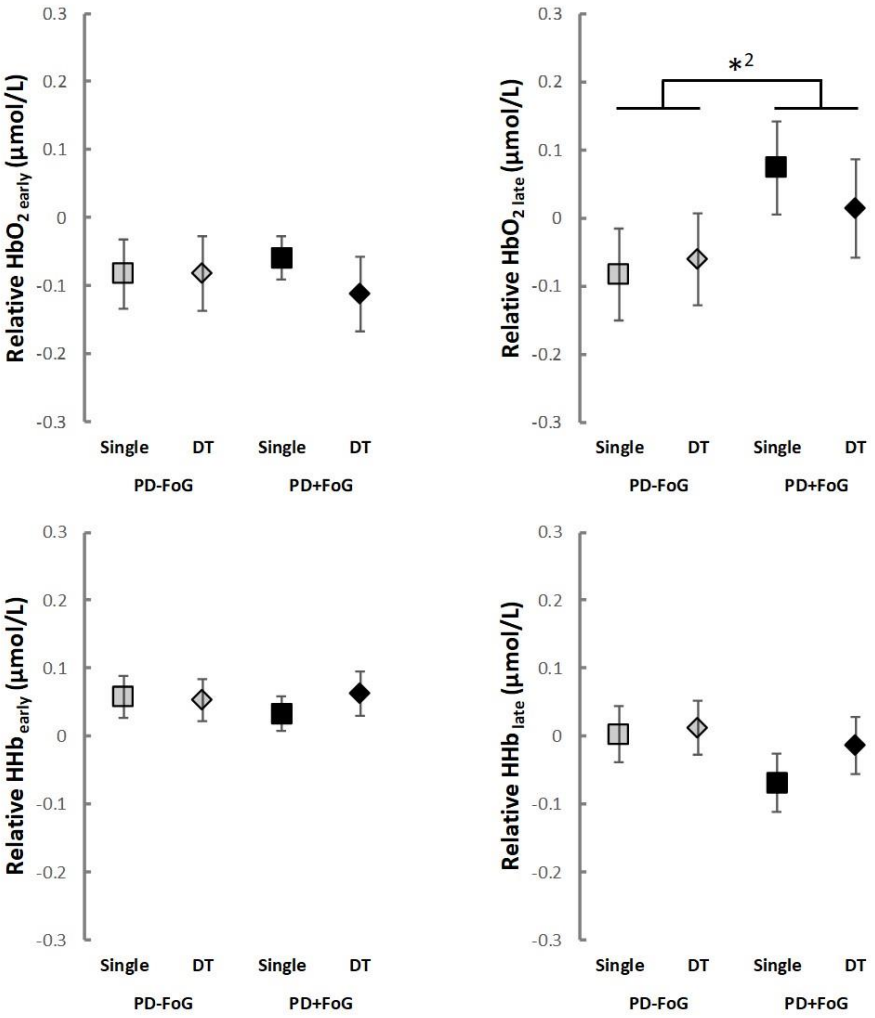

Relative HbO2 early (µmol/L)
Relative HbO2 late (µmol/L)
Relative HHb early (µmol/L)
Relative HHb late (µmol/L)
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
*2
Single
DT
Single
DT
PD-FoG
PD+FoG

Fig. 2

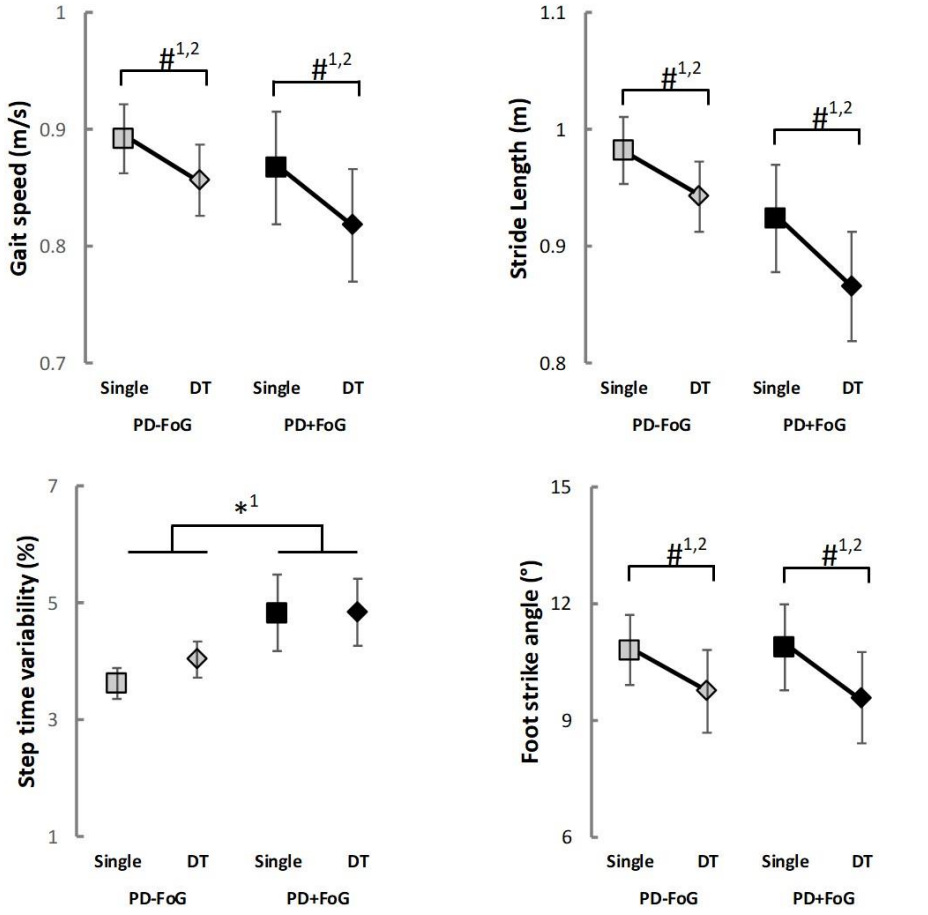
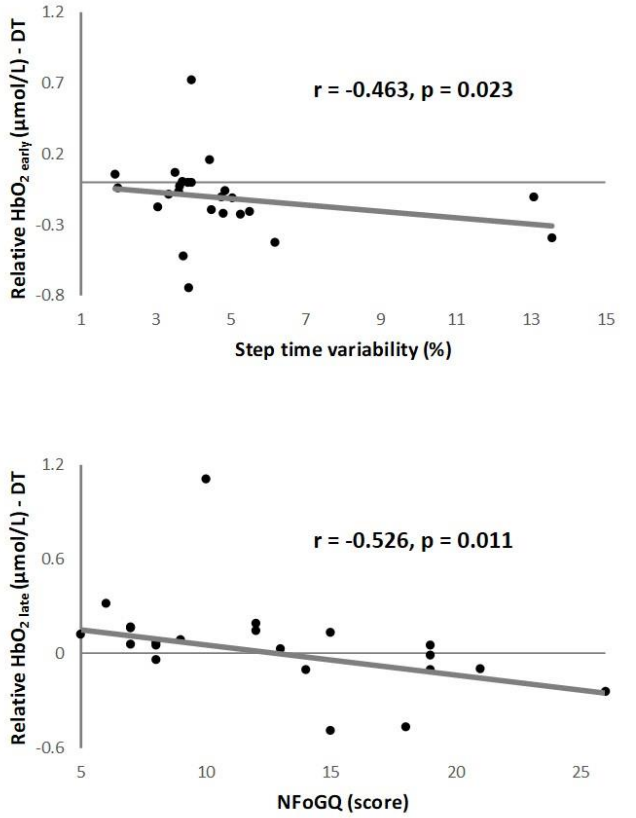

Gait speed (m/s)
1
0.9
0.8
0.7
#1,2
#1,2
Single
DT
Single
DT
PD-FoG
PD+FoG
Stride Length (m)
1.1
1
0.9
0.8
#1,2
#1,2
Single
DT
Single
DT
PD-FoG
PD+FoG
Step time variability (%)
7
5
3
1
*1
Single
DT
Single
DT
PD-FoG
PD+FoG
Foot strike angle (°)
15
12
9
6
#1,2
#1,2
Single
DT
Single
DT
PD-FoG
PD+FoG

Fig. 3


r = -0.463, p = 0.023
Relative HbO2 early (µmol/L) - DT
Step time variability (%)
1.2
0.7
0.2
-0.3
-0.8
1
3
5
7
9
11
13
15
r = -0.526, p = 0.011
Relative HbO2 late (µmol/L) - DT
NFoGQ (score)
1.2
0.6
0
-0.6
5
10
15
20
25