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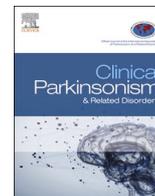
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An intensive exercise-based training program reduces prefrontal activity during usual walking in patients with Parkinson's disease

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ABSTRACT

Introduction: Parkinson's disease (PD) leads to a progressive loss of locomotor automaticity. Consequently, PD patients rely more on executive resources for the control of gait, resulting in increased prefrontal activity while walking. Exercise-based training programs may improve automaticity of walking and reduce prefrontal activity in this population. This study aimed to assess the effect of an intensive multidisciplinary exercise-based training program on prefrontal activity and gait performance during usual walking in PD patients.

Method: Fourteen patients (mean age: 67 ± 9 ; disease duration: 6 ± 5 years; Hoehn and Yahr score: 1.9 ± 0.6) were included in this study. They were assessed in ON stage at three different times at 5-week intervals: two times before the training program (T0 and T1) and once after the training program (T2). Gait performance (stride time, speed, stride length, cadence, and their respective coefficient of variation) and cortical activity in the dorsolateral prefrontal cortex (DLPFC) using functional near infrared spectroscopy (fNIRS) were measured during usual walking.

Results: Patients had reduced cortical activity of the DLPFC at T2 compared to T1 ($p = 0.003$). Patients had shorter stride time at T2 compared to T1 ($p = 0.025$) and tended to have longer stride length at T2 than at T1 ($p = 0.056$).

Conclusion: The training program led to positive effects on prefrontal activity and gait performance. Reduced prefrontal activity during usual walking after training program suggests that patients may have a greater reserve capacity to face more challenging walking conditions. Further studies will investigate the effect of this training on cortical activity during dual-task walking.

1. Introduction

Parkinson's disease (PD) is characterized by a reduction of dopaminergic neurons leading to a progressive loss of automaticity that may impact walking [8]. Patients with PD had increased dorsolateral prefrontal cortex (DLPFC) activity compared to healthy older adults during usual walking [10]. This finding suggests that PD patients rely more on executive functions and attentional resources to compensate for the loss

of gait automaticity [9].

Exercise has beneficial effects on motor and functional capacities of patients with PD [3]. Moreover, exercise induces neuroplasticity by strengthening synaptic connections [9]. Continued practice and motor learning promote to reduce executive control as movement patterns become more automatic [2]. Multidisciplinary interventions may show beneficial effects on walking as different aspects of gait (e.g. coordination, balance, speed movement, etc.) are being targeted [8]. An intensive

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multidisciplinary exercise-based rehabilitation training program, called Sirocco, has been developed for patients with PD in France [11] with the objective to improve or maintain functional abilities.

To our knowledge, few studies have investigated exercise-induced changes in prefrontal activity after physical training [4–6]. Yet, these changes would give insight on neuroplasticity in PD and on the efficacy of the training. The objective of this study was to assess the effect of the intensive exercise-based Sirocco training program on prefrontal activity and gait performance during usual walking in PD patients. We hypothesize that the training program will decrease DLPFC activity and will improve gait performance during usual walking in PD patients.

2. Methods

2.1. Participants

Fourteen patients (mean age = 67 ± 9 ; Hoehn and Yahr score = 1.9 ± 0.6 ; Montreal Cognitive Assessment (MoCA) score = 26.9 ± 1.9 ; 4 females/10 males, Unified Parkinson Disease Rating Scale (UPDRS) motor score = 21.57 ± 11.65 ; disease duration = 6 ± 5 years; 13 right handed) were included in this study. They were recruited from the Henry-Gabrielle Hospital, Lyon (France). Inclusion criteria were: a Hoehn and Yahr score from 1 to 3, ability to walk 20 min without assistance. Exclusion criteria were: a MoCA score lower than 18, severe dyskinesia, presence of other known neurologic or rheumatologic or orthopedic disorders, and presence of any device-aided therapies (apomorphine or levodopa-carbidopa pumps). All participants were assessed during the “ON” medication periods, two hours after the first oral levodopa dose. This study involving human participants were reviewed and approved by Comité de Protection des Personnes Nord Ouest III; Réf. CPP: 2018-01 No. ID RCB: 2017-A03187-46. All participants provided their written informed consent to participate in this study.

2.2. Sirocco training program

Sirocco training program is a collective intensive exercise-based rehabilitation-training program, unique in France. Each session of the Sirocco program was composed by a group of eight patients who stayed at the hospital for five weeks, except for weekends. The training program gathers several activities such as adapted physical activity, physiotherapy, occupational therapy and speech therapy. All these activities are practiced in group sessions. Adapted physical activity included Nordic walking, cross training, balneotherapy, collective sport and stretching. Physiotherapy focused on speed, obstacle crossing, static and dynamic balance. Occupational therapy focused on gestural and handwriting. Finally, speech therapy intended to work on vocal intensity, respiration, articulatory functions. All activities were divided into 45-minutes session, with 5 sessions per day, five days a week. The difficulty of each activity increased over the 5 weeks.

2.3. Protocol

Participants served as their own control. They were assessed 3 times: 5 weeks before the beginning of the training program (T0), three days before (T1) and after (T2) the training program. Time interval between T0 and T1 corresponds to the duration of Sirocco program (i.e. 5 weeks). At each time, they performed usual walking task in which patients were asked to walk at a freely-selected comfortable speed. The block design task alternated approximately 30 s of resting and 30 s of walking periods. The task began with 45 s of quiet standing (see Ranchet et al. [10] for more details in the protocol).

2.4. Gait assessment

Gait parameters were recorded at a sampling rate of 200 Hz during

T0, T1 and T2 with two inertial foot-sensors (Physilog®5, Gait Up, Switzerland). Mean stride time (second), speed (meter per second), stride length (meter) and cadence (number of steps per second), as well as their respective coefficient of variation (CV, [standard deviation/mean]*100) were computed.

2.5. Functional near infrared spectroscopy

Relative changes in oxy- and deoxy-hemoglobin concentration (ΔHbO_2 and ΔHbR in $\mu\text{mol/L}$) in the DLPFC were recorded at a sampling frequency of 7.8 Hz using a wireless continuous waves fNIRS device (NIRSport, NIRx Medical Technologies). Optodes (4 sources and 6 detectors) were placed on the DLPFC of both hemispheres according to the modified international EEG 10–10 system. Interoptode distance were ~ 30 mm for eight regular channels and ~ 15 mm for two short separation channels.

2.6. Data processing

A data processing chain was applied following recent recommendations [7] using Homer 2 (Matlab, version 2.8, R2018b, MathWorks). The first step was a visual inspection to identify and remove manually motion artefact for each task. If missing data during the recording were inferior to 1% of the entire participant data, they were replaced using a linear regression. Then, motion artefacts were corrected and a low pass filter with a cut-off frequency of 0.1 Hz was applied. Finally, contribution of short separation channels was removed. At the end, relative changes (Δ) in HbO_2 and HbR concentrations were obtained using the last 5 s of the resting state before each task as a baseline and were averaged over the 5 trials and over the first 20-sec time period.

2.7. Statistical analysis

ΔHbO_2 and ΔHbR were reported but only ΔHbO_2 in the DLPFC were analyzed due to its higher sensitivity and signal-to-noise ratio for detecting cognitive activity; ΔHbR remaining stable. Kolmogorov-Smirnov tests were used to determine the normality of variables. Three repeated measures analysis of variance (ANOVA) with time (T0, T1 and T2) as within-subject factor were performed on ΔHbO_2 in the whole DLPFC (both hemispheres averaged) and on each hemisphere separately. A repeated measures ANOVA with time (T0, T1 and T2) as within-subject factor was performed on each gait parameters. Post-hoc Bonferroni test was used for multiple comparisons. Spearman correlations (ρ) were used to investigate associations between ΔHbO_2 and gait parameters. All statistical analyses were conducted using SPSS software, version 26.

3. Results

3.1. Effect of training on changes in DLPFC activity

Main effect of time on ΔHbO_2 was found in the whole DLPFC ($F_{(2,26)} = 6.599$, $p = 0.005$, $\eta^2 = 0.337$). Participants exhibited decreased DLPFC activity at T2 compared to T1 ($p = 0.003$) whereas no significant difference in DLPFC activity between T0 and T1 was found ($p = 0.806$) (see Fig. 1).

When analyzing each hemisphere, main effect of time on ΔHbO_2 was found in the right hemisphere ($F_{(2,26)} = 6.899$, $p = 0.004$, $\eta^2 = 0.347$). Participants exhibited decreased DLPFC activity at T2 compared to T1 in the right hemisphere only (HbO_2 at T1: $0.35 \mu\text{mol/L} \pm 0.23$ versus T2: $0.14 \mu\text{mol/L} \pm 0.18$, $p = 0.006$).

3.2. Effect of training on gait performance

Main effect of time was found on all mean gait parameters (see Fig. 2). Participants had shorter stride time at T2 compared to T1 ($p =$

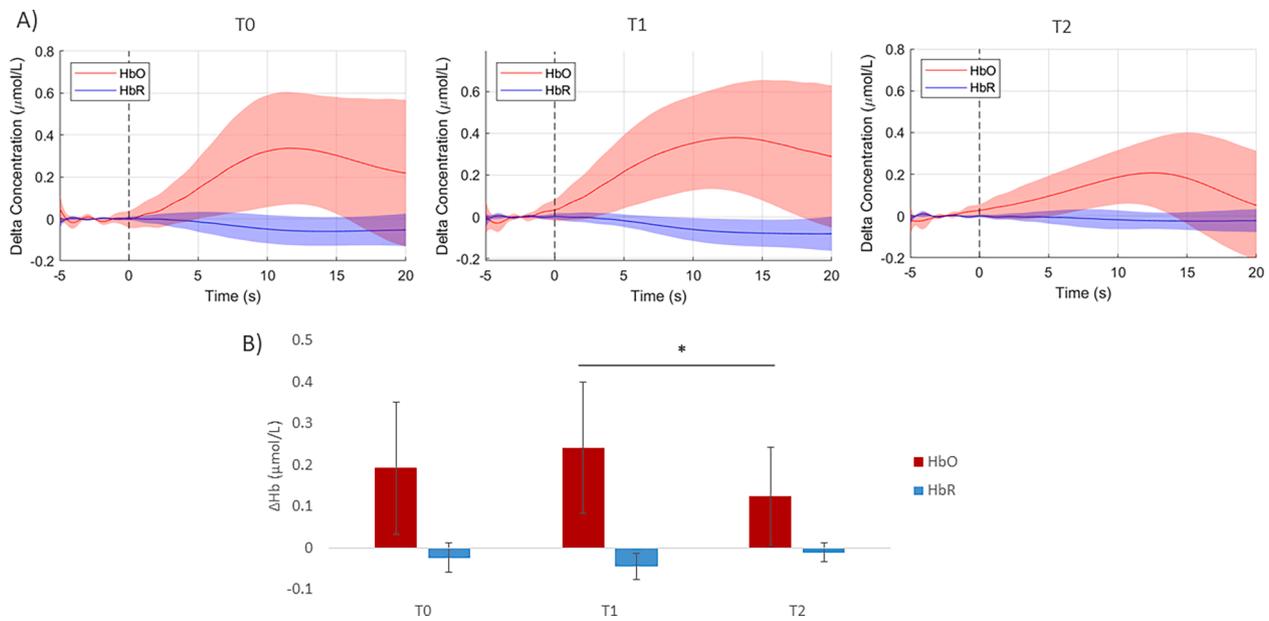


Fig. 1. Mean time courses (A) and mean relative changes (B) in HbO₂ and HbR at each testing time for the whole DLPFC. Legend: *, $p < 0.05$, adjustment using Bonferroni correction.

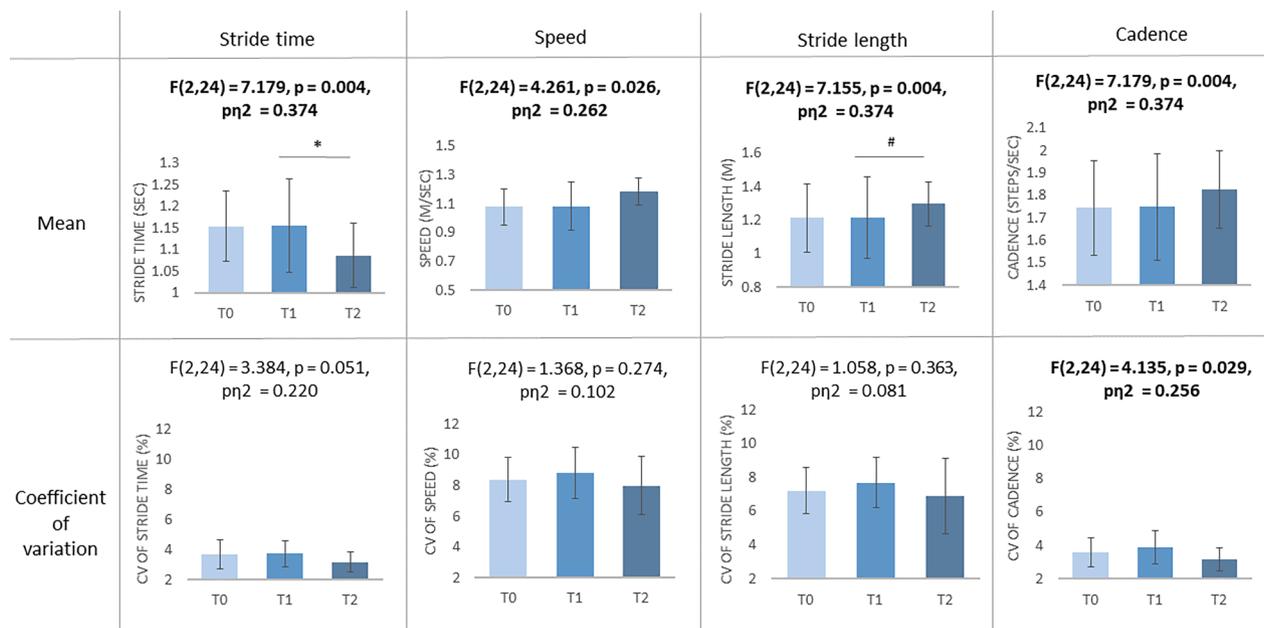


Fig. 2. Multivariate analysis of variance and mean values and CV of gait performance. Legend: *, $p < 0.05$; #, $0.05 < p < 0.06$; Adjustment using Bonferonni correction.

0.025). Participants tended to have longer stride length at T2 than at T1 ($p = 0.056$). No significant pairwise comparisons were found for cadence and speed. Main effect of time was found on CV of cadence but pairwise comparisons did not show any significant differences.

3.3. Association between DLPFC activity and gait performance

At T1, ΔHbO_2 in the right hemisphere was negatively correlated to CV of cadence ($\rho = -0.591, p = 0.026$) and CV of stride length ($\rho = -0.578, p = 0.030$). At T2, ΔHbO_2 in the right hemisphere was negatively correlated to stride length ($\rho = -0.588, p = 0.035$). Also at T2, ΔHbO_2 in the left hemisphere was positively correlated to CV of stride length ($\rho = 0.670, p = 0.012$) and CV of speed ($\rho = 0.703, p = 0.007$). No significant

correlations were found at T0.

4. Discussion

Results showed that patients with PD had decreased prefrontal activity in the DLPFC and shorter stride time during usual walking after the training program, suggesting positive effects of the training program on prefrontal activity and gait performance.

Interestingly, only the right prefrontal cortex exhibited reduced activity after the training program. This area is responsible for the control of sustained attention [12]. Walking is a visually guided activity that involves sustained visual attention in order to adapt gait activity. The right dorsolateral prefrontal cortex is also involved in visual working

memory as well as visual-motor adaptation [1]. Reduction of the prefrontal activity after the training program would reflect that PD patients rely less on executive control to walk. It suggested that this intensive training program improves automaticity of movement [2]. This result is in accordance with that of Maidan et al. [6] which found a reduction of the right PFC activity during usual walking after training program in PD patients. However, reduction of the right PFC activity during usual walking was greater in the present study compared to their study (61% against 18%). This difference may be explained by the fact that in this study, the training program included several kinds of physical activities and was intensive whereas in Maidan's study (2017), the program was a treadmill training program combined with virtual reality.

During usual walking, stride time was shorter and stride length tended to be longer after the training program. Reducing the stride time would suggest that patients may reduce their double support time [13]. They may feel more confident in their balance to lengthen the proportion of single limb support. These findings are consistent with previous studies that showed an improvement of stride length after treadmill training [3]. No notable improvement was found for speed, cadence, and CV of cadence although significant main effects and medium to large effect sizes were found. The lack of significant effect may be due to our small sample size.

Interestingly, associations between prefrontal activity and gait performance differed after the training program. Just before the training program (T1), an increased prefrontal activity in the DLPFC was associated with lower CV (i.e. more stability) which may reflect a compensatory mechanism for impaired motor automaticity. After the training program, a decreased prefrontal activity was associated with a lower CV (i.e. greater stability). These findings suggest that patients who had better walking performance after the training program are those who rely less on executive resources. This indicates that walking became more regular and automatic after the training program.

Nevertheless, the small sample size and the lack of control group lead to interpret these results cautiously. Test-retest reliability of the hemodynamic response in the DLPFC between the two first sessions at 5-week interval has not been investigated yet. However, decreased DLPFC activity between T2 and T1 versus no significant changes between T0 and T1 suggest a positive effect of the program on DLPFC activity. Another study is warranted to better investigate the between-sessions test-retest reliability of prefrontal cortical activity during usual walking in patients with Parkinson's Disease. Moreover, only the DLPFC was assessed in this study. Other studies are needed to have a better understanding on the effects of a training program on other brain regions in PD.

To conclude, the intensive exercise-based training program seemed to show positive effects in PD patients by reducing prefrontal activity and improving gait performance during usual walking. It suggests that patients may have a better utilization of their executive and attentional resources. Consequently, they would have a greater reserve capacity to face more challenging walking conditions. This study may help to improve rehabilitation of gait in patients with PD, and therefore prevent the risk of falling". Further studies will also investigate the effect of Si-rocco program on cognition, prefrontal activity, and walking performance during dual-task walking conditions in PD.

CRedit authorship contribution statement

I. Hoang: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **M. Ranchet:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision. **M. Cheminon:** Methodology, Investigation, Resources, Writing – review & editing. **R. Derollepot:** Software, Formal analysis, Data curation, Visualization. **H. Devos:** Writing – review & editing. **S. Perrey:** Writing – review & editing. **J. Luauté:** Methodology, Resources,

Writing – review & editing. **T. Danaila:** Methodology, Investigation, Resources, Writing – review & editing. **L. Paire-Ficout:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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