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Between-sessions test-retest reliability of prefrontal cortical activity  
during usual walking in patients with Parkinson's Disease: a fNIRS  
study

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Abstract:

**Background:** Examining between-sessions test-retest reliability of functional near-infrared spectroscopy (fNIRS) data is crucial to better interpret rehabilitation-related changes in the hemodynamic response.

**Research question:** This study investigated test-retest reliability of prefrontal activity during usual walking in 14 patients with Parkinson's Disease with a fixed retest intervals of five weeks.

**Methods:** Fourteen patients performed usual walking in two sessions (T0 and T1). Relative changes in cortical activity (oxy and deoxyhemoglobin:  $\Delta\text{HbO}_2$  and  $\Delta\text{HbR}$ , respectively) in the dorsolateral prefrontal cortex (DLPFC) using fNIRS system and gait performance were measured. Test-retest reliability of mean  $\Delta\text{HbO}_2$  for the total DLPFC and for each hemisphere were measured using paired t-test, intraclass correlation coefficient (ICC), and Bland-Altman plots with 95% agreement. Pearson correlations between cortical activity and gait performance were also performed.

**Results:** Moderate reliability was found for  $\Delta\text{HbO}_2$  in the total DLPFC (mean difference of  $\Delta\text{HbO}_2$  between T1 and T0 =  $-0.005 \mu\text{mol}$ ,  $p = 0.93$ ; ICC average = 0.72). However, test-retest reliability of  $\Delta\text{HbO}_2$  was poorer when considering each hemisphere.

**Significance:** Findings suggest that fNIRS may be used as a reliable tool for rehabilitation studies in patients with PD. Test-retest reliability of fNIRS data between 2 sessions during walking tasks should be interpreted respectively of gait performance.

## Introduction

Patients with Parkinson's Disease (PD) may have impaired walking, which is linked to a reduction in automatic control of movement. Consequently, PD patients compensate their reduced automaticity by recruiting a greater amount of cognitive resources, mainly located in the prefrontal cortex (PFC). Thus, they have usually greater cortical activity in the PFC during usual walking [1,2]. Cortical activity during walking may be assessed by functional near infrared spectroscopy (fNIRS). Compared to other neuroimaging techniques, this tool is less invasive, portable, and quite low-cost. This technique could be well suited for research and clinical use, such as measuring cortical activity before and after a specific intervention. In PD patients, few studies investigated the effect of a training program on cortical activity during usual walking [3–6]. Findings in patients with PD consistently showed reduced prefrontal activity during usual walking after the training, reflecting a possible improvement of automatic control of movement. In our recent study on the effect of a training program on cortical activity, patients with PD were their own controls and performed a walking task 3 times: 5 weeks before the training program (T0), just before the training program (T1) and 5 weeks after the training program (T2). Findings showed a reduction of prefrontal activity during usual walking after the training program[6]. To ensure that the reduction of prefrontal activity between T2 and T1 is not due to a learning effect or test-retest effects, test-retest reliability between T1 and T0 at 5-weeks interval needs to be considered.

Examining test-retest reliability between testing sessions will also help to determine to what extent the fNIRS data are reproducible. Findings in young adults consistently showed reasonable test-retest reliability of the hemodynamic response of the frontal region during fluency tasks at least when responses are considered at the group level (*i.e.* when averaging hemodynamic responses of all participants within the same group) and when averaged across multiple channels overlying a cortical region of interest (ROI). [7–10]. However, differences in

the methodology were found between these studies as the number of participants (from 5 to 20 participants), test-retest intervals (ranging from 1 week to 1 year), number of sessions (from 2 to 4) and the type of chromophores used (HbO, HbR, HbT).

To our knowledge, only two studies investigated test-retest reliability of fNIRS data during walking tasks in young adults [2,11] and patients with multiple sclerosis [11]. Stuart et al. (2019) showed moderate test-retest reliability for prefrontal activity, using  $\Delta\text{HbO}_2$  in young adults during usual walking [2]. Similarly, a recent study showed fair to excellent test-retest reliability in young adults analyzing several indicators (absolute and relative mean, slope coefficient, area under the curve of HbO/HbR) [11]. However, results demonstrated a relatively limited inter-session reliability of prefrontal activity in people with neurological disorders such as multiple sclerosis..

In the present study, the test-retest reliability of prefrontal activity during usual walking in patients with PD between the first two sessions (T0 and T1) at 5 weeks interval was examined at a group level for the total dorsolateral PFC (DLPFC) and for each hemisphere (left and right DLPFC).

## Materials and Methods

### Participants

Eighteen patients with Parkinson's Disease were recruited (for more details, see our previous study [1]). Among them, 14 patients (4 women and 10 men; mean age:  $67 \pm 9$  years old, 13 right-handed, Hoehn and Yahr stage:  $1.9 \pm 0.6$ ) were included. They came to the lab three times, with a 5 weeks interval between the two sessions. All patients were medicated and tested in the "on" medication state. Twelve participants out of 14 had stable medication between the two sessions. They provided written informed consent prior to participation. The study was

approved by the French biomedical ethics committee on March, 9 2018 (Comité de Protection des Personnes Nord Ouest III Réf. CPP: 2018-01 N° ID RCB: 2017-A03187-46).

### Walking task

Participants performed 4 conditions: 1) standing while subtracting, 2) usual walking, 3) walking while counting forward, and 4) walking while subtracting. This study focused on the usual walking in order to compare with findings from previous studies: 1) which observed significant differences between patients and controls in prefrontal activity [1], 2) which investigated reproducibility of fNIRS data [2,11]. Participants were asked to walk at their “normal pace”. The walking path configuration was an oval shape whose dimensions are displayed in Figure 1.A. It started with 45 seconds of standing quietly. Then, the participants were asked to walk continuously on the path for 30 s. They began their walk on a straight line in a counter clockwise direction. This was followed by a rest period that lasted from 25 to 35 s to diminish possible resonance effects[12] . Each trial (walking + rest periods) was repeated 5 times. Gait parameters were recorded at a sample rate of 200 Hz with two inertial foot-sensors (Physiolog® 5, Gait Up, Switzerland). Speed (meter per second), cadence (number of steps per minute), stride length (meter), stride time (second), as well as the coefficient of variation ( $CV = (\text{standard deviation}/\text{mean}) * 100$ ) were averaged over the 5 walking trials. Based on previous findings, we have a sufficient number of steps for each trial to present gait variability (average number of steps:  $103.03 \pm 9.42$  [13]). Relative concentration changes of HbO<sub>2</sub> and HbR ( $\Delta\text{HbO}_2$  and  $\Delta\text{HbR}$  in  $\mu\text{mol/L}$ ) in the DLPFC were measured using a wireless continuous waves fNIRS device (NIRSport, NIRx Medical Technologies).

## NIRS measurements

Test re-test reliability of the fNIRS measurement of DLPFC activity within the group of patients was conducted between two sessions (T0 and T1) with an interval of five weeks, which corresponds to the duration of the training program.

Fourteen optodes, corresponding to the 8 sources and 6 detectors separated by approximately 30 mm, were placed on the DLPFC according to the modified international EEG 10-10 system. Two short separation channels (channels 9 and 10, see figure 1.B.) with an interoptode distance of 15 mm were used in order to account for peripheral tissue signals. Raw intensities were recorded using the software provided by the manufacturer (NIRStar, version 15.1 and 15.2).

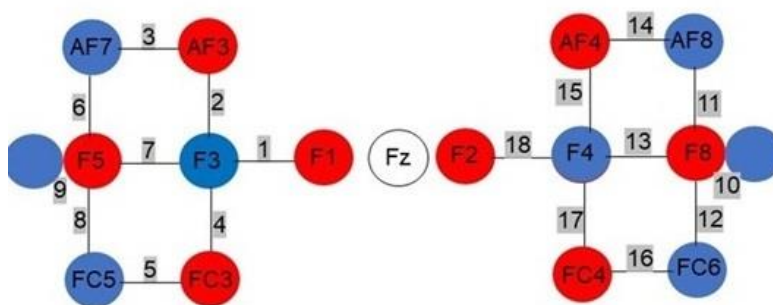
## Data processing

The data were analyzed using the open-access software Homer 2 within MATLAB (R2019b, Mathworks). Recommendations and good practices were followed according to recent guidelines [12,14]. The first processing step was to convert raw data into optical density. Then, a low pass filter with a cut-off of 0.1 Hz was applied to attenuate respiration and cardiac activity and high frequency noise [15]. The next step was a motion artifact correction using wavelet-based filters ( $iqr = 1.5$ ) [16,17]. After motion correction, optical density was converted into  $\Delta HbO_2$  and  $\Delta HbR$  using the modified Beer-Lambert law with constant differential path length factors values of 6 [18]. Finally, contribution of short separation channels was removed from the signal using a Kalman filter dynamic estimator [19]. Using the block average method, mean amplitude difference of  $\Delta HbO_2$  and  $\Delta HbR$  for each channel was obtained using the last 5 seconds of the resting state before each trial and 30 seconds after the “start” instruction. Signal quality of each channel was visually checked to ensure divergence between the  $HbO_2$  and  $HbR$  traces [2] and extreme values were detected using the box-plot method. When the number of

extreme values were inferior to 2 (< 15%) for a channel, values were replaced by mean values of the group for this channel. Otherwise, the channel was removed for all participants. No channel was removed. At T0, 2 participants had extreme values for HbO<sub>2</sub>: for 1 participant, 4 channels were suppressed and removed by the mean values (C12 C15 C17 C18). For another one, 1 channel (C16) has also been removed by the mean values. At T1, 3 participants had extreme values for HbO<sub>2</sub>. Two participants had 2 channels suppressed and replaced by the mean value (C12 C16; C4 C8, respectively) and 1 participant had 1 channel suppressed and replaced by the mean value (C8).

Test-retest reliability has been explored for mean  $\Delta\text{HbO}_2$ , known to be relatively robust against motion artefacts [20], and also due to its sensitivity for walking [1]. Although no test-retest reliability was done for mean  $\Delta\text{HbR}$ , values were reported. Signals from channels were averaged by hemisphere and over the PFC (left: channels 1 – 8; right: 11 - 18) (Figure1), in line with previous research [21].

*Please, insert Figure 1 here*



## Statistical analysis

Walking performance was compared with ANOVA for repeated measures with session (T0 and T1) as within-subject factor. Reproducibility of walking performance was assessed using Pearson's correlation coefficients. To examine the test-retest reliability of PFC activity



measurement between T0 and T1 in patients with PD, three statistical tests assessing different type of reliability were performed: two-tailed paired t-tests, intraclass correlations coefficients, and Bland-Altman plots with 95% of agreement were performed. Two-tailed paired sample t-tests were performed to evaluate differences in mean  $\Delta\text{HbO}_2$  between the two sessions. Single and average measure intraclass correlations coefficients (ICCs, one-way random effect model [7]) for each channel and for each ROI (total, left and right DLPFC) were calculated. Acceptance ratings for ICCs were set at excellent ( $>0.75$ ), moderate ( $0.40\text{--}0.75$ ), and poor ( $<0.40$ ) agreement [22]. An ICC close to one means that the within-subject variation is low over time. Single measure ICCs deliver information about the reproducibility of a single measure. Average measure ICCs provide information about the reproducibility of the mean of repeated measures [23]. Bland-Altman plots with 95% limits of agreement (95%) was also calculated to visualize the measurement precision of  $\Delta\text{HbO}_2$  values across the sessions [24]. Replicability in time course was investigated by calculating Pearson's correlation coefficients between time series of the averaged  $\Delta\text{HbO}_2$  across the ROI between T0 and T1.

#### *Correlation between walking performance and fNIRS signals*

Pearson's correlation coefficients were calculated between walking performance and mean  $\Delta\text{HbO}_2$  across the ROI in each single session

## Results

### Behavioral data

#### Walking performance

No significant between-sessions changes on gait parameters were found. Pearson correlation coefficients showed significant associations between T0 and T1 for all mean gait parameters, CV of stride time, and CV of cadence (table 1).

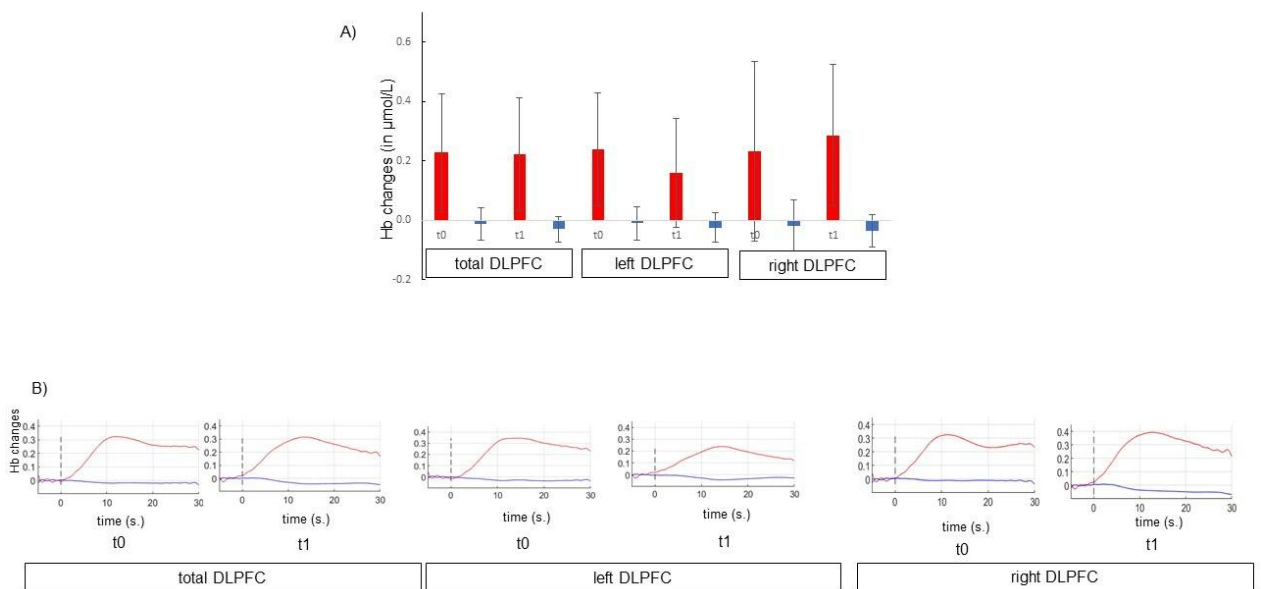
*Please, insert Table 1 here*

### Test-retest reliability at group level

Differences in HbO<sub>2</sub> values between T0 and T1 using two-tailed paired sample t-tests

Figure 2 displays Hb changes for each session and each ROI (total DLPFC, left DLPFC, right DLPFC).

*Please, insert Figure 2 here*



There were no significant differences between mean  $\Delta\text{HbO}_2$  over the two sessions, with very low average difference between the two sessions (Mean difference for the left DLPFC =  $-0.08 \mu\text{mol}$ ,  $p = 0.19$ ; right DLPFC =  $0.05 \mu\text{mol}$ ,  $p = 0.52$ ; total DLPFC =  $-0.005 \mu\text{mol}$ ,  $p = 0.93$ ). Paired sample t-tests were also performed on each channel. Among 14 channels, 3 channels showed significant differences in mean  $\Delta\text{HbO}_2$  between the two sessions (C1, mean difference =  $-0.17$ ,  $p = 0.002$ ; C4, mean difference =  $-0.17$ ,  $p = 0.01$ ; C15 mean difference =  $-0.22$ ,  $p = 0.02$ ).

## Intraclass correlations for $\Delta\text{HbO}_2$

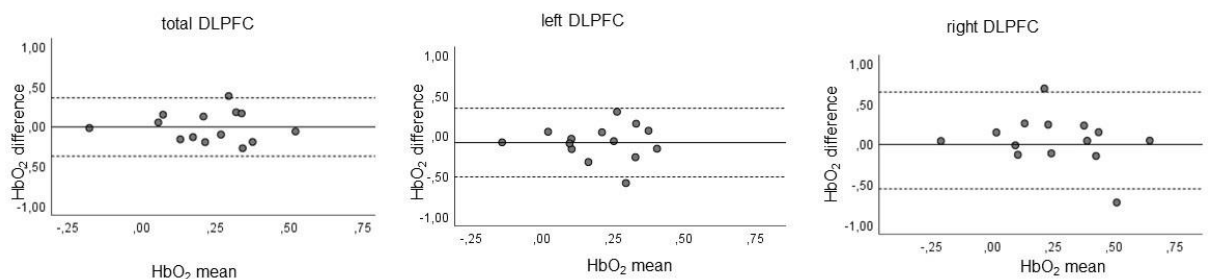
Table 2 shows ICCs for mean  $\Delta\text{HbO}_2$  in the left, right and the total DLPFC at group level for the usual walking. For ICC single, moderate mean values were observed for the association between T0 and T1 for mean  $\Delta\text{HbO}_2$  in the total DLPFC. Poor mean values were found for the association between T0 and T1 for mean  $\Delta\text{HbO}_2$  in the left DLPFC and right DLPFC. For ICC average, moderate mean values were found for mean  $\Delta\text{HbO}_2$  for all associations. Note that for ICC average, there is almost excellent reliability for mean  $\Delta\text{HbO}_2$  in the total DLPFC for the association between the two sessions.

*Please, insert Table 2 here*

## Bland Altman Plot

Figure 3 shows the Bland-Altman plots for  $\Delta\text{HbO}_2$  in the total, left, and right DLPFC.

*Please, insert Figure 3 here*



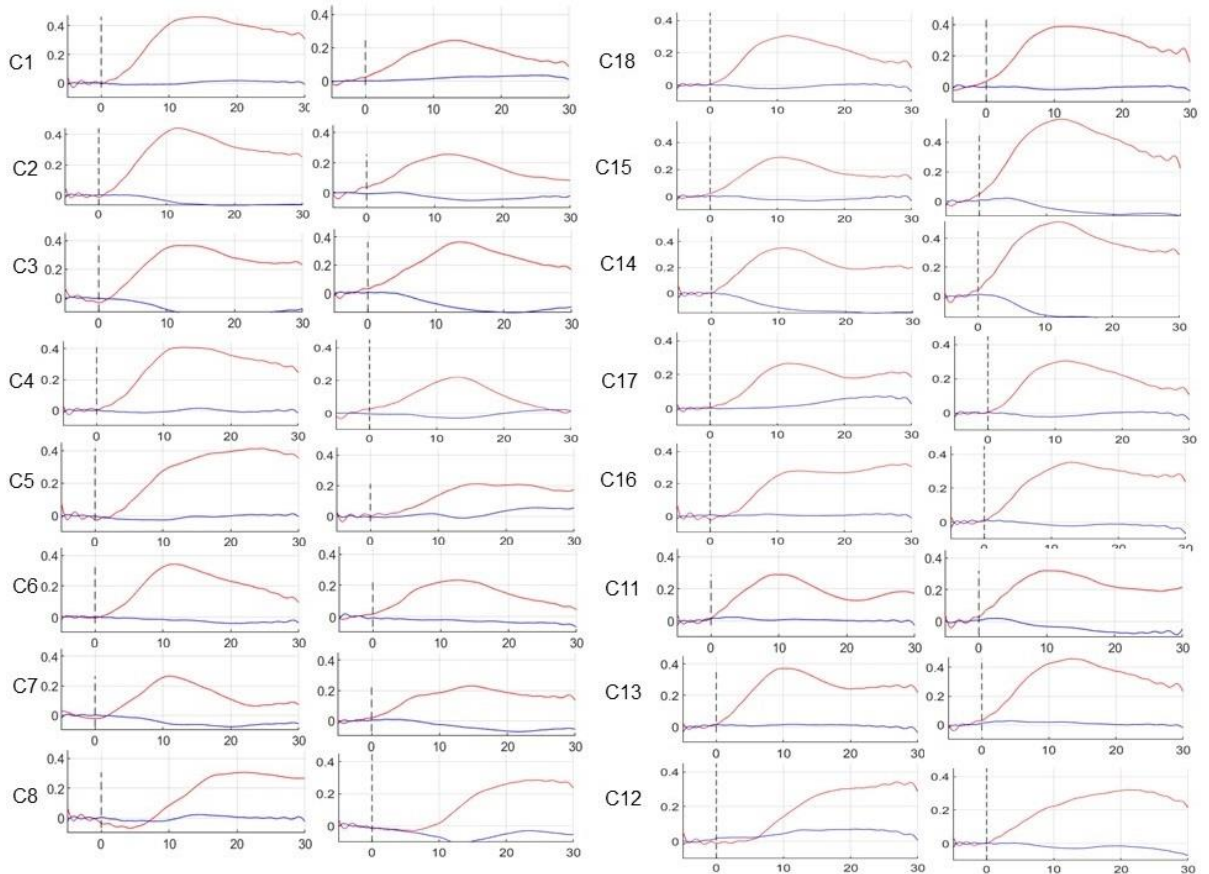
For  $\Delta\text{HbO}_2$ , linear regression showed no proportional bias/mean difference in the results in the left and right DLPFC ( $t = -0.124$ ,  $p = 0.903$ ,  $t = -0.912$ ,  $p = 0.38$ , respectively) and in the total DLPFC ( $t = -0.195$ ,  $p = 0.849$ ).

## Replicability of magnitude activation

Correlation Pearson coefficients are displayed in the table 2. Pearson  $r$  correlations ranged from 0.33 (mean  $\Delta\text{HbO}_2$  in the left DLPFC) to 0.54 (mean  $\Delta\text{HbO}_2$  in the total DLPFC). Significant correlations between  $\Delta\text{HbO}_2$  in the total DLPFC was found between the two

sessions ( $p < 0.05$ ). Figure 4 shows grand average waveforms of hemoglobin concentration (Hb) changes during usual walking across all the subjects for every channel in each session.

*Please, insert Figure 4 here*



#### Correlation between $\Delta\text{HbO}_2$ and walking performance

At T0, no significant correlations were found between  $\Delta\text{HbO}_2$  and all gait parameters (mean and CV) for the right, left and the total DLPFC ( $p > 0.05$ ). At T1,  $\Delta\text{HbO}_2$  in the total DLPFC was negatively correlated with CV of gait cycle time ( $r = -0.56$ ,  $p = 0.04$ ). Moreover,  $\Delta\text{HbO}_2$  in the right DLPFC was negatively correlated with CV of gait cycle time ( $r = -0.64$ ,  $p = 0.02$ ) and CV of cadence ( $r = -0.59$ ,  $p = 0.03$ ).

## Discussion

This study examined the between-session test-retest reliability of cortical activity in the DLPFC during usual walking, as measured by fNIRS. The novelty of this study was to examine whether prefrontal activity is reliable at 5-weeks interval in patients with PD. This interval was much longer than those used in previous studies (~ 5-10 min [2], 24h [11]). This interval has been chosen to compare changes in cortical activity between two sessions (where patients did not change their lifestyle) with those related to the rehabilitation program.

Overall, findings consistently showed moderate test-retest reliability for mean HbO<sub>2</sub> for the total DLPFC. No notable differences for mean values of  $\Delta$ HbO<sub>2</sub> were found between the two sessions. ICC findings showed moderate (almost excellent) reliability (average ICC = 0.72) of the  $\Delta$ HbO<sub>2</sub> signal in the DLPFC, which is consistent with a previous study in young adults that found moderate reliability (ICC = 0.67) of the HbO<sub>2</sub> signal in the PFC during continuous walking and turning tasks [2]. Moreover, strong associations were also observed for mean  $\Delta$ HbO<sub>2</sub> in the total DLPFC between the two sessions.

Between-sessions test-retest reliability for mean  $\Delta$ HbO<sub>2</sub> in both left and right DLPFC was moderate. No notable differences for mean values of  $\Delta$ HbO<sub>2</sub> in both left and right DLPFC were found between the two sessions. However, average ICC shows moderate test-retest reliability for cortical activity in the right PFC whereas poor (almost moderate) test-retest reliability for cortical activity in the left PFC was found. No notable associations between the two sessions were found, which may be partly due to our small sample size. Our results are relatively close to those of Stuart et al. (2019) where participants also perform walking and turning tasks. They also showed a greater heterogeneity between young adults in  $\Delta$ HbO<sub>2</sub> signals in the left DLPFC and in the right DLPFC as compared to  $\Delta$ HbO<sub>2</sub> signals in the total DLPFC [2]. The lower stability of fNIRS signal for each hemisphere compared to the total DLPFC

cannot be due to the lower number of channels used to measure  $\Delta\text{HbO}_2$  in each hemisphere: The cortical activity of the total DLPFC has also an excellent between-session test-retest reliability when it is calculated from 6 channels. The lower stability of cortical activity for each hemisphere may be partly due to the involvement of right and left DLPFC during the usual walking. The left DLPFC is usually involved in executive functions [25] whereas the right DLPFC is involved in spatial working memory [26], self-control and planning [27]. Changes in cortical activity for each hemisphere of the DLPFC between different sessions should therefore be carefully interpreted.

At T1, patients who had an increase of  $\Delta\text{HbO}_2$  in the right hemisphere are those who had a better walking stability (as reflected by a decrease of CV of gait cycle time and cadence), which was not the case for T0. Since walking task is easy to remember, less cognitive resources are needed to perform the usual walking the second time. At the second session, it's possible that patients allocated their cognitive resources, by recruiting the right DLPFC to better improve walking performance. Future studies examining test-retest reliability of fNIRS data during walking should also report behavioral performance in order to better understand  $\text{HbO}_2$  changes that may appear between sessions.

Note that a great heterogeneity was observed in our data suggesting a high interindividual variability in our group of PD patients, which is consistent with previous studies [28,29]. This may be explained by differences in the baseline physiology, cognitive state, motivation and the medication.

At the behavioral level, walking performance was very similar at all time points, which is in line with previous studies showing stable performance over time [8,9]. Strong associations between the two sessions were found for most of gait parameters. A previous study using the same methodology showed that walking performance of patients did not differ from that of controls during usual walking [1], which is in accordance with the literature [21]. However,

patients with PD showed increased prefrontal cortical activity compared to controls, already during usual walking, which is in line with other studies [20,30,31]. These findings suggest that a neurodegenerative disease, such as PD, affects the cortical activity in DLPFC: patients in the early stages need to recruit more resources in the DLPFC during usual walking to compensate for subcortical dysfunction and executive deficits.

### Limitations of the study

Test-retest reliability within the same walking session was not examined in the present study. This could help to better understand learning mechanisms during the walking task. Since PD may affect hemodynamics, future studies should also investigate the test-retest reliability of other additional measures, such as regional cortical activation ratio, the tissue oxygenation index, previously mentioned in a literature review [14]. The removal and replacement of the probe could also affect the between-session test-retest reliability [32], which needs to be further investigated.

## Conclusions

Findings suggest that fNIRS may be used as a reliable tool for rehabilitation studies in patients with PD. Moderate, almost excellent between-session test-retest reliability was shown for mean  $\Delta\text{HbO}_2$  of the total DLPFC. Although the  $\Delta\text{HbO}_2$  signal for each hemisphere was found reliable between sessions, the between-session test-retest reliability was poorer, suggesting more caution with interpretation. Further studies investigating test-retest reliability of fNIRS data over time during walking are warranted.

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**Contributors:** LPF MR conceived and designed the study. IH LPF MR RD contributed to data collection. IH LPF MR RD contributed to data analysis and interpretation. IH LPF RD contributed to the critical revision for important intellectual content. MR wrote the first draft.



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Table 1. Gait performance of PD patients during usual walking for each session

		T0	T1	Pearson correlation
Speed, m/sec.	Mean	1.06 ± 0.20	1.07 ± 0.24	0.91***
	CV	8.42 ± 1.39	8.83 ± 1.60	0.46
Cadence, steps/minute.	Mean	103.03 ± 9.42	103.51 ± 11.07	0.88***
	CV	3.62 ± 0.82	3.84 ± 1.00	0.58*
Stride length, m.	Mean	1.22 ± 0.20	1.23 ± 0.23	0.94***
	CV	7.20 ± 1.32	7.67 ± 1.43	0.33
Stride time, sec.	Mean	1.18 ± 0.12	1.17 ± 0.13	0.87***
	CV	3.71 ± 0.97	3.68 ± 0.85	0.62*

\*P<0.05 \*\*P<0.01 \*\*\*P<0.001

Table 2: Intraclass correlation coefficients (ICC) and Pearson correlations of mean  $\Delta\text{HbO}_2$  in the total, left, and right DLPFC during usual walking between two sessions

$\Delta\text{HbO}_2$ during usual walking	Single measure	Average measure	Pearson correlation
Total DLPFC <sup>a</sup>	0.566 (0.09 - 0.835, 25%)	0.723 (0.164 - 0.910, 63%)	0.541*
Left DLPFC	0.297 (-0.240 - 0.701, 13%)	0.458 (-0.631 - 0.824, 50%)	0.325
Right DLPFC	0.377 (-0.153 - 0.744, 38%)	0.548 (-0.362 - 0.853, 75%)	0.370

Mean, range, percentage of channels with ICC > 0.5

<sup>a</sup>Note that test-retest reliability of  $\Delta\text{HbO}_2$  in the total DLPFC was moderate to excellent when  $\Delta\text{HbO}_2$  in the total DLPFC was calculated from 6 channels (3 channels in the right hemisphere and 3 in the left hemisphere) instead of 12 channels (single ICC = 0.68; average ICC = 0.81) meaning that the number of channels did not influence results

Figure 1.A) Walking path configuration B) Optode configuration with respect to the Fz locations of the international 10-10 system.

B) Red circles represent the sources and blue circles represent the detectors. The numbers in gray represent the channels. Channels 9 and 10 represent the short separation channels.

Figure 2. A) Mean  $\Delta\text{HbO}_2$  and mean  $\Delta\text{HbR}$  for each session in 14 patients. B) Averaged time courses of  $\text{HbO}_2$  and  $\text{HbR}$  during usual walking in the total DLPFC, the left DLPFC and the right DLPFC for each session.

A) Red bars represent  $\Delta\text{HbO}_2$  and blue bars represent  $\Delta\text{HbR}$ . B)  $\Delta\text{HbO}_2$  and  $\Delta\text{HbR}$  were colored in red and blue, respectively. Vertical dashed lines indicate start of the task.

Figure 3. Bland-Altman plots for  $\Delta\text{HbO}_2$  for each ROI

The solid lines represent the mean difference of  $\Delta\text{HbO}_2$  values between the two sessions and dashed lines represent limits of agreement

Figure 4: Grand average waveforms of hemoglobin concentration (Hb) changes during usual walking across all the subjects for every channel in each session.

For each channel, T0 is displayed on the left and T1 on the right.  $\Delta\text{HbO}_2$  and  $\Delta\text{HbR}$  were colored in red and blue, respectively. Vertical dashed lines indicate start of the task.