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Functional near-infrared spectroscopy measures of frontal hemodynamic responses in Parkinson's patients and controls performing the Timed-Up-and-Go test

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ABSTRACT

Using functional near-infrared spectroscopy (fNIRS), hemodynamic responses (i.e., changes in oxygenated and deoxygenated hemoglobin) were measured while participants with Parkinson's disease (PD) and healthy controls performed the Timed-Up-and-Go test (TUGT), and differences in cortical activity at baseline and three different intervals were examined between the two groups. Seventeen PD patients and twenty-two controls participated in the study, but two PD patients were excluded from statistical analysis due to the presence of freezing of gait and using walking aids during the TUGT. During the TUGT, activity in the front, left, right and total frontal cortices initially decreased significantly, then significantly increased in PD participants and low-risk faller PD participants, compared to when in a sitting position. ΔHbO (HbO change from baseline) over the front, left and total frontal cortices in the PD group was significantly lower than the control group in interval 1 ($P = 0.019$, $P = 0.014$ and $P = 0.031$, respectively), while significantly higher than the control group in interval 2 over the left frontal cortex ($P = 0.010$). No significant differences were observed between the high-risk faller and low-risk faller subgroups of PD participants in ΔHbO and ΔHbR in the three intervals ($P > 0.05$). In the high-risk faller subgroup, ΔHbO over the left frontal cortex was significantly higher than the right frontal cortex in interval 2 and interval 3 ($P = 0.015$, $P = 0.030$, respectively). There was a strong positive correlation between education and HbR concentration over the right frontal cortex in PD participants (rho = 0.557, $P = 0.031$), while there were strong negative correlations between PD duration and HbR concentration over the right and total frontal cortices in the high-risk faller subgroup of PD participants (rho = −0.854, $P = 0.014$ for the right; rho = −0.784, $P = 0.037$ for the total). The falls prediction cutoff TUGT time for PD participants was 14.2 s. These results suggest that frontal cognition training, along with exercise training, could be used as an effective training method to improve motor performance in PD patients, especially for those at high-risk for falls.

1. Introduction

The Timed-Up-and-Go test (TUGT) is a useful, reliable and valid tool [1] used to assess dynamic balance, mobility, and fall risk in patients with Parkinson's disease (PD) [1–3] as well as in older populations [4]. The TUGT might be a prodromal marker for the risk of PD development

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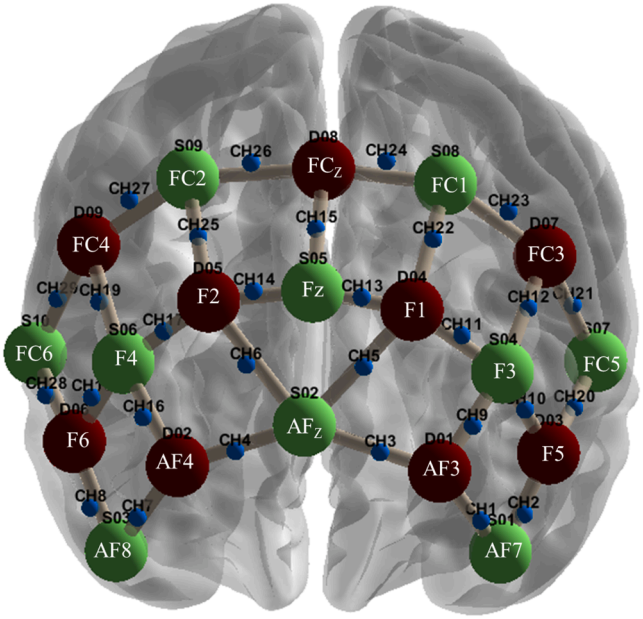

Fig. 1. The fNIRS optode locations with the ICBM-152 template. The green dots represent sources, while dark red dots represent detectors. The CH1–CH29 represent 29 channels.

[5], and can even predict falls in PD patients [6–8]. Recent studies using functional magnetic resonance imaging (fMRI) in PD have found that TUGT performance scores were correlated with some neuronal outcome measures of brain network characteristics [9–11]. However, resting-state fMRI assesses brain activity only at rest not during ankle movements [9,10]. The task-based fMRI design is used in the case of ankle movements [11], or using virtual-reality walking tasks [12–14], rather than in a real walking or functional task such as the TUGT.

Functional near-infrared spectroscopy (fNIRS) is a brain-imaging technique that provides non-invasive, long-term measurements of cortical hemodynamic responses (i.e., changes in oxygenated and deoxygenated hemoglobin) in natural situations, even during movement [15]. Stuart et al.[16] pointed out in a systematic review that performing the TUGT increased frontal and central cortical activity in PD patients, but few studies have reported associations between cortical outcomes and behavioral data [17]. Maidan et al. [17] found that PD patients without freezing of gait (FOG) had greater activation of the frontal cortex during turning, while there was relative inactivation during walking, especially in those PD patients with the worst ambulation (<1 m/sec speed) who had greater activation of the prefrontal cortex during turning, but this research did not focus on functional tasks that combined walking and turning (e.g. TUGT).

In the present research, using fNIRS, we measured hemodynamic responses in the frontal cortex during performance of the TUGT in PD and control participants. The aims were: (1) to determine whether frontal cortex hemodynamic response changed significantly during TUGT in PD participants; (2) to examine any differences in the frontal cortex hemodynamic response during TUGT between PD and control participants; (3) to assess the correlation between frontal cortex hemodynamic response and TUGT time in PD and control participants.

2. Materials and methods

The research was approved by the Scientific Research Ethics Committee of Shanghai University of Sport (Approval number:102772019RT068) and Jinhua Polytechnic Approval number:20190523). The study protocol was prospectively registered in the Chinese Clinical Trial Registry (www.chictr.org.cn, registration No. ChiCTR2000038852). All participants gave informed, written consent prior to participation.

2.1. Participants

Two groups were recruited; people diagnosed with PD, and an age-comparable healthy group. Inclusion criteria were (a) age between 40 and 80 years old; (b) no known neurological conditions other than PD; (c) able to walk safely and continuously for at least 30 m. Participants in the PD group were included if they were: (a) diagnosed with idiopathic PD more than 6 months; (b) scored at 1–4 on the Modified Hoehn and Yahr (H&Y) staging scale; (c) on stable medications for the past month. Participants were excluded if they had a history of brain surgery, stroke, heart disease, dementia, psychiatric comorbidity, clinically significant traumatic brain injury, or any orthopedic problems that may affect their

Table 1
Demographic characteristics of included participants.

Characteristics	PD patients (n = 15)	Healthy adults (n = 22)	P
Age (years)	67.99 ± 10.83	63.38 ± 8.53	0.191[a]
Sex (male/female)	10/5	7/15	
Handedness	right	right	
Education	8.60 ± 6.38	9.64 ± 3.79	0.867[a]
MMSE	27.13 ± 1.03	29.23 ± 0.61	**0.002**[a]
Disease duration (years)	6.04 ± 5.16	NA	
Modified H&Y stage	1.87 ± 0.97	NA	
1-no. (%)	6(40.00)		
1.5-no. (%)	2(13.33)		
2-no. (%)	3(20.00)		
3-no. (%)	3(20.00)		
4-no. (%)	1(6.67)		
Levodopa dosage (mg)	506.67 ± 283.39	NA	
FOGQ	9.67 ± 7.84	NA	
UPDRS III	14.27 ± 8.21	NA	
TUGT	15.22 ± 5.40	9.64 ± 1.50	**< 0.001**[a]

Abbreviations: FOGQ, Freezing of Gait Questionnaire; UPDRS, Unified Parkinson's Disease Rating Scale; NA, not available. Plus–minus values are means ± SD.

[a] Mann-Whitney *U* Test, results are presented as mean ± SD.

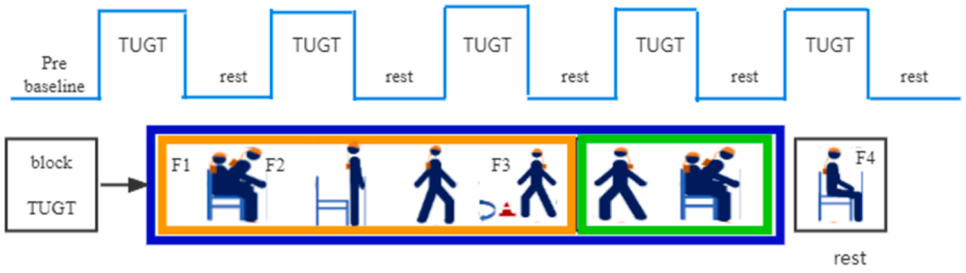

Fig. 2. Schematic overview of the fNIRS measurement. Baseline measurements during quiet sitting were conducted before the experiment. The orange box represents interval 1, the green box interval 2, and the blue box interval 3 (the entire TUGT).

Table 2
HbO and HbR difference (μmol) between different TUGT periods within the PD and control groups.

		HbO/HbR Mean value (μmol/L) (Mean±SD)				Within-Subjects Effects			
		INVL0	INVL1	INVL2	INVL3	df	F	P	η_P^2
PD group (n = 15)									
HbO	Front	-0.024 ± 0.277	-0.243 ± 0.417	0.298 ± 0.333	0.028 ± 0.197	1.809,25.332	7.126	**0.004**	0.337
	Left	-0.047 ± 0.256	-0.326 ± 0.370	0.354 ± 0.392	0.014 ± 0.180	1.547,23.848	11.536	**0.001**	0.452
	Right	-0.079 ± 0.176	-0.275 ± 0.380	0.276 ± 0.317	0.001 ± 0.184	1.602,22.435	9.909	**0.002**	0.414
	Total	0.000 ± 0.308	-0.300 ± 0.361	0.315 ± 0.344	0.007 ± 0.174	1.882,26.342	9.245	**0.001**	0.398
HbR	Front	-0.006 ± 0.042	0.030 ± 0.085	-0.038 ± 0.096	-0.004 ± 0.054	1.499,20.984	2.529	0.115	0.153
	Left	0.009 ± 0.012	0.016 ± 0.077	-0.009 ± 0.074	0.003 ± 0.056	1.723,24.118	0.657	0.505	0.045
	Right	0.008 ± 0.037	0.005 ± 0.086	-0.038 ± 0.068	-0.016 ± 0.052	1.768,24.756	2.072	0.151	0.129
	Total	0.009 ± 0.008	0.010 ± 0.076	-0.023 ± 0.069	-0.007 ± 0.051	1.662,23.262	1.494	0.244	0.096
Control group (n = 22)									
HbO	Front	-0.086 ± 0.254	0.015 ± 0.153	-0.013 ± 0.177	0.001 ± 0.110	1.903,39.953	1.726	0.192	0.076
	Left	-0.031 ± 0.263	-0.015 ± 0.157	-0.054 ± 0.111	-0.022 ± 0.091	1.793,37.659	0.259	0.749	0.012
	Right	-0.060 ± 0.260	-0.065 ± 0.194	0.014 ± 0.176	-0.013 ± 0.126	2.042,42.880	1.026	0.368	0.047
	Total	-0.028 ± 0.273	-0.041 ± 0.158	-0.007 ± 0.163	-0.018 ± 0.098	1.916,40.239	0.177	0.830	0.008
HbR	Front	0.001 ± 0.111	0.006 ± 0.068	0.016 ± 0.057	0.011 ± 0.032	1.771,37.197	0.165	0.823	0.008
	Left	0.020 ± 0.076	-0.003 ± 0.071	0.029 ± 0.040	0.013 ± 0.030	1.947,40.887	1.229	0.302	0.055
	Right	-0.002 ± 0.082	0.016 ± 0.029	0.007 ± 0.043	0.001 ± 0.032	1.543,32.397	0.591	0.517	0.027
	Total	0.001 ± 0.084	-0.003 ± 0.062	0.019 ± 0.037	0.007 ± 0.029	1.932,40.569	0.659	0.518	0.030

Abbreviation: INVL- interval, the same in Tables 3, 4, and 6.

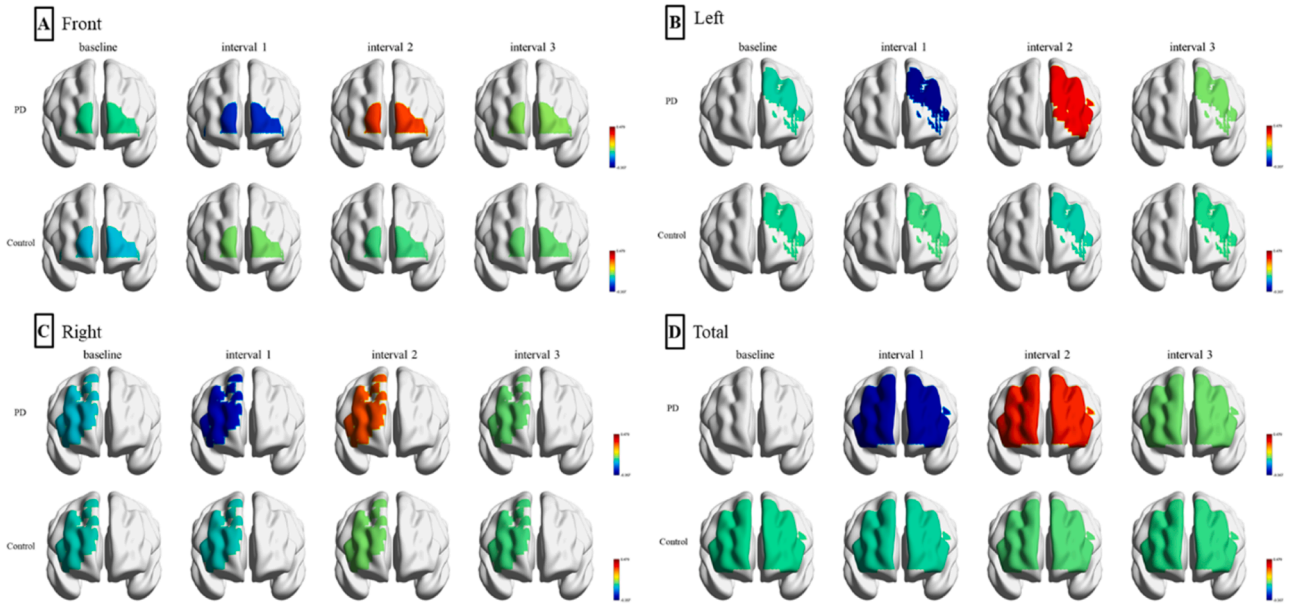

Fig. 3. Brain topographic map showing mean HbO concentration in different TUGT periods over the front, left, right and total frontal cortices in the PD and control groups. The color bar indicates the HbO concentration from −0.357 to 0.479 μmol/L, −0.357 at the bottom and 0.479 at the top are the minimum and maximum HbO values, respectively, in all situations (four groups or subgroups, four frontal cortices, and four TUGT periods) in this study.

gait, or visual disturbance that affected walking.

PD participants were recruited from Xinhua Hospital affiliated with the Shanghai Jiaotong University School of Medicine in Shanghai City, and Jinhua Hospital of Traditional Chinese Medicine in Zhejiang Province.

2.2. Procedure

For characterization of the PD participants, the unified Parkinson's disease rating scale (UPDRS) III and Chinese version of the Freezing of Gait Questionnaire (FOGQ-CH) [18] were used to evaluate motor function and perceived FOG status. The TUGT was conducted in a quiet room in the hospital facility, without distraction or interruption. Before the formal test, participants were asked to practice the TUGT twice to ensure that they could complete the task. TUGT time and cortical hemodynamic response changes were evaluated synchronously while participants performed the TUGT. All PD patients were assessed during the "ON" state, which was about 2 h after taking anti-Parkinsonian medication.

2.3. fNIRS data measurements and pre-processing

Cortical hemodynamic response changes during the TUGT were assessed using a wireless, portable, continuous-wave NIRSport2 16–16 fNIRS System (NIRx Medizintechnik GmbH, Berlin, Germany) with silicon photodiodes as detectors and operating with simultaneous frequency-encoded dual-wavelength illumination at 760 and 850 nm. According to the international electroencephalogram (EEG) 10/20 system, there is a 29-channel array of optodes (10 light sources and 9 detectors) with source–detector distances of 30 mm approximately covering the frontal cortex (see Fig. 1).

During the fNIRS measurement, all participants were asked to finish

Table 3
Pairwise comparisons of HbO (μmol) between different TUGT periods within the PD group.

Region	(I) Period	(J) Period	(I-J) Mean Difference Mean (SE)	P-value	95%CI
Front	INVL2	INVL0	0.322(0.125)	0.133	-0.062–0.706
	INVL2	INVL1	0.541(0.166)	**0.034**	0.032–1.050
	INVL2	INVL3	0.271(0.083)	**0.034**	0.016–0.525
	INVL3	INVL1	0.271(0.083)	**0.034**	0.016–0.525
	INVL3	INVL0	0.052(0.097)	1.000	-0.246–0.349
	INVL1	INVL0	-0.219(0.130)	0.686	-0.618–0.180
Left	INVL2	INVL0	0.401(0.136)	0.064	-0.016–0.819
	INVL2	INVL1	0.680(0.173)	**0.009**	0.148–1.211
	INVL2	INVL3	0.340(0.087)	**0.009**	0.074–0.606
	INVL3	INVL1	0.340(0.087)	**0.009**	0.074–0.606
	INVL3	INVL0	0.061(0.084)	1.000	-0.195–0.318
	INVL1	INVL0	-0.278(0.102)	0.099	-0.592–0.036
Right	INVL2	INVL0	0.355(0.104)	**0.025**	0.036–0.674
	INVL2	INVL1	0.550(0.154)	**0.018**	0.079–1.022
	INVL2	INVL3	0.275(0.077)	**0.018**	0.039–0.511
	INVL3	INVL1	0.275(0.077)	**0.018**	0.039–0.511
	INVL3	INVL0	0.080(0.073)	1.000	-0.143–0.303
	INVL1	INVL0	-0.195(0.108)	0.544	-0.526–0.135
Total	INVL2	INVL0	0.315(0.137)	0.221	-0.104–0.734
	INVL2	INVL1	0.615(0.158)	**0.010**	0.129–1.101
	INVL2	INVL3	0.307(0.079)	**0.010**	0.064–0.551
	INVL3	INVL1	0.307(0.079)	**0.010**	0.064–0.551
	INVL3	INVL0	0.007(0.103)	1.000	-0.308–0.323
	INVL1	INVL0	-0.300(0.123)	0.169	-0.676–0.076

five blocks according to the protocol, each block including rising from a chair, walking 3 m, turning around, walking backward, and sitting down; with the blocks interspersed by 40-second rest periods to allow the TUGT-induced hemodynamic responses to return toward baseline levels (**see** Fig. 2). The sampling rate for measurement was 8.36 Hz. The F1-F4 markers were manually set by key-press using the Aurora fNIRS Acquisition Software, with F1 marked at the 40th second of quiet sitting (fNIRS signal stabilization); F2 marked at the moment of rising from the chair along with the instruction, about 40 s after F1; while F3 and F4 were marked at the moment of turning to face the chair, and at the end of sitting down, respectively (**see** Fig. 2).

The fNIRS data were pre-processed using the Homer2 toolbox of the MATLAB software package (v2014.05; NIRx Medical Technologies LLC, 15 Cherry Lane, Glen Head, NY, USA). The pre-processing steps followed the current recommendations for fNIRS studies [19]. The HbO and HbR signals were corrected using a bandpass filter (0.01–0.2 Hz) and correlation was based on the signal improvement (CBSI) method. The major concerns for fNIRS data quality are physiological oscillations in the frequency band from 0.005 to 0.2 Hz [20]; however, the frequency of Mayer waves (MW) is around 0.1 Hz [21,22], which are also observed in cerebral oxygenation levels [23]. Although MW contributed to the changes in the HbO signal [20], if the bandpass filter method were to be used to filter out the signal components around 0.1 Hz, part of the brain's functional response activity components could be eliminated, so the filtering of the interference components at about 0.1 Hz must be carefully treated. In addition, we found in other similar studies, most of the physiological disturbances around 0.1 Hz were not treated separately [22]. We also found that brain functional activity information could be better extracted from fNIRS signals without processing the 0.1 Hz physiological disturbance. Therefore, in this research, a 4th order Butterworth band-pass filter with cutoff frequencies of 0.01 Hz and 0.2 Hz was used in accordance with relevant literature [24]. In addition, the CBSI method was adopted for motion artifact removal from fNIRS signals [25].

In the fNIRS signal extraction, there were four periods: baseline, interval 1, interval 2 and interval 3 (see Fig. 2). The baseline referred the period from 12.5 s after F1 to F2, lasting for 27.5 s, interval 1 referred to the period between F2 and F3, interval 2 referred to the period between F3 and F4, and interval 3 referred to the period between F2 to F4 (see Fig. 2). Mean HbO and HbR values for the front (channel 1–9, 16), left (channel 1–3, 5, 9–13, 15, 20–24), right (channel 4, 6–8, 14, 16–19, 25–29) and total (29 channels) frontal cortices were computed from 5 blocks in each period, where the channels in the left and right frontal cortices were divided according to Montreal Neurological Institute (MNI) coordinates.

2.4. Brain topographic map making

The current standard MNI brain template we use is the ICBM (International Consortium for Brain Mapping)− 152, which is the average of 152 normal MRI scans that have been matched to the MNI-305 using a 9-parameter-affine-transform[26]. We used the template ICBM-152 as the standard template for the projection of brain topographic maps and location of light sources and detectors.

The BrainNet View toolbox was used to create the task brain activation topographic map. During the drawing process, the NIRS-SPM toolbox was used to convert the actual coordinates of fNIRS measurement channels to MNI coordinates, and the HbO activation were assigned to each channel. Projection of brain topographic maps was used to draw the brain activation topographic maps under different task states by BrainNet View toolbox.

2.5. Statistical analysis

Statistical analysis was performed using SPSS software version 25. Data were tested for normality using the Shapiro-Wilk test. An independent-samples *t*-test (two-tailed) or Mann-Whitney U test was used to compare the demographic measures between the PD and control groups, or high-risk fall and low-risk fall PD subgroups, for normality and non-normality of data, respectively. For HbO and HbR change analyses, within-group comparisons were analyzed using the general linear model (GLM)-repeated measures analysis of variance with intervals as the repeated-measures factor, while between-group comparisons from baseline were analyzed using a GLM-repeated measures analysis of covariance, with groups and intervals as factors and baseline value as a covariate. Levodopa dosage was also a covariate in the between-subgroup comparisons of the PD participants, and left-right comparison was analyzed using the paired-samples *t*-test. Pearson or Spearman's correlation was used to assess any potential association between HbO/HbR concentration and relevant variables (including TUGT time, disease duration, modified H&Y stage, FOGQ, UPDRS III, MMSE and education). The significance level was set at $P < 0.05$, and the Bonferroni correction was applied to the statistical results in all the variables to reduce type I errors from multiple comparisons.

3. Results

3.1. Participants

The thirty-nine participants included 17 PD patients and 22 healthy age-matched controls. Subsequently, two PD patients presented with FOG during the TUGT task, including one with a walking aid, and these two PD patients were excluded from the statistical analysis. Table 1 shows the demographic characteristics of thirty-seven study subjects. There were no significant differences in age and education between two groups. However, MMSE in the PD group was significantly lower than the control groups ($P = 0.002$). No falls occurred during the assessment.

3.2. TUGT time

The TUGT time was significantly higher in the PD group (mean, 15.22 s; standard deviation [SD]: 5.40) compared with the control group (mean, 9.64 s; standard deviation [SD]: 1.50) using the Mann-Whitney U Test ($P < 0.001$).

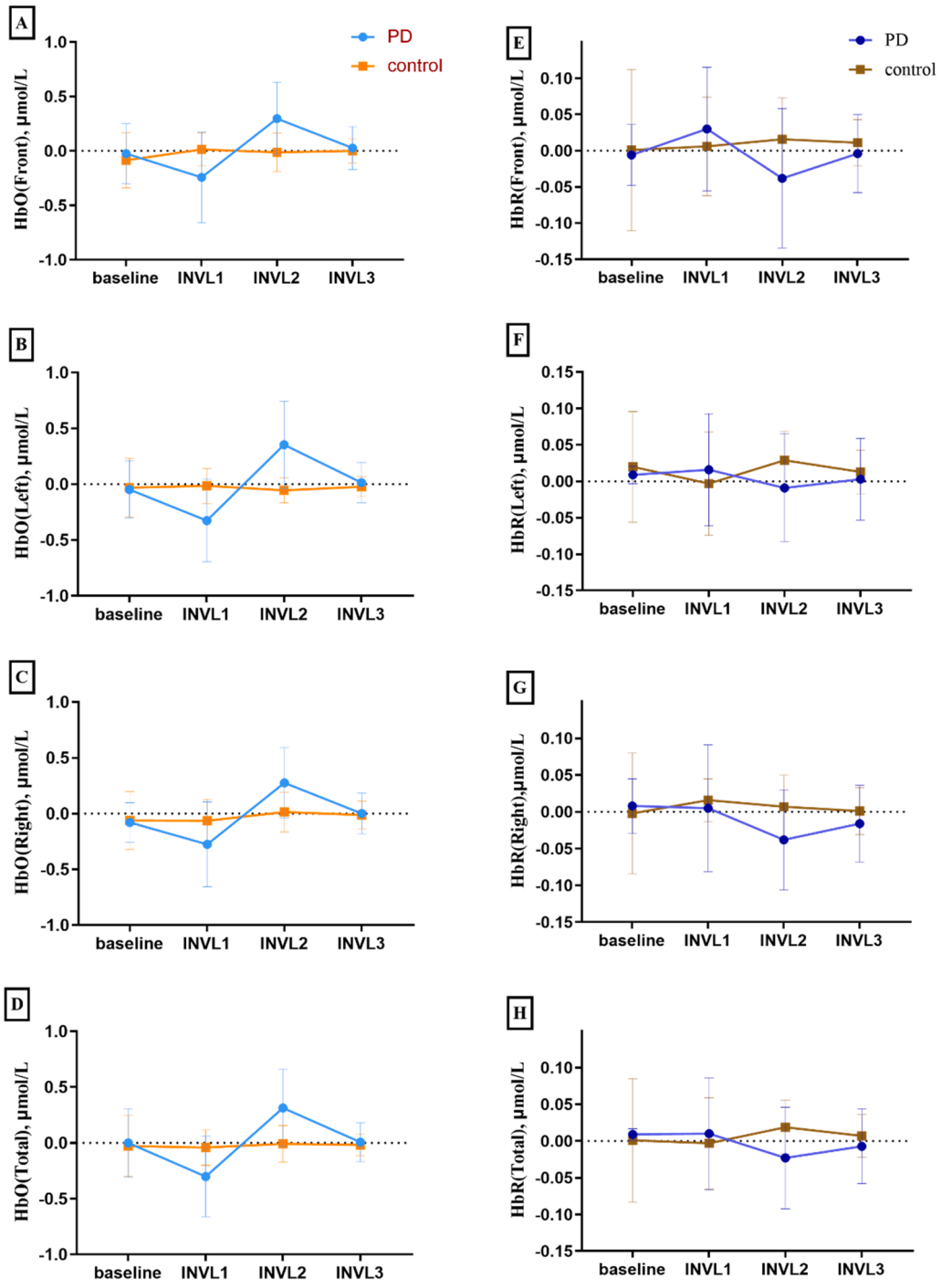

Fig. 4. Mean HbO and HbR concentration in four periods over the front, left, right and total frontal cortices within the PD and control groups.

According to the presence or absence of falls, PD participants were divided into fall and non-fall subgroups. With one or more falls designated as positive, after receiver operating characteristic (ROC) analysis, the area under the ROC curve (AUC) was 0.864 ($p = 0.037$) for TUGT times, and the cutoff point for predicting falls in PD participants was 14.2 s. The sensitivity, specificity, and positive likelihood ratios were 100%, 72.7%, and 3.66, respectively.

3.3. Hemodynamic changes in PD and control groups

3.3.1. Within-group comparisons

In the PD group, one-way repeated measures analysis of variance indicated that HbO in different periods was significantly different over the front, left, right and total frontal cortices (see Table 2, Fig. 3). Additional pairwise comparisons found HbO significantly and sequentially decreased in interval 2, interval 3, baseline and interval 1 (See Table 3; Fig. 4A, B, C, D). While HbR in different periods was not significantly different over these four frontal cortices within the PD group (see Table 2; Fig. 4E, F, G, H). There were also no significant differences in HbO and HbR over these four cortices within the control group (see Table 2; Figs. 3, 4).

3.3.2. Between-group comparisons

At the baseline, there were no significant differences in HbO and HbR

Table 4
HbO Difference (μmol/L) in four cortexs between PD and control groups.

	PD group (n = 15) ΔHbO, Mean (SE)	Control group (n = 22) ΔHbO, Mean (SE)	Mean difference (95% CI)	P Value
Front				
INVL1	-0.219 ± 0.130	0.102 ± 0.061	-0.321(−0.585 to −0.057)	**0.019**
INVL2	0.322 ± 0.125	0.073 ± 0.059	0.249(−0.039 to 0.537)	0.087
INVL3	0.052 ± 0.097	0.087 ± 0.054	-0.036(−0.245 t0 0.173)	0.730
Left				
INVL1	-0.278 ± 0.102	0.015(0.063)	-0.294(−0.524 to −0.063)	**0.014**
INVL2	0.401 ± 0.136	-0.023(0.058)	0.425(0.115–0.734)	**0.010**
INVL3	0.061 ± 0.084	0.008(0.051)	0.053(−0.135 to 0.241)	0.570
Right				
INVL1	-0.195 ± 0.108	-0.005(0.067)	-0.191(−0.434 to 0.053)	0.121
INVL2	0.355 ± 0.104	0.074(0.060)	0.281(0.053–0.509)	**0.017**
INVL3	0.080 ± 0.073	0.046(0.051)	0.033(−0.142 to 0.208)	0.702
Total				
INVL1	-0.300 ± 0.123	-0.013(0.064)	-0.287(−0.546 to −0.028)	**0.031**
INVL2	0.315 ± 0.137	0.021(0.055)	0.294(−0.015 to 0.602)	0.061
INVL3	0.007 ± 0.103	0.010(0.052)	-0.003(−0.216 to 0.210)	0.978

ΔHbO: HbO change from baseline; SE: Standard Error Mean.

Table 5
Demographic characteristics of PD participants with high-risk and low-risk faller.

Characteristics	High-risk faller (n = 7)	Low-risk faller (n = 8)	P
Age (years)	76.04 ± 5.26	60.94 ± 9.43	**0.002**[a]
Sex (male/female)	5/2	5/3	
Education	9.29 ± 6.80	8.00 ± 6.39	0.712[b]
MMSE	27.29 ± 1.89	27.00 ± 2.27	0.797[b]
Disease duration (years)	9.14 ± 6.15	3.33 ± 1.69	**0.047**[b]
Modified H&Y stage	2.57 ± 0.98	1.25 ± 0.38	**0.009**[a]
1-no. (%)	1(14.29)	5(62.50)	
1.5-no. (%)	0(0.00)	2(25.00)	
2-no. (%)	2(28.57)	1(12.50)	
3-no. (%)	3(42.86)	0(0.00)	
4-no. (%)	1(14.19)	0(0.00)	
Levodopa dosage (mg)	642.86 ± 255.65	387.50 ± 264.24	0.189[a]
UPDRS III	20.29 ± 2.36	9.00 ± 7.87	**0.003**[b]
FOGQ	14.86 ± 7.69	5.13 ± 4.67	**0.010**[b]
TUGT time	18.99 ± 5.69	11.92 ± 1.99	**< 0.001**[a]

[a] Mann-Whitney U test, results are presented as mean ± SD.
[b] Independent-samples *t*-test.

between the PD and control groups over these four cortices (P > 0.05). Two-factor repeated measures analysis of covariance indicated that groups showed no significant main effects in ΔHbO (HbO change from baseline) over the front, left, right and total frontal cortices ($F_{(1, 34)} = 0.286$, $P = 0.596$, $\eta_P^2 = 0.008$ for the front; $F_{(1, 34)} = 1.029$, $P = 0.318$, $\eta_P^2 = 0.029$ for the left; $F_{(1, 34)} = 0.213$, $P = 0.647$, $\eta_P^2 = 0.006$ for the right; $F_{(1, 34)} = 0.432$, $P = 0.516$, $\eta_P^2 = 0.013$ for the total). However, the independent-samples *t*-test indicated that ΔHbO over the front, left and total frontal cortices in the PD group was significantly lower than in the control group in interval 1 (P = 0.019, P = 0.014 and P = 0.031, respectively) (see Table 4), while significantly higher than the control group in interval 2 over the left and right frontal cortices (P = 0.010 and P = 0.017, respectively) (see Table 4). In interval 3, there were no significant differences in ΔHbO between the two groups over these four frontal cortices (P > 0.05) (see Table 4). In addition, no significant differences in ΔHbR (HbR change from baseline) were observed between the two groups over these four frontal cortices in the four intervals (P > 0.05).

3.3.3. Left-right comparisons

At baseline, no significant differences of HbO and HbR were observed between the left and right frontal cortices in both groups. In the PD group, no significant differences of ΔHbO and ΔHbR were observed between the left and right frontal cortices in three intervals (P > 0.05). In the control group, compared with the right frontal cortex, ΔHbR over the left frontal cortex significantly decreased by 0.041 ± 0.019μmol /L(95% CI = −0.081 to −0.001, t = −2.121 , P = 0.046) in interval 1, while there were no significant differences in ΔHbO in three intervals between the left and right frontal cortices.

3.4. Hemodynamic changes in high-risk faller and low-risk faller subgroups

Based on the cutoff point of TUGT (14.2 s) to predict falls in PD patients (see *3.2 TUGT Time*), we divided PD patients into a high-risk faller subgroup (≥14.2 s) and low-risk faller subgroup. Table 5 shows the demographic characteristics of the patients in two subgroups**.** There were significant differences in age, disease duration, modified H&Y stage, unified Parkinson's disease rating scale (UPDRS) III, FOGQ, and TUGT time between the two subgroups. No significant differences were observed in education, Levodopa dosage or MMSE.

3.4.1. Within-subgroup comparisons

In the high-risk faller subgroup, one-way repeated measures analysis of variance indicated that there were no significant differences of HbO and HbR in different periods over these four frontal cortices (see Table 6; Figs. 5; 6); while HbO in different periods was significantly different over the four frontal cortices in the low-risk faller subgroup (see Table 6; Figs. 5; 6A, B, C, D). Further pairwise comparisons showed that there were no significant differences of HbO and HbR in different periods over these four frontal cortices within the two subgroups (P > 0.05).

3.4.2. Between-subgroup comparisons

At the baseline, there were no significant differences in HbO between the high-risk faller and low-risk faller subgroups over these four frontal cortices (P > 0.05). Two-factor repeated measures analysis of covariance indicated no groups main effects in ΔHbO over the front, left, right and total frontal cortices ($F_{(1, 11)} = 1.263$, $P = 0.285$, $\eta_P^2 = 0.103$ for the front; $F_{(1, 11)} = 2.607$, $P = 0.135$, $\eta_P^2 = 0.192$ for the left; $F_{(1, 11)} = 0.177$, $P = 0.682$, $\eta_P^2 = 0.016$ for the right; $F_{(1, 11)} = 0.980$, $P = 0.343$, $\eta_P^2 = 0.082$ for the total).

At baseline, HbR over the left frontal cortex in the high-risk faller subgroup was significantly decreased by 0.016 ± 0.006μmol /L(95% CI = −0.029 to −0.004, t = −2.773 , P = 0.016) compared with the low-risk faller subgroup, while there were no significant differences in HbR over the front, right and total frontal cortices between these two subgroups (P > 0.05). Two-factor repeated measures analysis of covariance indicated no groups main effects in ΔHbR over these four frontal cortices ($F_{(1, 11)} = 0.872$, $P = 0.370$, $\eta_P^2 = 0.073$ for the front; ($F_{(1, 11)} = 3.442$, $P = 0.091$, $\eta_P^2 = 0.238$ for the left; $F_{(1, 11)} = 0.059$, $P = 0.812$, $\eta_P^2 = 0.005$ for the right; $F_{(1, 11)} = 1.181$, $P = 0.300$, $\eta_P^2 = 0.097$ for the total).

3.4.3. Left-right comparisons

At the baseline, no significant differences of HbO and HbR were observed between the left and right frontal cortices in both subgroups. In the high-risk faller subgroup, compared with the right frontal cortex, ΔHbO over the left frontal cortex was significantly increased by 0.250 ± 0.074 μmol /L(95% CI = 0.068–0.432, t = 3.361 , P = 0.015) and

Table 6
HbO and HbR difference (μmol) between different TUGT periods within the high-risk faller and low-risk faller subgroups.

		HbO/HbR Mean value (μmol/L) (Mean±SD)				Within-Subjects Effects			
		INVL0	INVL1	INVL2	INVL3	df	F	P	η_p^2
high-risk faller subgroup (n = 7)									
HbO	Front	-0.059 ± 0.233	-0.027 ± 0.608	0.314 ± 0.393	0.143 ± 0.239	1.501,11.351	1.185	0.332	0.165
	Left	-0.124 ± 0.284	-0.295 ± 0.502	0.479 ± 0.510	0.092 ± 0.184	1.296,7.773	4.494	0.062	0.428
	Right	-0.074 ± 0.242	-0.181 ± 0.410	0.278 ± 0.383	0.049 ± 0.151	1.589,9.537	2.287	0.159	0.276
	Total	-0.099 ± 0.255	-0.238 ± 0.445	0.378 ± 0.443	0.070 ± 0.166	1.429,8.573	3.526	0.086	0.370
HbR	Front	0.004 ± 0.013	-0.009 ± 0.098	-0.057 ± 0.103	-0.033 ± 0.055	1.311,7.866	0.911	0.398	0.132
	Left	-0.001 ± 0.010	-0.028 ± 0.068	-0.038 ± 0.083	-0.013 ± 0.007	1.305,7.828	0.539	0.531	0.082
	Right	0.035 ± 0.083	-0.019 ± 0.081	-0.048 ± 0.084	-0.034 ± 0.043	1.647,9.845	1.657	0.238	0.216
	Total	0.007 ± 0.009	-0.023 ± 0.072	-0.043 ± 0.082	-0.033 ± 0.039	1.234,7.402	1.018	0.365	0.145
low-risk faller subgroup (n = 8)									
HbO	Front	0.064 ± 0.259	-0.256 ± 0.391	0.202 ± 0.306	-0.027 ± 0.297	1.953,13.673	5.404	**0.019**	0.436
	Left	0.020 ± 0.224	-0.353 ± 0.236	0.245 ± 0.235	-0.054 ± 0.157	1.926,13.485	12.170	**0.001**	0.635
	Right	0.153 ± 0.467	-0.357 ± 0.357	0.274 ± 0.274	-0.041 ± 0.209	1.770,12.390	5.029	**0.028**	0.418
	Total	0.087 ± 0.340	-0.355 ± 0.289	0.259 ± 0.248	-0.048 ± 0.172	1.905,13.335	7.445	**0.007**	0.515
HbR	Front	-0.029 ± 0.077	0.046 ± 0.090	-0.108 ± 0.282	-0.031 ± 0.164	1.153,8.073	2.277	0.170	0.245
	Left	0.015 ± 0.012	0.054 ± 0.067	0.016 ± 0.059	0.035 ± 0.052	1.983,13.880	1.694	0.220	0.195
	Right	0.012 ± 0.041	0.026 ± 0.090	-0.029 ± 0.055	-0.001 ± 0.057	1.720,12.040	1.428	0.274	0.169
	Total	0.008 ± 0.009	0.04 ± 0.071	-0.006 ± 0.055	0.017 ± 0.05	1.910,13.370	1.696	0.221	0.195

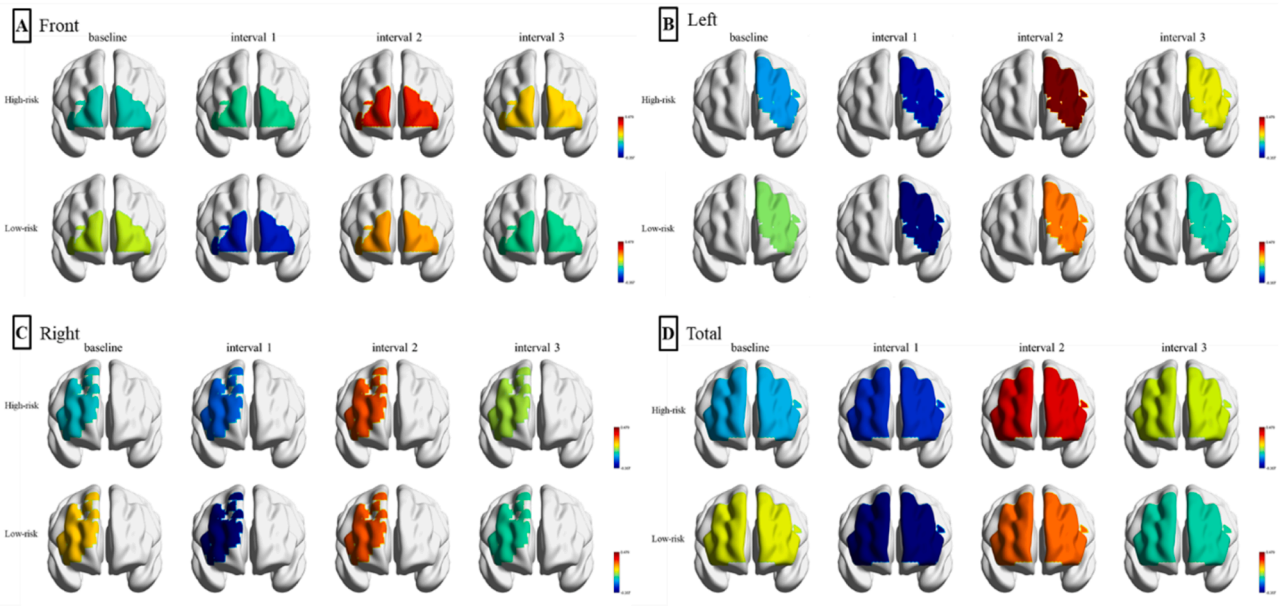

Fig. 5. Brain topographic map showing mean HbO concentration in different TUGT periods over the front, left, right and total frontal cortices in the high-risk faller and low-risk faller subgroups. The color bar indicates the HbO concentration from −0.357 to 0.479 μmol/L, −0.357 at the bottom and 0.479 at the top are the minimum and maximum HbO values, respectively, in all situations (four groups or subgroups, four frontal cortices, and four TUGT periods) in this study.

0.093 ± 0.033 μmol /L(95% CI = 0.012–0.173, t = 2.826 , P = 0.030) in interval 2 and interval 3, respectively, while no significant differences in ΔHbR were observed between the left and right frontal cortices in the three intervals (P > 0.05). In the low-risk faller subgroup, no significant differences in ΔHbO and ΔHbR were observed between the left and right frontal cortex in the three intervals (P > 0.05).

3.5. Correlation between cortical hemodynamic response and relevant variables

A strong correlation was defined as absolute rho value greater than 0.5, and a moderate correlation was defined as absolute rho value between 0.3 and 0.5. There was no significant correlation between cortical hemodynamic response and TUGT, MMSE in both PD patients and healthy control participants. In the PD group, a strong positive correlation between education and HbR over the right frontal cortex was observed (rho = 0.557, P = 0.031) (Fig. 7). There was no significant correlation between cortical hemodynamic response and duration, modified H&Y stage, FOGQ or UPDRS III.

In the high-risk faller subgroup, there was a strong negative correlation between duration and HbO over the right and total frontal cortices (rho = −0.854, P = 0.014 for the right; rho = −0.784, P = 0.037 for the total) (see Fig. 8). No significant correlations were observed between cortical hemodynamic response and other variables in both subgroups.

4. Discussion

This research using fNIRS explored the relationship between TUGT performance and frontal cortex activity in PD and control participants, and yielded 5 main findings. Firstly, a TUGT cutoff time was found that significantly predicted high-risk faller and low-risk faller PD participants. Secondly, compared with the sitting baseline, cortical activity initially decreased significantly, then significantly increased in the following interval in PD participants and the low-risk faller PD

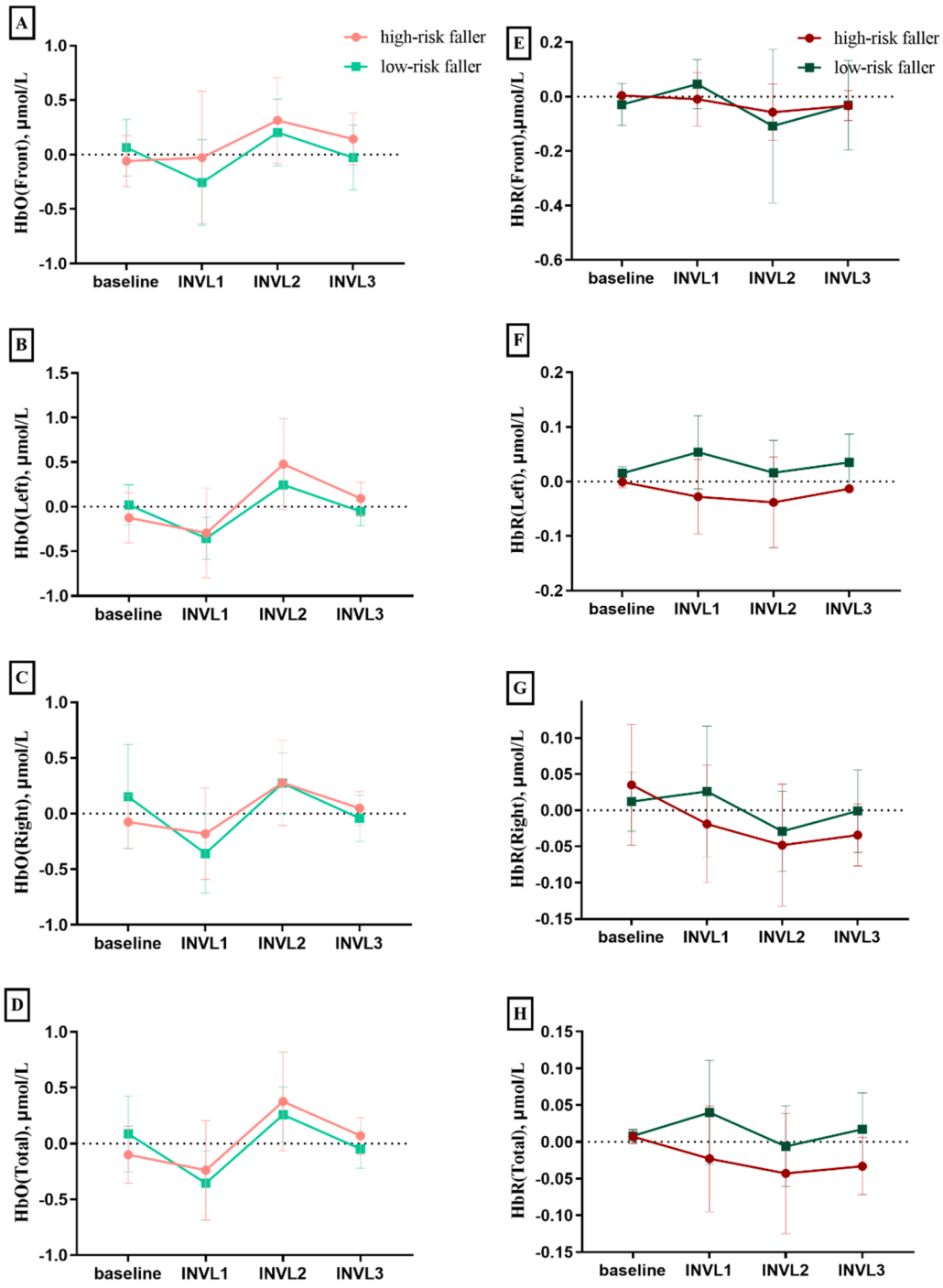

Fig. 6. Mean HbO and HbR concentration in four periods over the front, left, right and total frontal cortices within the high-risk faller and low-risk faller subgroups.

participants, but no significant differences were observed in high-risk faller PD participants or the healthy control participants. Thirdly, ΔHbO in the PD group was significantly lower than in the control group in interval 1, while it was significantly higher in interval 2. Fourthly, in the high-risk faller subgroup, ΔHbO over the left frontal cortex was significantly higher than the right frontal cortex in interval 2 and interval 3. Fifthly, there was a strong positive correlation between education and HbR concentration over the right frontal cortex in PD participants, while there were strong negative correlations between PD duration and HbR concentration over the right and total frontal cortices in the high-risk faller PD participants.

In this research, a TUGT time of 14.2 s was found to be the cutoff point that predicted PD participants as being high-risk or low-risk fallers. This was similar to the 15.2 s reported earlier [6], but considerably higher than the 10.1 s for all PD patients and 10.8 s for PD fallers obtained in other research [27]. This discrepancy may be associated with the severity of the disease (e.g. H&Y stage, FOGQ, UPDRS), and rates and frequency of falls. However, there were no significant correlations between HbO/HbR and TUGT time in PD participants (including the high-risk faller and low-risk faller subgroups).

In interval 1, HbO concentration in PD participants significantly decreased compared to sitting position or the control group. There were two possible reasons why HbO concentration might have decreased in interval 1. Firstly, the attention-demanding task caused cortical blood flow to decrease [28]. In interval 1, participants were asked to stand up, to walk, and then to turn around, all of which required a high degree of

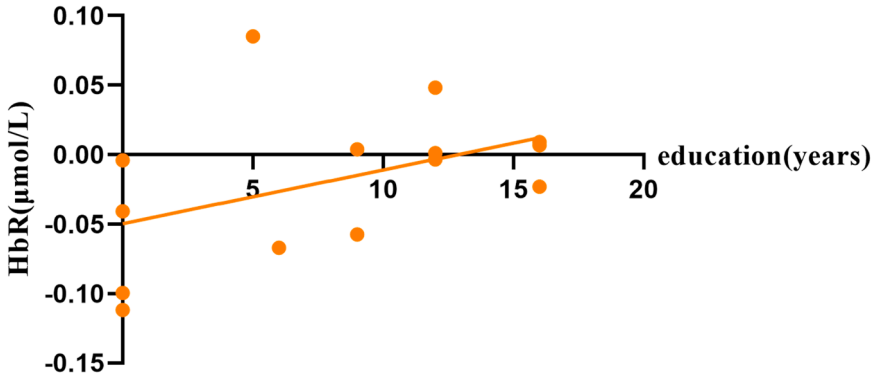

Fig. 7. Correlation between education and HbR over the right frontal cortex in PD group.

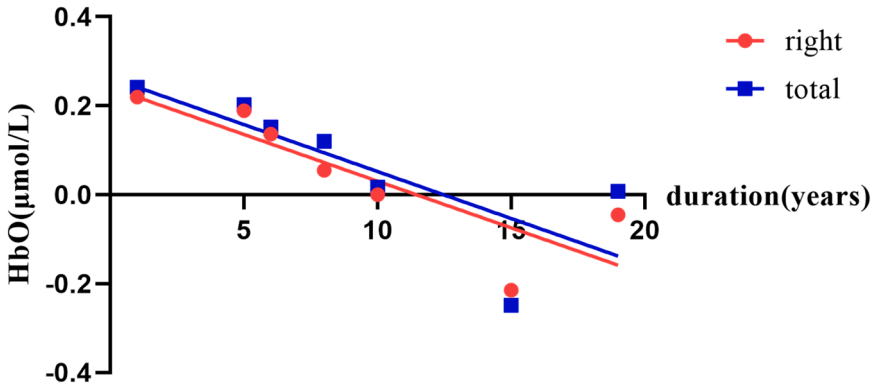

Fig. 8. Correlation between PD duration and HbO over the right and total frontal cortices in the high-risk faller subgroup of PD participants.

attention. Secondly, fNIRS measured the hemodynamic response rather than neural activity, while its typical peaks arise after 6 s following stimulus onset [29]. Therefore, HbO concentration in interval 1 can be seen as reflecting the cortical activity of postural transition (from sitting to standing) and walking, which is similar to previous research [30]. Nevertheless, the comparison between the PD and control groups revealed that there were significant differences in HbO concentration during the TUGT. Consequently, it could be assumed that the differences were caused by the TUGT task rather than postural transition.

In interval 2, frontal cortex HbO concentration in PD participants was significantly increased compared to the other three periods, and compared to control participants. HbO concentration was also significantly increased, compared to sitting position, during the entire TUGT. That is, there was greater activation of the frontal cortex during walking and TUGT in PD patients, a finding which is similar to other studies [16]. Singh et.al [31] found that PD patients increased beta-band power in the frontal region during pedaling , and cortico-basal beta-band synchrony promotes tonic activity that slows down lower-limb movements. PD patients had lower MMSE scores compared to the control participants in this study, while frontal theta rhythms are a mechanism of cognitive control that is impaired in PD [32], thus theta oscillations may contribute to the sensorimotor integration needed to execute a task [33].

A dominant left frontal cortex activity was observed in the high-risk faller PD participants. This left-lateralized activation is consistent with previous studies [34,35]. Left-lateralized vulnerability has been related to left hemisphere dominance [36]. The left hemisphere is highly specialized for the control of skilled movements, including planning and implementation of complex movements, bimanual coordination, and motor learning [36]. While left hemisphere-predominant atrophy has been observed across the spectrum of PD, it is most evident early in PD, whereas more diffuse and widespread brain atrophy is seen with increasing disease duration [37]. In the present study, all participants were right-handed, so we could exclude the influence of handedness on left-lateralized activation. In addition, there were strong negative correlations between PD duration and HbR concentration over the right and total frontal cortices in the high-risk faller PD participants. That is, the longer duration of PD, the higher the cortical activity observed in the frontal cortex, to enhance motor control.

Potential limitations of our work include: (1) The small sample, since size may be a lack-of-power reason for failure to find any significant difference in hemodynamic response between the two PD subgroups. This also leads to a high heterogeneity of clinical characteristics and limits the generalizability of the results. (2) The respiration and Mayer wave oscillations fall into the same frequency range as the hemodynamic response and cannot simply be removed by bandpass filtering [19]. Unlike electroencephalography (EEG), fNIRS measures brain activity indirectly in superficial brain areas with a low spatial resolution (1 cm) [38]. (3) No other kinematic variables were able to be assessed due to equipment limitation. (4) By targeting PD patients during “ON” medication, the effects of anti-Parkinson medication cannot be excluded.

5. Conclusions

During TUGT, frontal cortex activity initially decreased significantly then significantly increased in PD participants, compared to sitting position or control population. HbO change over the left frontal cortex was significantly higher than the right frontal cortex in the high-risk faller subgroup. There were strong negative correlations between PD duration and HbR concentration over the frontal cortices in the high-risk faller PD participants. These results suggest that frontal cognition training, along with exercise training, could be used as an effective training method to improve motor performance in PD patients, especially for those at high-risk for falls.

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Ethics approval and consent to participate

The research involving human participants was reviewed and approved by the Scientific Research Ethics Committee of Shanghai University of Sport and Jinhua Polytechnic. The study protocol was prospectively registered in Chinese Clinical Trial Registry (www.chictr.org.cn, registration No.ChiCTR2000038852). All participants gave informed, written consent prior to participation.

CRediT authorship contribution statement

Ping Tao and Xuerong Shao made substantial contributions to study design, data collection, analysis, interpretation and visualization and drafting the manuscript. Yuchen Dong made substantial contributions in experimental design, data collection, data analysis and drafting the manuscript. Roger Adams and Elisabeth Preston helped to edit the manuscript. Ying Liu instructed fNIRS technology. Jia Han participated in the study design, analyzed data, and edited the manuscript. All authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2022.114219.

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