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Cerebrovascular function during cognition in Parkinson's disease: A functional transcranial Doppler sonography study

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ABSTRACT

Objective: Recent evidence has linked cerebrovascular abnormalities with Parkinson's Disease (PD), which may provide a new neurophysiological understanding of cognitive impairment in PD. The current study aimed to compare cerebrovascular functioning, during a cognitive task and at rest, in those with and without PD.

Methods: Idiopathic PD patients (n = 30) and age- and gender-matched healthy controls (n = 30) undertook cognitive testing and completed a word generation task while blood flow velocity was monitored bilaterally with functional transcranial Doppler sonography (fTCD) of the middle cerebral arteries. The lateralisation index and its standard deviation and timing, along with the maximum peak velocity for the left and right hemispheres and their latencies and standard deviations, were calculated for each participant.

Results: The PD patients showed significantly more variability of the lateralisation index compared to the control group; but there were no differences in the lateralisation index itself nor in the peak velocities. In the PD group, the variability in the peak velocities showed significant positive correlations with performance on executive function tests.

Conclusion: Normal ageing has been associated with a reduction in the lateralisation index, but no alterations in the standard deviation, suggesting that cerebrovascular functional changes associated with PD differ from those of typical ageing. The within-subject variability observed in the PD group indicate abnormalities within the neurovascular coupling response. Further, the association between the within-subject variability and executive functioning in the PD group, suggests that cerebrovascular dysfunction plays an important role in cognitive impairment in PD.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that shows increasing prevalence with age [1]. Although PD is primarily characterised by motor symptoms, non-motor deficits such as cognitive impairment are highly prevalent and have major ramifications [2]. It is estimated that mild cognitive impairment is present in between 15 and 40% of newly diagnosed PD patients, and that 25% of PD patients with normal cognition convert to mild cognitive impairment over three years [3,4]. Up to 80% of PD patients will eventually develop dementia within 20 years of diagnosis [5]. This is of particular concern as dementia, including PD dementia, is linked with a reduced life expectancy [6]. Further, cognitive impairment in PD has been found to be a leading cause of reduced quality of life, and to increase caregiver burden and economic costs of the disease [7]. PD patients often show a wide and heterogeneous range of cognitive impairments, which cannot be fully explained by dopaminergic degeneration or related neurochemical circuits alone; of these, frontal-executive and attention impairments appear to be the most prominent [8]. As it stands, the underlying brain mechanisms that contribute to cognitive dysfunction in PD are still poorly understood.

A proposed mechanism underlying cognitive decline in PD is cerebrovascular dysfunction [9]. The cerebrovascular system plays a vital role in cognitive functioning, as the limited energy storage of the brain, combined with its high energetic cost, requires an expedient regulation of cerebral blood flow (CBF) [10]. Functional magnetic resonance

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imaging (fMRI) studies have reported that PD patients with cognitive impairments display reduced frontal and temporal CBF, compared to PD patients with normal cognitive functioning [11,12]. However, fMRI studies have a poor temporal resolution, providing limited insight into the underlying CBF regulatory mechanisms. The CBF is regulated through an integrative process that involves several mechanisms [10]: (1) cerebral autoregulation, (2) metabolic regulation, including cerebrovascular reactivity, and (3) autonomic regulation with neurovascular coupling. Neurovascular mechanisms underlying CBF regulation are of particular concern in PD, as 50–70% of PD patients experience significant autonomic-nervous dysfunction, such as orthostatic hypotension [9,13,14]. Whilst autonomic dysfunction is more commonly associated with later PD, recent research has shown that autonomic dysfunction can appear years before the onset of motor symptoms, making it a potential target for early identification of those at risk for PD [15,16] (see review by Mendoza-Velásquez et al. [17]).

Transcranial Doppler (TCD) sonography, is a non-invasive and cost-effective tool that provides high temporal resolution of the CBF velocity (CBFv), making it ideal for the assessment of cerebrovascular functioning, including the mechanisms of cerebrovascular reactivity and neurovascular coupling [18,19]. The middle cerebral artery (MCA) is commonly examined using TCD, as it supplies 50–80% of the CBF within the brain, including language-relevant brain areas [18,20,21].

Previous TCD studies suggest that patterns of cerebrovascular reactivity to hypercapnia (CO_2 and breath-holding) appear to differ between neurologically healthy older adults and those with a cognitive impairment [9,22]. Ruitenberg et al. reported that healthy older participants with a larger response to hypercapnia, assessed using a TCD inhale task, were less prone to develop cognitive impairment over a six-year period [22]. Camargo et al. reported that PD patients displayed a substantially smaller CBFv increase during the breath-holding test compared to healthy controls, and this effect was particularly marked in PD patients with orthostatic hypotension [9]. This supports the notion that PD patients experience cerebrovascular dysfunction and goes further, to suggest that problems with cerebral autoregulation play a key role in PD. However, using the breath-holding task in order to assess cerebrovascular reactivity predominantly provides information linked to the metabolic mechanism, but not necessarily about autonomic regulation, including the process of neurovascular coupling during cognition [10,23].

In order to gain a better understanding of the cerebrovascular factors, including the autonomic regulation of the CBF, that may underlie the onset of cognitive dysfunction in PD, the current study is the first to continuously assess the cerebrovascular response during a cognitive task through functional TCD (fTCD) [19,24]. The word generation task is a commonly used cognitive task in fTCD studies and has been reported to have high reliability in determining cerebral language lateralisation [25,26]. The lateralisation in fTCD is estimated using a lateralisation index (LI), which locates the maximum velocity difference between the hemispheres, with a positive LI corresponding to leftwards (typical language) lateralisation [27,28].

Previous studies assessing the relationship between lateralisation and cognitive functioning report that reduced lateralisation relates to lower cognitive performance [29,30]. A reduction in lateralisation is often explained as being a result of the recruitment of non-specific neural structures, as a compensatory mechanism [31]. FTCD studies commonly examine the amplitude and temporal characteristics of the CBFv response to a cognitive stimulus, in the individual hemispheres, to investigate neurovascular coupling [19]. Gröschel et al. found that the amplitude of the CBFv response to a word generation task was significantly lower in older participants with vascular risk factors compared to older healthy adults [24].

The current study aimed to examine cerebrovascular functioning in PD patients by assessing CBFv at rest and during a word generation task using TCD, as compared to healthy age-matched controls. Further, the current study aimed to assess whether these TCD measures, at rest and during cognition, were correlated with cognitive performance. Therefore, this study provides a unique assessment of cerebrovascular response in PD patients that can help to better understand the contribution of the neurovascular coupling response to cognitive dysfunction in PD. As PD patients have previously been found to show a reduction in CBF [9,11], we expected that the resting CBFv and the peak velocity in both hemispheres would be lower for the PD group compared to the healthy control group. Furthermore, we hypothesised that there would be higher within-subject variability in both the cerebrovascular response, measured by the peak CBFv increase, and in the LI, as well as an increased latency in the PD group. Lastly, we expected that the lower CBF changes to cognitive stimuli would be related to poorer cognitive performance in PD and the control group.

2. Method

2.1. Participants

Thirty-six PD patients diagnosed by a Consultant Neurologist were recruited in 2016 and 2017 through Parkinson's South Australia and other local Parkinson's support groups in Adelaide, Australia. All participants gave their informed consent prior to their inclusion in the study. The exclusion criteria were: (a) having a brain disorder other than PD; (b) not being a native English speaker; (c) not being predominantly right-handed, assessed via the Flinders Handedness Survey [32]; (d) having ever been unconscious for more than five minutes; (e) having a diagnosed learning disability; (f) having uncorrected visual impairment; (g) having a non-removable hearing aid; (h) or having uncontrolled hypertension. From the 36 recruited PD participants, one participant was excluded due to a change in diagnosis during the course of the study and five participants were excluded as no TCD signal could be located, leading to a final study sample of 30 PD participants. For eight of the 30 PD participants, the CBFv could only be recorded on one side, and for three PD participants, only the resting TCD data was of sufficient quality. De-identified data of 30 sex and age matched (within a range of five years) neurologically healthy controls were obtained from a prior study investigating the relationship between cognition and cerebrovascular function in older adults [29]. The applied inclusion and exclusion criteria for the healthy controls have been previously outlined [29]. The demographic information of all participants is presented in Table 1. This study was approved by the Human Research Ethics Committees of both the University of South Australia and the University of Adelaide in accordance with national guidelines.

2.2. Measures

2.2.1. Addenbrooke's Cognitive Examination Revised (ACER)

The ACER Australian version was used as a measure of general cognitive functioning [33]. The ACER assesses five neuropsychological domains that make up a total score of 100 and has an administration time of approximately 15 min. This study uses the previously recommended cut off score of 88 (reported to have a sensitivity of 69% and specificity of 84% in a PD sample), in order to classify a participant as having MCI and a cut off score of 82 for dementia (found to have a sensitivity of 84% and specificity of 1.00 in a mixed clinical sample) [33,34].

2.2.2. The Hayling and Brixton Tests

The Hayling and Brixton tests assess executive function and takes around 15 min to complete. The Hayling comprises two sections in which the participants complete sentences with a missing final word, with either a connected (section one) or unconnected (section two) word. In the current study, the overall scaled score was used, with a possible score range of 1 (impaired) to 10 (very superior). The Brixton test consists of a stimulus book, in which each page has ten circles of which one circle is coloured in depending on a particular pattern. The

Table 1
Demographic characteristics of PD and control participants.

	PD patients	Control group
Sex *N* (F/M)	7/23	7/23
Age in years		
Mean (SD)	70.3 (7.6)	70.5 (6.5)
Range	55–87	60–85
Age at PD Diagnosis (years)		
Mean (SD)	62.7 (9.3)	
Range	40–81	n/a
Disease Duration (years)		
Mean (SD)	7.7 (5.0)	
Range	0.5–18.5	n/a
PD medication		
Medication, *N*	17 LD, 4 DA, 7 LD + DA	n/a
DBS, *N* (%)	4 (13%)	
GDS15		
Mean (SD)	2.0 (2.9)	0.5 (0.7)
Range	0–8	0–3
ACER		
MCI, *N* (%)	5 (17%)	3 (10%)
Dementia, *N* (%)	5 (17%)	2 (7%)
Previous Hypertension, *N* (%)	11 (37%)	9 (30%)
Current Hypertension, *N* (%)	3 (10%)	10 (33%)
Previous Hypotension, *N* (%)	5 (17%)	3 (10%)
Current Hypotension, *N* (%)	3 (10%)	2 (7%)
Previous Smoker, *N* (%)	13 (43%)	16 (53%)
Current Smoker, *N* (%)	0	1 (3%)
High Cholesterol, *N* (%)	10 (33%)	9 (30%)
Diabetes, *N* (%)	3 (10%)	1 (3%)

Note: PD Parkinson's disease, *n/a* non-applicable, *LD* L-Dopa, *DA* Dopamine Agonist, 2 PD participants had missing information about medication, *DBS* Deep Brain Stimulation, *ACER* Addenbrooke's Cognitive Examination Revised, *GDS15* 15 item Geriatric Depression Scale.

participants are required to predict the location of the coloured circle on the next page by evaluating the patterns that occur throughout the book. The scaled score was used for the Brixton, with scores ranging from 1 (impaired) to 10 (very superior) [35].

2.2.3. National Adult Reading Test (NART)

The NART is a word-reading test that is comprised of 50 words with increasing difficulty. The score reflects the number of errors made [36]. The NART has been designed as a measurement of premorbid intelligence for adults and has an administration time of approximately 10 min [36].

2.2.4. FTCD Experimental Paradigm

The word generation task was used as the cognitive task to elicit an increase in CBFv during the fTCD recording. The word generation task consisted of 24 letters that were presented in the following order: Q, G, Y, E, S, I, O, W, U, M, H, D, A, J, C, K, B, V, F, P, R, T, N, L. Before each letter was presented the screen displayed *clear mind* that served as a preparation cue for the onset of the letter. This was followed by an auditory beep signal just before the presentation of the letter. In order to avoid interference with the TCD signal due to muscle movement, participants were first given 12.5 s to silently think of as many words as possible that begin with the displayed letter. This was followed by another auditory beep signal and a five second phase, in which the participants spoke aloud the generated words. Each letter was followed by a relax phase (35 s) (Fig. 1), allowing for the CBFv to go back to the baseline. The first letter was considered to be a practice trial and was removed from the subsequent analysis, leaving 23 letters. The words that the participants said in the allocated five second period were recorded and averaged across the 23 trials, as a measurement of cognitive performance. Verbal fluency tasks, including the letter fluency task, are a commonly used neurophysiological assessment tool for the assessment of the verbal fluency and executive control [37]. Previous studies have reported those with PD perform significantly worse in letter fluency tasks, compared to control, even with a concomitant diagnosis of dementia [38,39].

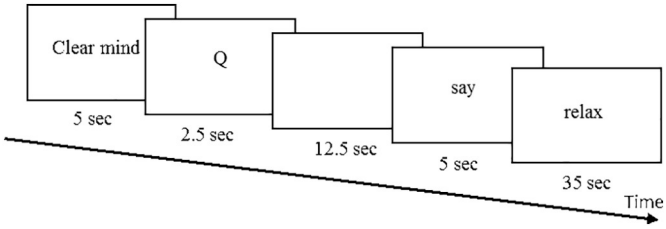

Fig. 1. One trial of the word generation task, the blank slide was presented during the silent word generation phase.

2.2.5. TCD/fTCD Recording and Processing

The QL 2.8 software with the DWL Doppler-Box hardware and 2 MHz ultrasonic probes, mounted on a Dia-Mon head fixation (Compumedics, DWL, Singen, Germany), were used to continuously record the CBFv of the MCAs bilaterally at 100 Hz. The temporal window was used to access the MCA signal. Participants sat in an upright position during the set-up and testing.

Resting TCD measures, including mean, maximum/systolic and minimum/diastolic CBFv, were recorded during eyes open and eyes closed for 65 s each. The first and last 2.5 s of the recording were excluded, to remove muscle artefacts, leaving 60s of recording for analysis. From the resting blood-flow measures, the pulsatility index (PI) was calculated by Gosling's formula, subtracting the diastolic velocity from the systolic velocity and then dividing it by the mean flow velocity [40]:

$$\mathrm{PI} = \frac{\text{Systolic velocity-Diastolic velocity}}{\text{Mean flow velocity}}$$

Data for the PI was averaged over the left and right MCAs, when both were available. The PI can be seen as a comparable measure to pulse pressure and has traditionally been used as a measurement of distal cerebrovascular resistance and can be interpreted as a measure of cerebral arterial stiffness [41].

To investigate the cerebral blood flow response to a cognitive task, the fTCD measures were taken during the word generation task, as outlined above. The DOPOSCCI program version 3.0 [27,42] is a MATLAB toolbox for processing fTCD data. In order to compute the CBFv response and the LI, the following processing steps were conducted through DOPOSCCI: the extracted data channels from both sides were downsampled to 25 Hz and the first epoch containing the CBFv response to the first letter was removed as practice, leaving 23 epochs for the analysis. The heart cycle patterns were then removed through a linear correction and the data was epoched for each letter from −10 to 15 s relative to the presentation of the letter, which is set as time zero. Data for each channel were normalised to 100 on an epoch by epoch basis, removing artefacts that occur through drifts of the probes. Values beyond −3 and 4 standard deviations of the mean where corrected by linear extrapolation between values 1.5 s either side of the extreme value if < 5% of the data were affected. Epochs were excluded in three circumstances: (1) if non-task behaviour was noted during the testing session (e.g., falling asleep, missing presentation of letter); (2) if left or right channel values were > 10 times the inter-quartile range, when > 5% were affected; and (3) if they contained values beyond ± 50% of the average signal (note: 2 and 3 reflect measurement artefacts). Participants with fewer than 10 acceptable epochs were excluded from the analysis. Each epoch was then baseline corrected by using the −10 to −5 s period, meaning that the average activation during the baseline was subtracted from the left and right activation in each epoch; hence, the deviation of the CBFv from zero reflected an increase or decrease relative to the baseline. Two different periods of interest were examined, one for the identification of the maximum velocity peak in

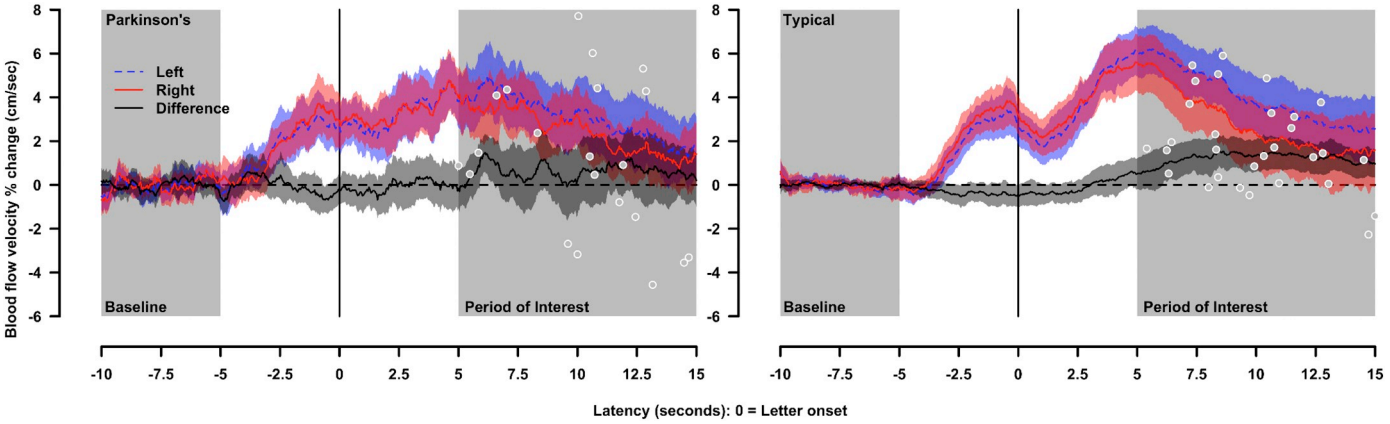

Fig. 2. Evoked flow plots to Word Generation task. Each panel represents the group average change in blood flow velocity in the left (blue dashed line) and right (red) middle cerebral arteries, as well as their difference (grey), relative to the baseline for the Parkinson's and Control groups respectively. There were two periods of interest, from 0 to 10 s for the peak velocity changes and the here indicated one from 5 to 15 s for the lateralisation index. The dots indicate the lateralisation index for each individual participant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

each hemisphere from 0 to 10 s, and the other from 5 to 15 s for the calculation of the LI. Finally, the remaining epochs were averaged and can be visualised for the group in overall evoked CBFv plot (evoked-flow plot), showing the average increase in the CBFv of the MCA in both hemispheres relative to word generation (Fig. 2).

The LI indicates the average maximum hemispheric difference of the CBFv and is computed by subtracting the baseline corrected peak CBFv increase of the left MCA from the right MCA, averaged across a two-second window that is centred on the maximum difference within the 5 s to 15 s period of interest for the averaged acceptable epochs for each individual. The latency of the LI represents the time at which the maximum difference between the hemispheres occurred. The cerebrovascular response was analysed through nine measurements in the evoked-flow plot: the LI; the standard deviation of the LI across acceptable epochs measuring the within-subject variance; the timing of the LI; peak velocity in the left and right MCA; variance of the peak velocity in each side, again measuring the within-subject variance and latency of the peak velocity for each hemisphere.

2.3. Procedure

All the testing took place at the Cognitive Ageing and Impairment Neurosciences Laboratory at the University of South Australia. The testing of each PD participant was performed within a single, 3-h session. All PD participants took their usual PD medication on the day of testing. Demographics, health and the cognitive measures of the ACER and NART were taken before the TCD/fTCD recording, and the Hayling and Brixton were administered after the TCD recording. Data collection for the control group occurred over two sessions, with cognitive testing in first session and TCD recordings in second session [29].

2.4. Analytical approach

The data set was analysed and screened through IBM SPSS v24. Outliers, with a cut off of three standard deviations (relative to group), in the TCD/fTCD data set were replaced with the highest acceptable value. The PI was calculated before the replacement of outliers. Within the cognitive test scores, there was only one outlier from the PD group, but as the scores have clinical utility, and the result did not change when replaced, the initial value was not changed. The resting TCD data were averaged across both hemispheres, where both sites were available, as there were no significant differences between the hemispheres present nor did the hemispheres show different association patterns with the other measurements (in initial analyses; not reported here). The mean resting CBFv showed no differences between eyes open and eyes closed and there were no differences in the association patterns (again, in initial analyses; not reported here), hence it was decided to only present the TCD values of eyes open. The PI and the three measures of the fTCD variance showed skewed and/or kurtotic distributions, hence non-parametric tests were chosen for those four measurements.

Three independent *t*-tests and one Mann-Whitney U test were used to compare resting TCD measures between the PD group and the control group, with the alpha level set at 0.013. For the fTCD data, six independent t-tests and three Mann Whitney U tests were used to compare the fTCD measures between the groups. Two Bonferroni adjustments were used, one for the three LI measures with an adjusted alpha level of 0.017, and one for the three peak velocity measures in each hemisphere with an adjusted alpha of 0.008. Effect sizes were measured using Cohen's d for the normally distributed data. For the nonparametric analyses, effect sizes were calculated through a normal approximation of z to r, as suggested by Field, computing r by dividing the z value by the square root of the total sample size [43].

Bivariate correlations, either Pearson's or Spearman's (dependent on distributions), were run to assess relationships between cognitive test performance and TCD/fTCD measures. As the current participant sample showed a high age range and disease duration range, a bivariate correlation was performed to assess the association with TCD/fTCD measures. Only one Bonferroni correction for the Hayling and Brixton score was applied, with an adjusted alpha set at 0.025, as the remaining test scores measured different cognitive domains.

3. Results

3.1. TCD/FTCD measure and cognitive test differences between the PD group and control group

Table 2 displays the TCD/fTCD values for each group. The independent *t*-tests and Mann Whitney *U* test revealed that the groups differed significantly on two of the four TCD measures, with the PD group showing significantly lower resting mean CBFv and lower diastolic CBFv than the control group. The independent t-tests and Mann Whitney *U* tests indicated that the groups differed significantly in one of the nine fTCD measures: with the PD group showing significantly higher variability in the LI than the control group (Table 2). The PD group and the control group showed only one significant difference in cognitive test performance, with the PD group performing significantly better on the NART assessment than the control group (Table 2).

Table 2
TCD/fTCD and cognitive measurements from the PD and control groups.

	PD group				Control group						
Variable	N	M	SD	Range	N	M	SD	Range	Test statistic	*p*	Effect size
Resing TCD											
Mean flow velocity[a] (cm/s)	30	40.42	10.90	21.62–66.92	30	49.55	13.79	27.46–79.27	***t* = 2.85**	**0.006**	**d = 735**
Systolic velocity[a] (cm/s)	30	66.66	19.65	40.16–106.76	30	79.34	20.79	48.18–127.09	*t* = 2.43	0.018	d = 0.627
Diastolic velcoity[a] (cm/s)	30	24.47	8.03	5.06–40.46	30	32.08	9.18	15.52–50.88	***t* = 3.42**	**0.001**	**d = 0.882**
PI[b]	30	1.05	0.25	0.68–1.73	30	0.96	0.19	0.69–1.45	U = 379.00	0.294	*r* = 0.136
fTCD											
LI[a]	21	1.17	3.50	−4.56-7.71	30	1.17	2.68	−5.40-5.90	*t* = 0.001	0.999	d < 0.001
LI latency[a] (s)	21	10.22	2.89	5.00–14.68	30	9.72	2.97	5.00–15.00	*t* = 0.602	0.550	d = 0.171
LI SD[b]	21	6.91	3.60	3.17–18.69	30	3.29	1.49	1.15–7.64	**U = 70.00**	**< 0.001**	***r* = 0.657**
Peak left % change[a]	23	5.65	2.34	1.48–11.19	30	6.61	3.11	0.08–13.12	*t* = 1.24	0.222	d = 0.349
Peak left latency[a] (s)	23	5.71	2.45	0.00–10.00	30	5.35	2.30	0.00–10.00	*t* = 0.56	0.580	d = 0.152
Peak left SD[b]	23	8.44	3.04	4.04–15.05	30	7.06	2.20	4.13–14.15	U = 244.00	0.070	*r* = 0.245
Peak right % change[a]	25	4.82	2.47	0.20–10.48	30	5.87	3.39	−1.64-11.98	*t* = 1.29	0.203	d = 0.354
Peak right latency[a] (s)	25	4.17	2.32	0.04–8.68	30	4.33	2.11	0.00–9.08	*t* = 0.26	0.797	d = 0.072
Peak right SD[b]	25	7.44	3.90	3.39–19.50	30	7.24	2.99	3.94–16.90	U = 369.50	0.926	*r* = 0.125
Cognitve tests											
WGT	28	3.21	0.61	2.22–4.43	30	3.50	0.53	2.57–4.35	*t* = 1.97	0.053	d = 0.508
Hayling	30	5.43	1.72	1.00–9.00	30	5.53	1.04	3.00–7.00	*t* = 0.27	0.786	d = 0.023
Brixton	30	3.43	2.37	1.00–7.00	30	4.30	1.92	1.00–7.00	*t* = 1.56	0.125	d = 0.403
NART	30	9.13	5.02	2.00–22.00	30	15.27	9.05	2.00–36.00	***t* = 3.25**	**0.002**	**d = 0.839**
ACER	30	89.27	8.32	68.00–99.00	30	91.90	4.74	82.00–99.00	*t* = 1.51	0.139	d = 0.388

Bold indicates statistically significant group differences.
[a] indicates parametric tests of independent samples t-test.
[b] indicates non-parametric Mann Whitney U tests, *PI* Pulsatility Index, *LI* Lateralisation Index, *Peak L and R* Blood flow velocity peak in the left or right middle cerebral artery, PD Parkinson's Disease, *WGT* Word Generation Task, *NART* National Adult Reading Test, *ACER* Addenbrooke's Cognitive Examination Revised,

3.2. TCD/ fTCD: associations with cognitive performance, age and disease duration

Resting TCD measures did not significantly correlate with cognitive performance in either the PD or healthy control group (Table 3). In the PD group, age was significantly positively correlated with the PI ($r_s = 0.559$, $p = .001$) and the ACER performance ($r = -0.529$, $p = .003$). Disease duration showed no significant associations with any of the TCD measures or cognitive measures. In the control group, age was significantly positively correlated with the PI ($r_s = 0.374$, $p = .042$). In the PD group, the Hayling and NART scores did show some significant correlations with the fTCD measures, the NART was significantly positive associated (and showed a large effect size) with both the left and right MCA peak velocity increase; while the Hayling score was negatively correlated with the within-subject variability of both the left and right MCA mean velocity increase, also with a large effect size (Table 3).

The disease duration of PD showed no significant association with any of the fTCD or cognitive measures. Age was, however, positively correlated with the within-subject variability of the right MCA mean CBFv increase ($r_s = 0.434$, $p = .030$).

In the healthy control group, the word generation task performance was significantly positively associated with the left MCA velocity peak, while the NART and ACER score were both positively associated with the LI. Conversely, the Hayling score showed a negative correlation with the variance of the LI (Table 3). Age showed no significant association with any of the fTCD measures in the control group.

4. Discussion

The present study is the first to use fTCD to examine the cerebrovascular response to cognitive stimuli in PD patients, which provides new insight into the autonomic regulation of the CBF. Findings demonstrate that PD patients display a reduced CBFv during rest (particularly mean and diastolic) and a more variable cerebrovascular response to cognitive stimuli, when compared to the healthy control. We have previously reported that healthy ageing is associated with increased PI during rest and reduced LI during periods of cognitive activity (using data from the healthy control group) [29]. Hence, the current findings suggest that changes in cerebrovascular functioning that occur in PD (reduced velocity during rest and higher variability in response during cognitive tasks) are different to those of healthy ageing (increased PI during rest and reduced lateralisation during cognition).

The PD group showed significantly reduced mean and diastolic CBFv in the MCAs during rest (the effect for systolic failed to meet the adjusted alpha value). This is in line with previous TCD literature, reporting that PD patients show a reduced mean CBFv [9,44]. Like healthy controls, none of the resting TCD measures displayed significant relationships with cognitive performance in the PD group. Given strong correlations were observed between fTCD and cognitive performance measures in the PD group, this may simply reflect that resting measures are not ideal to index cognitive processes in PD. Alternatively, we may have been under-powered to detect these associations.

The cerebrovascular response during the verbal fluency task showed that both groups showed a typical left lateralisation, which is consistent with previous fTCD studies [18,27,45]. However, in contrast to our prediction, there was no significant difference in the magnitude or latency of this lateralisation (indexed by the LI) between those with and without PD, suggesting that PD patients still recruit specialised language-related neural regions [46]. Previous lateralisation studies have focused on the magnitude of this response and its relationship with cognitive performance [18]. However, within-subject variability can also provide valuable information about cognitive performance and underlying brain mechanisms [47]. Whilst mechanisms underlying the within-subject variability of the lateralisation as measured using TCD have not been directly investigated, the mechanisms for fMRI blood-oxygen-level-dependent (BOLD) within-subject signal variability have been explored [47]. This is significant, as, like an increase in the BOLD signal, an increase in the CBFv assessed over fTCD predominantly relates to an increase in neural activity [48]. Variability in the BOLD signal is due to changes in neural activation and/or alterations in the

Table 3
Correlations between TCD/ fTCD measures and cognitive test performances within groups.

	PD group					Control group				
Variables	WGT	Hayling	Brixton	NART	ACER	WGT	Hayling	Brixton	NART	ACER
Resting TCD										
Mean flow velocity	0.120[a]	0.226[a]	−0.016[a]	0.099[a]	0.217[a]	0.050[a]	0.050[a]	−.051[a]	−.130[a]	−.077[a]
	(0.543)	(0.230)	(0.931)	(0.604)	(0.249)	(0.791)	(0.791)	(0.789)	(0.494)	(0.685)
	n = 28	*n* = 30	*n* = 30	n = 30	n = 30	n = 30	n = 30	n = 30	n = 30	*n* = 30
Systolic velocity	0.099[a]	0.143[a]	−0.002[a]	0.139[a]	0.139[a]	0.039[a]	0.039[a]	−0.095[a]	−0.084[a]	−0.066[a]
	(0.615)	(0.452)	(0.993)	(0.464)	(0.464)	(0.840)	(0.840)	(0.616)	(0.659)	(0.729)
	n = 28	*n* = 30	*n* = 30	*n* = 30	*n* = 30	n = 30	n = 30	*n* = 30	*n* = 30	*n* = 30
Diastolic velocity	0.083[a]	0.324[a]	0.015[a]	−0.045[a]	0.239[a]	0.025[a]	0.025[a]	−0.010	−0.084[a]	−0.038[a]
	(0.615)	(0.080)	(0.938)	(0.814)	(0.204)	(0.895)	(0.895)	(0.959)	(0.659)	(0.840)
	n = 28	*n* = 30	*n* = 30	*n* = 30	*n* = 30	n = 30	n = 30	n = 30	n = 30	n = 30
PI	−.005[b]	−0.197[b]	−0.081[b]	0.275[b]	−0.125[b]	−.002[b]	−.002[b]	−0.032[b]	−0.196[b]	−0.018[b]
	(0.978)	(0.297)	(0.671)	(0.141)	(0.512)	(0.990)	(0.990)	(0.866)	(0.300)	(0.926)
	n = 28	*n* = 30	*n* = 30	*n* = 30	*n* = 30	n = 30	n = 30	n = 30	n = 30	n = 30
fTCD										
LI	0.274[a]	0.381[a]	0.253[a]	0.240[a]	0.000[a]	0.013[a]	0.176[a]	0.045[a]	**0.449[a]**	**0.433[a]**
	(0.230)	(0.088)	(0.269)	(0.295)	(0.999)	(0.946)	(0.352)	(0.815)	**(0.013)**	**(0.017)**
	n = 21	*n* = 21	n = 21	n = 21	n = 21	*n* = 30	n = 30	n = 30	**n = 30**	**n = 30**
LI latency	0.150[a]	−0.019[a]	−0.037[a]	0.240[a]	−0.018[a]	−0.030[a]	0.053[a]	−0.101[a]	−0.068[a]	−0.276[a]
	(0.517)	(0.933)	0.875	(0.295)	(0.939)	(0.876)	(0.780)	(0.595)	(0.723)	(0.140)
	n = 21	*n* = 21	n = 21	n = 21	n = 21	*n* = 30	n = 30	*n* = 30	n = 30	n = 30
LI SD	0.133[b]	−0.367[b]	−0.025[b]	0.272[b]	−0.059[b]	0.015[b]	−0.372[b]	0.321[b]	−0.310[b]	0.118[b]
	(0.564)	(0.102)	(0.915)	(0.233)	(0.798)	(0.939)	(0.043)	(0.084)	(0.096)	(0.534)
	n = 21	n = 21	n = 21	n = 21	n = 21	*n* = 30	*n* = 30	n = 30	n = 30	n = 30
Peak left % change	0.406[a]	0.420[a]	0.198[a]	**0.525[a]**	0.282[a]	**0.441[a]**	0.305[a]	0.168[a]	−0.027[a]	0.129[a]
	(0.054)	(0.046)	(0.366)	**(0.010)**	(0.192)	**(0.015)**	(0.101)	(0.376)	(0.889)	(0.497)
	n = 23	*n* = 23	n = 23	**n = 23**	n = 23	***n* = 30**	*n* = 30	n = 30	*n* = 30	n = 30
Peak left latency	0.071[a]	0.352[a]	0.208[a]	0.088[a]	0.022[a]	−0.082[a]	0.410[a]	−0.257[a]	0.234[a]	0.098[a]
	(0.749)	(0.100)	(0.340)	(0.689)	(0.919)	(0.668)	(0.025)	(0.170)	(0.214)	(0.605)
	n = 23	*n* = 23	n = 23	n = 23	n = 23	*n* = 30	n = 30	*n* = 30	n = 30	n = 30
Peak left SD	−0.131[b]	**−0.558[b]**	−0.103[b]	0.167[b]	−0.306[b]	0.047[b]	−0.087[b]	0.131[b]	−0.037[b]	0.352[b]
	(0.552)	**(0.006)**	0.642	(0.447)	(0.156)	(0.806)	(0.647)	(0.491)	(0.844)	(0.057)
	n = 23	***n* = 23**	(n = 23)	n = 23	n = 23	*n* = 30	*n* = 30	*n* = 30	n = 30	n = 30
Peak right % change	0.200[a]	0.157[a]	−0.006[a]	**0.530[a]**	0.265[a]	0.329[a]	0.401[a]	−0.156[a]	0.001[a]	−0.003[a]
	(0.338)	(0.455)	(0.977)	**(0.006)**	(0.200)	(0.076)	(0.028)	(0.409)	(0.994)	(0.987)
	n = 25	*n* = 25	*n* = 25	**n = 25**	n = 25	*n* = 30	n = 30	*n* = 30	n = 30	*n* = 30
Peak right latency	−0.057[a]	−0.158[a]	0.036[a]	0.010[a]	0.060[a]	0.028[a]	0.163[a]	0.118[a]	−0.267[a]	−0.155[a]
	(0.788)	(0.452)	(0.863)	(0.960)	(0.777)	(0.881)	(0.390)	(0.533)	(0.154)	(0.414)
	n = 25	*n* = 25	n = 25	n = 25	n = 25	n = 30	*n* = 30	*n* = 30	*n* = 30	n = 30
Peak right SD	−0.238[b]	**−0.495[b]**	−0.093[b]	−0.040[b]	−0.349[b]	−0.076[b]	−0.150[b]	−0.005[b]	−0.140[b]	0.094[b]
	(0.252)	**(0.012)**	(0.659)	(0.851)	(0.087)	(0.691)	(0.429)	(0.981)	(0.460)	(0.622)
	n = 25	***n* = 25**	n = 25	n = 25	n = 25	n = 30	n = 30	n = 30	n = 30	n = 30

Bold indicates significant correlations.
[a] indicates a parametric bivariate Pearson's correlation.
[b] indicates a nonparametric spearman's correlation, *PD* Parkinson's disease, *PI* Pulsatility Index, *WGT* Word generation task, *NART* National Adult Reading Test, *ACER* Addenbrooke's Cognitive Examination Revised, *LI* Lateralisation Index, *Peak L and R* Blood flow velocity peak in the left or right middle cerebral artery.

coupling between the neural activity and the cerebrovascular response [49]. Given that the mean LI showed no significant difference between the PD group and the healthy control group, PD patients appear to show no pronounced deficits in the recruitment of language-specific neural regions. Hence, the increased within-subject variability of the LI in the PD group is more likely an indicator of abnormalities in neurovascular coupling mechanisms, which would support the notion that PD patients experience changes in the autonomic regulation of the CBF. The neurovascular coupling response occurs very fast in response to the stimulus; thus, the analysis of the amplitude, as well as the latency of, the CBFv increase can provide valuable information about the cerebrovascular functioning of the participants [19].

Whilst we found no significant differences between those with PD and healthy controls for other fTCD measures (i.e., other than LI SD), the differences between the groups were in the predicted direction: with PD patients showing attenuated and delayed responses (which did not reach conventional significance levels). A factor that may have contributed to these non-significant effects is the sample characteristics of the PD and control groups. Camargo et al. reported that PD participants with orthostatic hypotension demonstrated a particularly attenuated CBFv response during a breath-holding task [9]. The number of participants that had orthostatic hypotension, or in general of autonomic-nervous dysfunctions, were not known in the current study. However, based on the self-reported hypotension data, the number of PD participants with orthostatic hypotension was likely low. Furthermore, previous neuroimaging literature examining CBF in PD patients suggests that PD patients with cognitive impairments (either MCI or dementia) show particularly low CBF compared to healthy controls [11,12]. However, two thirds of our PD participant sample did not fall within the cognitive impairment category (MCI or dementia according to ACER cut-offs). Future research should look into the cerebrovascular response to a cognitive task specifically in individuals with PD that have known autonomic or cognitive impairment, in order to better understand the link between these variables and cerebrovascular functioning in PD.

There were some significant correlations between fTCD measures and cognitive test performance in both groups. These were in the predicted directions, with larger increases in mean CBFv related to better cognitive performance, and increased within-subject variability related to poorer cognitive performance. These findings are in line with a

previous report that a reduced cerebrovascular response contributes to cognitive dysfunctions in PD [9]. Interestingly, the PD group showed a negative association between both the within-subject left and right CBFv peak and executive functioning, with greater variability associated with poorer executive function. These findings are potentially of great interest, given the significant body of literature linking PD with deficits in executive functioning [50]

This study has a number of limitations. Firstly, we employed one cognitive task in the fTCD assessment that is reliant upon verbal fluency and we only assessed CBFv from the MCA. It would be beneficial in the future to assess cognition more broadly, as well as to investigate other cerebral arteries, to assess neurovascular coupling. In addition, we cannot exclude the possibility that potential changes in blood pressure or arterial gases during our fTCD assessment influenced our CBFv measures [51]. In regard to participant characteristics, the PD sample was heterogeneous in relation to age, disease duration, and medication. Due to our recruitment approach (non-population based), our group were relatively cognitively healthy, demonstrated by lack of differences in cognitive performance between PD and control groups; even on tests like the Hayling and Brixton, which have previously been shown to be sensitive to detecting executive function impairment in people with PD [52,53]. Lastly, all PD participants were tested on their medication, hence a possible medication effect cannot be omitted.

Notably, while using fTCD to investigate cerebrovascular functioning in PD patients has many advantages, including its non-invasive nature and the unique insight it provides into autonomic regulation of the CBFv, it also presents some disadvantages. Due to the skull thickening with advancing age, 14% of the current participants had to be excluded due to an inadequate insonation window, leading to a small final sample. Although this small sample size is typical of studies in this field [21], it may have resulted in us being underpowered to detect differences in measures between the two groups. A poor insonation through the temporal window is quite common, limiting the efficiency of TCD in older populations [54]. Therefore, it may be advantageous for future studies to bypass this difficulty by utilising near-infrared spectroscopy, allowing for the inclusion of larger participant sample sizes.

In summary, PD patients showed a significantly higher variability of the lateralisation of cerebrovascular response during a language task, as compared to healthy older adults. This suggests that PD-related cerebrovascular changes are different from those seen in healthy ageing, which has been associated with an attenuation of lateralisation (but not variability) [29]. PD appears to involve, neurovascular coupling abnormalities during cognitive processing, which appear to relate to cognitive impairments, particularly within the executive function domain. Thus, cerebrovascular dysfunction could represent a potentially novel therapeutic avenue for the treatment of cognitive dysfunction in PD, currently a major area of unmet clinical need.

Ethical standards

This study was approved by the Human Research Ethics Committees of both the University of South Australia and the University of Adelaide in accordance with national guidelines. Therefore, this study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study and details that might disclose the identity of the subjects have been omitted.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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