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Cerebrovascular responses to somatomotor stimulation in Parkinson's disease: A multivariate analysis

Sam C Barnes[1], Ronney B Panerai[1,2], Lucy Beishon[1,2], Martha Hanby[1], Thompson G Robinson[1,2] and Victoria J Haunton[1,2]

Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder, yet little is known about cerebral haemodynamics in this patient population. Previous studies assessing dynamic cerebral autoregulation (dCA), neurovascular coupling (NVC) and vasomotor reactivity (VMR) have yielded conflicting findings. By using multi-variate modelling, we aimed to determine whether cerebral blood flow (CBF) regulation is impaired in PD patients.

55 healthy controls (HC) and 49 PD patients were recruited. PD subjects underwent a second recording following a period of abstinence from their anti-Parkinsonian medication. Continuous bilateral transcranial Doppler in the middle cerebral arteries, beat-to-beat mean arterial blood pressure (MAP; Finapres), heart rate (HR; electrocardiogram), and end-tidal CO_2 ($EtCO_2$; capnography) were measured. After a 5-min baseline period, a passive motor paradigm comprising 60 s of elbow flexion was performed. Multi-variate modelling quantified the contributions of MAP, $ETCO_2$ and neural stimulation to changes in CBF velocity (CBFV). dCA, VMR and NVC were quantified to assess the integrity of CBF regulation.

Neural stimulation was the dominant input. dCA, NVC and VMR were all found to be impaired in the PD population relative to HC ($p < 0.01$, $p = 0.04$, $p < 0.01$, respectively). Our data suggest PD may be associated with depressed CBF regulation. This warrants further assessment using different neural stimuli.

Keywords

Cerebral autoregulation, multi-variate modelling, neurovascular coupling, Parkinson's disease, vasomotor reactivity

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that affects 2-3% of those over the age of 65.[1] It is characterised pathologically by the degeneration of dopaminergic neurones in the substantia nigra and the presence of Lewy bodies.[1,2] Despite advancements in functional and molecular imaging, PD primarily remains a clinical diagnosis based on the presence of the cardinal symptoms of bradykinesia, tremor, rigidity and postural instability.[3] Non-motor symptoms are common, including cognitive dysfunction which is the leading cause of reduced quality of life, carer burden and economic cost associated with the disease.[4–6] Autonomic dysfunction is also common, with clinical symptoms including orthostatic hypotension.[7]

Cerebral autoregulation (CA) describes the ability of the cerebrovasculature to maintain a relatively constant blood supply to the brain, despite fluctuations in blood pressure (BP).[8] The autoregulation of cerebral blood supply can be described as either static (sCA) or

[1]Department of Cardiovascular Sciences, University of Leicester, Robert Kilpatrick Clinical Sciences Building, Leicester, UK
[2]NIHR Leicester Biomedical Research Centre, BHF Cardiovascular Research Centre, Glenfield Hospital, Leicester, UK

Corresponding author:
Sam C Barnes, Department of Cardiovascular Sciences, University of Leicester, Leicester LE2 7LX, UK.
Email: scbarnes@doctors.org.uk

dynamic (dCA). sCA describes the response of the cerebrovasculature to long term changes in BP (minutes), while dCA refers to the response to acute fluctuations in BP (seconds).[9] dCA can be quantified using the autoregulation index (ARI) as described by Tiecks et al.,[9] which allows for the objective comparison of autoregulatory capacity between individuals and patient populations.

Vasomotor reactivity (VMR) is the ability of arterioles in the cerebrovascular tree to alter their diameter in response to changes in the partial pressure of carbon dioxide (pCO_2).[10] Hypercapnia causes vasodilation, while hypocapnia causes vasoconstriction. Hypercapnia is known to impair CA, while conversely hypocapnia is associated with improved metrics of autoregulation.[11] The mechanisms underlying VMR remain uncertain. Recent work suggests that the arterial partial pressure of CO_2 plays a role independent of pH;[12] the autonomic nervous system has also been implicated.[13]

During times of increased cognitive activity, there is an associated increase in cerebral blood flow (CBF), termed neurovascular coupling (NVC).[14] This is mediated through a complex series of interactions by cells surrounding the microcirculation, including smooth muscle cells, astrocytes, neurones and vascular endothelial cells. Together, these cells comprise the neurovascular unit.[15,16] Through the neurovascular unit, NVC provides a temporal and regional link between blood flow and cognitive load, with the dual purpose of substrate provision and the removal of metabolic by-products from the active tissue.[17]

NVC can be assessed using a variety of stimuli to create a local or global cerebral blood flow (CBF) response. These include cognitive assessment tools,[18,19] writing,[20] visual stimuli,[19] speaking[21] and sensori-motor tasks.[22] The changes in CBF can be quantified using imaging techniques such as functional MRI (fMRI) and near infrared spectroscopy (NIRS).[23] An alternative to these techniques is transcranial Doppler ultrasound (TCD), which allows for the non-invasive measurement of CBF velocity (CBFV) as a surrogate measure for CBF.[24,25] Its ease of use, excellent temporal resolution and low cost make it a suitable and reliable bedside alternative to fMRI or NIRS.[26]

Previous studies assessing cerebral haemodynamics in PD are heterogenous and of varying quality. A variety of paradigms and stimuli have been employed to assess CA in this population, including head-up tilt,[27] the cold-pressor test,[28] breath holding[29] and acetazolamide.[30] Some studies have found CA to be abnormal,[28,29,31] while others report it to be preserved in this population.[32–34] Only one study employed transfer function analysis (TFA),[33] which is a widely accepted and verified technique for the reliable assessment of dCA.[35,36] Studies have found VMR to be both impaired[29] and intact,[37–39] while the general consensus is that NVC is intact in PD patients when assessed by TCD.[31,32,34]

However, the majority of these studies have reported changes in CBFV as a direct reflection of NVC, without considering the influence of the co-variates of pCO_2 and BP on the cerebrovascular response to the stimulus. While pCO_2 and BP are usually measured and reported as baseline values, there is rarely a quantification of their contribution to the CBFV response.[18–22] This can be addressed with the use of multivariate modelling, whereby CBFV is modelled as the output, with BP, pCO_2, and a neural stimulation function, $s(t)$, as inputs.[40,41] The added benefit of this approach is that it allows for the simultaneous assessment of dCA, VMR and NVC through the quantification of the contributions of BP, pCO_2 and $s(t)$, respectively, all through the use of a sole stimulus, and at the same period of time.[42] Additionally, the majority of these studies have been performed in relatively small populations of PD patients, which further diminishes the reliability of the conclusions that can be drawn from their data.

Through the use of a multi-variate modelling approach in a comparatively larger study population, we aimed to address the heterogeneity, variable quality and contradictory findings of the existing literature by testing the hypothesis that CBF regulation is depressed in PD, as manifested by alterations in dCA, VMR or NVC. Furthermore, we aimed to ascertain whether anti-parkinsonian medication had an effect on cerebral haemodynamics in PD patients.

Materials and methods

Patients with PD were recruited from specialist clinics at the University Hospitals of Leicester NHS Trust, or by direct invitation from Parkinson's Disease UK. All patients had received a diagnosis of PD from a specialist physician. Age matched healthy controls (HC) were defined as those with stable and well-controlled medical co-morbidities and were recruited locally or from the partners of PD patients. We excluded patients with diabetes mellitus, dementia, peripheral neuropathy, ischaemic heart disease or cerebrovascular disease. Patients with PD whose swallowing was dependent on their medication or who had undergone deep brain stimulation were also excluded.

The study had ethical approval from a UK Ethics Committee (ref: 11/EM/0369). All procedures were conducted in accordance with the Declaration of Helsinki 1975. All participants provided written informed consent.

Data collection was undertaken in the Cerebral Haemodynamics in Ageing and Stroke Medicine (CHIASM) laboratory, which is kept at a constant temperature and free from distraction to provide a suitable environment for uninterrupted data collection. Participants were asked to abstain from caffeine, alcohol, chocolate, large meals and smoking in the 4 hours prior to data collection. Upon arrival, baseline parameters of age, sex and handedness, as assessed by the Edinburgh Handedness Inventory, were collected.[43]

Experimental methods

Following a 10 minute period of rest and stable recordings, a series of recordings were obtained. First, we obtained a 5 minute recording of the patient at rest, lying supine, awake and with their eyes open. Next, participants underwent a respiratory paradigm; the results of which are reported elsewhere.[37] Finally, participants underwent a passive motor paradigm, which is the focus of the present study. Following a 90 s period of rest, the researcher passively flexed the participants dominant arm at the elbow for 60 s, at a frequency of 1 Hz, as guided by a metronome. This was followed by a 90 s period of silent recovery. The passive elbow flexion manoeuvre was selected due to its proven validity and reproducibility in older adults.[44]

PD patients were invited to attend the laboratory on two occasions, no more than two weeks apart. On the second visit they attended after a period of abstinence from their anti-Parkinsonian medications for either 12 or 24 hours depending on the drugs and their preparations.

Instrumentation

Heart rate (HR) was measured using 3-lead electrocardiography. Bilateral insonation of the middle cerebral artery (MCA) was performed using 2 MHz TCD probes (Viasys Companion III). Once the MCA was identified and a good trace obtained, probes were held in a fixed position by a custom-built headset. Continuous beat-to-beat estimates of blood pressure (BP) were obtained through arterial clamping of the digital artery (Finometer, Finapres Medical Systems, Amsterdam). End-tidal CO_2 ($EtCO_2$) was measured with nasal capnography (Salter labs, ref. 4000) Intermittent brachial BP was measured using a validated electrosphygmomanometer (Omron UA 767) to calibrate recordings from the Finometer.

Data processing

Data were visually inspected, and non-physiological spikes in CBFV were removed through linear interpolation. Files that contained poor quality or unilateral TCD signals were excluded from further analysis. Narrow spikes and artefacts in other physiological parameters in remaining files were removed through linear interpolation. Data were filtered in the forward and reverse direction using a low-pass Butterworth filter with a cut-off frequency of 20 Hz. The beginning and end of each cardiac cycle were detected in the ECG signal, and mean values of BP, CBFV and HR were obtained for each cardiac cycle. End-expiratory values were detected in the $EtCO_2$ signal, linearly interpolated, and resampled at each cardiac cycle.

The effects of BP, $EtCO_2$ and the passive elbow flexion manoeuvre were expressed in the time domain as an autoregressive moving average model (ARMA).[40,45,46] At each time point, CBFV was modelled as the previous Nv CBFV values, plus the sum of the relative contributions of BP, $EtCO_2$ and neural stimulation resulting from the manoeuvre (Figure 1 adapted with permission from Panerai et al.[42]). The moving average terms, representing each of the three inputs, was comprised of Np (BP), Nc ($EtCO_2$) and Ns (neural stimulation) samples, respectively.[42] [Nv,Np,Nc,Ns] represent the orders of the ARMA model. These were chosen as [2, 4, 1, 1] based on previous studies, and their suitability was assessed by the model prediction error, expressed as the correlation coefficient between measured and model predicted CBFV.[40,45,46] The neural stimulation input was expressed by a gate function obtained by recording the electrical output of a metronome during the activation phase of the manoeuvre.[46] The relative contributions to the CBFV response by BP, CO_2 and stimulation were quantified by their variance, notated as VAR_{BP}, VAR_{CO2} and VAR_{STIM}.

Once the ARMA model coefficients were estimated by means of least squares, CBFV step responses were obtained for each input, creating CBFV/BP, CBFV/CO_2 and CBFV/STIM step responses. The CBFV/BP

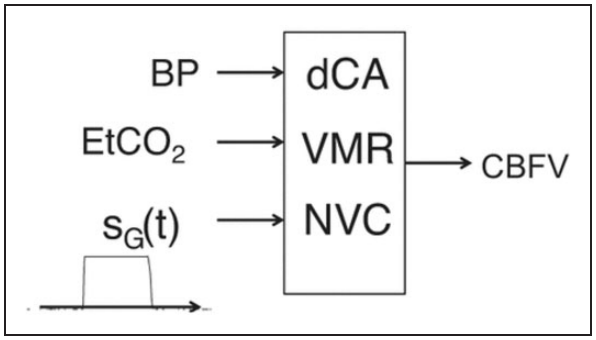

Figure 1. Schematic model of the contribution of blood pressure (BP), dynamic cerebral autoregulation (dCA), end-tidal CO_2 ($EtCO_2$), vasomotor reactivity (VMR), gate function ($S_G(t)$) and neurovascular coupling (NVC) to the cerebral blood flow velocity (CBFV) response to the passive elbow flexion paradigm. Adapted with permission from Panerai et al, 2019.[42]

step response represents dCA, and allows for the estimation of the autoregulation index (ARI), by fitting of the Tiecks et al. model.[9,46] The ARI ranges from zero to nine, with zero representing absence of autoregulation and nine the most efficient autoregulation that can be observed. The CBFV/CO_2 step response represents the integrity of VMR, which was assessed by measuring the plateau of the CBFV/CO_2 step response in $cm.s^{-1}.mmHg^{-1}$ of $EtCO_2$. Finally, we quantified the effect of motor stimulation by the mean value of the CBFV/STIM step response for the same time interval of 30–40 s into the response.

Data were visually inspected, and participants with poor quality data were rejected. Step responses generated by the ARMA model from remaining participants were visually inspected, and those with temporal patterns that were not physiologically plausible were also rejected.

Statistical analysis

Demographic data. Physiological parameters at rest were inspected for normality using Q-Q plots. Values were compared between groups using independent t-tests for ordinal data, and the chi-squared test for nominal data.

Inputs into the CBFV response. A hierarchal approach was employed, whereby the Wilcoxon-signed rank test was utilised initially to compare the contribution of these inputs between hemispheres. In instances where significant hemispheric differences were noted, hemispheric data were analysed separately. Where no significant differences existed between hemispheres, bilateral data were subsequently averaged before testing for the effect of medication with Friedman ANOVA. In instances where there was no significant effect of medication, PD data were averaged between visits, prior to testing for the effect of disease state with the Mann-Whitney U test.

Step responses. Paired t-tests were used to compare bilateral hemispheric outputs for ARI, CBFV-$EtCO_2$ and CBFV-STIM. In HC, data were compared between the dominant and non-dominant hemispheres, as assessed by the Edinburgh Handedness Inventory.[43] For PD participants, data were compared between the onset and non-onset hemispheres, as detailed by clinician assessment. Where no significant differences existed, these data were averaged.

Subsequently, the effect of medication was assessed using repeated measures ANOVA, with PD participants grouped by medication state (medicated vs. unmedicated). Where no significant differences existed, these data were averaged before independent t-tests were used to compare HC vs. PD. For parameters which demonstrated hemispheric differences, we employed the General Linear Model (GLM) to compare the dominant/non-dominant hemispheres (HC) against the onset/non-onset hemispheres (PD). Tukey post-hoc testing was utilised where significant differences were detected. Significance was set at $p < 0.05$.

Results

Recruitment and data quality

Fifty-five HC and forty-nine PD participants were recruited. Four participants within the HC group had their data rejected due to non-physiological model outputs, leaving 51 good quality, bilateral data sets. Of the forty-nine PD participants, three did not return for a repeat visit. Participants whose data were excluded, in either the medicated or unmedicated state, were entirely removed from the study, leaving 34 good quality, repeated, PD datasets. Supplementary Table S.1 details the rationale for exclusion and the numbers of excluded participants for each reason.

The correlation coefficient between the recorded CBFV signal and the model predicted output was 0.99 ± 0.01 for HC, PD (medicated) and PD (unmedicated) inclusive.

Participant demographics and baseline physiological parameters

In those included, the mean age was 62.2 ± 10.3 years (31/51 male) for HC and 67.6 ± 9.4 years (22/34 male) for PD patients. Representative data from a single participant and mean population responses to stimulation are given in Figures 2 and 3, respectively. Resting CBFV was comparable between hemispheres in both study groups, and so these data were averaged for further analysis. The two groups were comparable with the exception of age. Disease state had no significant effect on resting parameters in either the medicated or unmedicated state (Table 1).

Variance contributions to the CBFV response

The contributions of BP, $EtCO_2$ and neural stimulation to ΔCBFV (VAR_{BP}, VAR_{CO2}, VAR_{STIM}, respectively) did not differ significantly between hemispheres across all groups; therefore, these data were averaged. Differences in medication state did not significantly affect VAR_{BP}, VAR_{CO2} or VAR_{STIM}, and therefore PD data were averaged across the two visits prior to comparisons against HC. VAR_{BP}, VAR_{CO2} and VAR_{STIM} were statistically similar between the HC and PD populations (Table 2). VAR_{STIM} was the

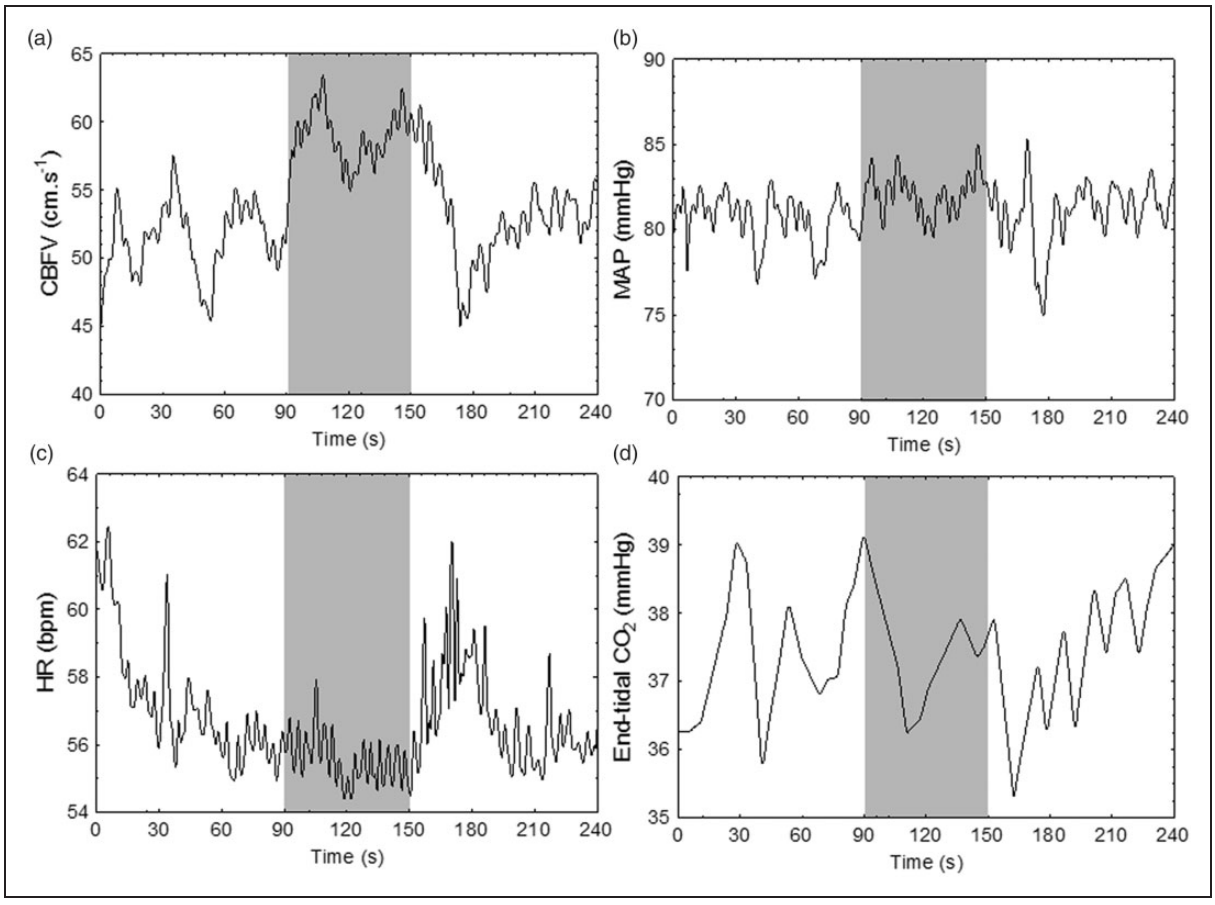

Figure 2. Representative data from a 51 year old female participant, demonstrating the physiological response to the passive elbow flexion manoeuvre. Shaded area represents period of stimulation. (a) CBFV, averaged cerebral blood flow velocity across hemispheres; (b) MAP, mean arterial pressure; (c) HR, heart rate; (d) end-tidal CO_2.

dominant input in both PD patients ($p < 0.01$) and HC ($p < 0.001$).

Step responses

CBFV step responses to the influences of BP, $EtCO_2$ and neural stimulation did not show significant differences between hemispheres in the PD population. However, the step response to neural stimulation was significantly greater in the dominant hemisphere in HC as compared to the non-dominant hemisphere ($p < 0.001$). Therefore, hemispheric data for the step response to neural stimulation were analysed separately for HC.

Estimates of ARI were significantly depressed in PD compared to HC (6.2 ± 2.3 vs 7.5 ± 1.5, $p < 0.001$, Figure 4(a)). The step response to changes in $EtCO_2$, used to quantify VMR, was significantly dampened in the PD population ($p < 0.01$, Table 3, Figure 4(b)). On GLM, significant differences existed in the CBFV/STIM step response, which on post-hoc testing was identified as being between the dominant hemisphere in HC and the onset hemisphere in the PD population (4.5 ± 0.6 vs 3.2 ± 0.5, $p = 0.04$, Table 3, Figure 4(c)). However, no other significant differences were detected between hemispheres and study groups.

Discussion

Key findings

To our knowledge, this is the first study to assess cerebral haemodynamics in a PD population through a multi-variate approach. We have demonstrated that the relative explanatory contribution of the inputs into the cerebrovascular response, namely BP, $EtCO_2$ and passive motor stimulation, do not vary significantly between hemispheres nor according to medication state or disease state as compared to HC. The passive elbow flexion manoeuvre was the dominant input in both HC and PD patients, with a variance contribution notably greater than that of BP or $EtCO_2$.

Additionally, our approach has shown that the autoregulatory response to fluctuations in BP is

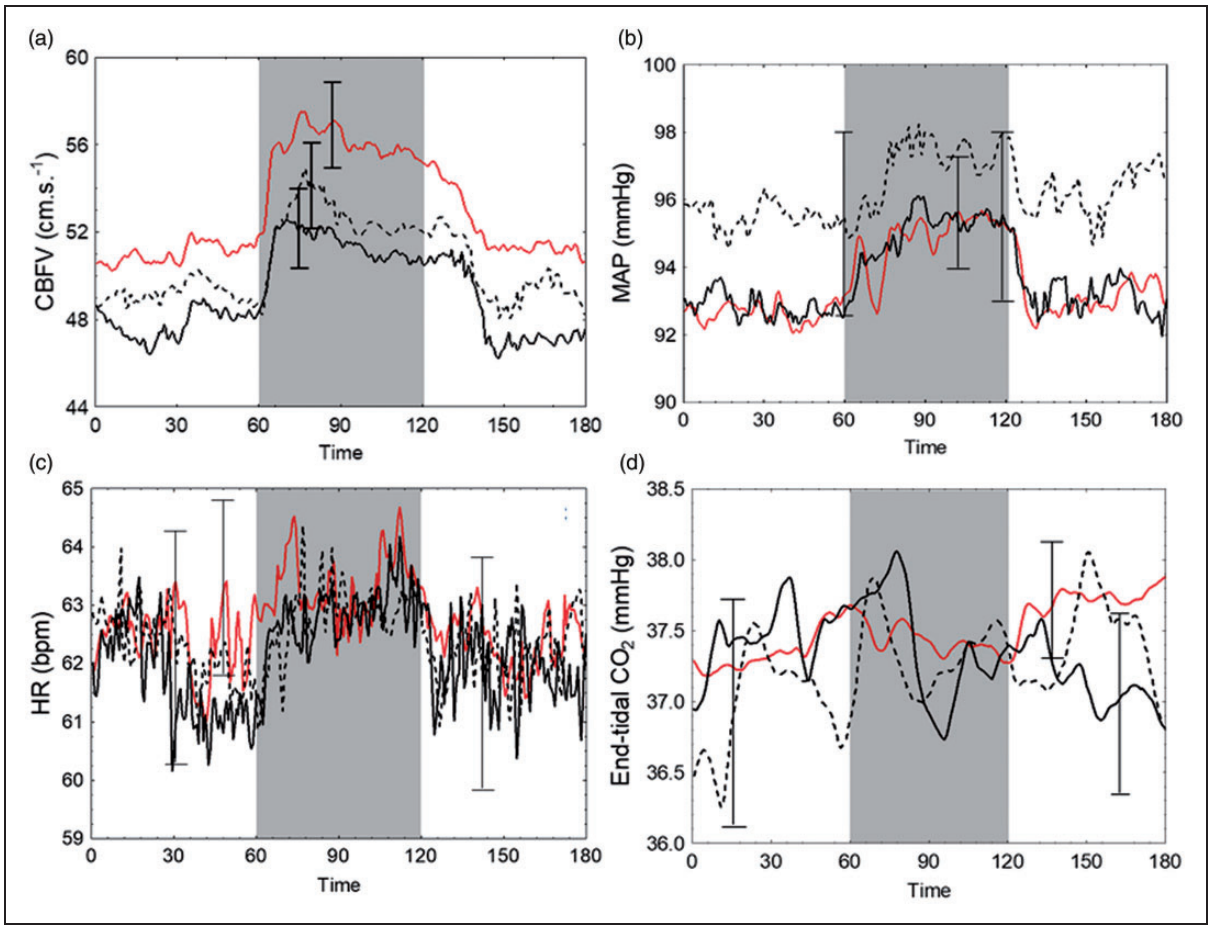

Figure 3. Average data for physiological parameters in response to neural stimulation for healthy controls and PD subgroups. Shaded area represents period of stimulation. Solid red line, healthy controls; solid black line, PD medicated; black dotted line, PD unmedicated. Error bars are largest ± standard error at the point of occurrence. (a) CBFV, averaged cerebral blood flow velocity across both hemispheres. (b) MAP, mean arterial pressure. (c) HR, heart rate. (d) end-tidal CO_2.

depressed in the PD population compared to HC, although whether this is a true impairment remains unclear and will be discussed further. VMR is also impaired, and we found that there was a statistically significant difference in the hemispheric response to passive motor stimulation between the dominant hemisphere in HC, and the onset hemisphere in the PD population.

Together, these results suggest that the relative contributory factors to CBF changes following neural stimulation are similar in both HC and PD patients, yet the disease process causes alterations in cerebrovascular regulatory functions that manifest as differences in dCA, VMR and NVC in those affected by the disease. This finding appears to be independent of the presence of anti-parkinsonian medication.

dCA in PD

Previous attempts to assess dCA in this population have led to conflicting results, most likely due to the substantial heterogeneity in these studies. Studies have used different techniques to induce changes in CBFV including head-up tilt (HUT)[27,33,47] and the cold-pressor test.[28,48] Importantly, a variety of modelling techniques have been employed. Several studies assessed CA by comparing CBFV between HC and PD patients before and after stimulation,[28,47,49] while others used both the pulsatility index and cerebrovascular reactivity.[27,48] No studies involving PD patients have employed ARI as their metric to assess CA, and only one study employed transfer function analysis (TFA),[33] which is a widely accepted and verified technique for the reliable assessment of dCA.[35,36] In their study, Haubrich et al.[33] used the tilt-table test, and demonstrated that PD patients with orthostatic hypotension had BP instability induced by tilting, but the dCA response was preserved as quantified by measures of phase and gain.

In the present study, we generated estimates of ARMA-ARI in response to BP fluctuations induced by a passive motor paradigm. Tiecks' classical paper

Table 1. Participant physiological parameters at rest. Values are population mean ± SD.

Parameter	HC (n = 51)	PD Medicated (n = 34)	PD Un-medicated (n = 34)	P-value - HC vs. medicated	P-value - HC vs. unmedicated
Mean CBFV ($cm.s^{-1}$)	49.7 ± 13.0	47.7 ± 9.6	48.6 ± 9.6	0.45	0.70
MAP (mmHg)	91.7 ± 10.0	90.9 ± 12.9	94.1 ± 13.1	0.73	0.35
Heart rate (bpm)	63.2 ± 9.1	61.8 ± 9.9	62.4 ± 9.4	0.48	0.68
End-tidal CO_2 (mmHg)	38.2 ± 4.3	37.3 ± 3.9	37.7 ± 4.0[a]	0.37	0.63

HC: healthy controls; PD-medicated: Parkinson's disease patients with medication ON; PD-unmedicated: Parkinson's patients with medication OFF; Mean CBFV: cerebral blood flow velocity averaged across hemispheres. MAP: mean arterial pressure.
P-value; unpaired t-tests.
[a]$EtCO_2$ data from two participants excluded due to unreliable capnography trace.

Table 2. Fraction of the CBFV response variance (mean ± SD) explained by each of the three inputs (BP, $EtCO_2$, stim) stratified by study group. PD data averaged between visits.

Parameter	HC (n = 51)	PD (n = 34)	P-value
VAR_{BP}	0.27 ± 0.19	0.31 ± 0.20	0.25
VAR_{CO2}	0.25 ± 0.18	0.25 ± 0.19	0.74
VAR_{STIM}	0.48 ± 0.16	0.43 ± 0.20	0.25
P-value	<0.001*	<0.01*	–

HC: healthy controls; PD: Parkinson's disease patients; VAR_{BP}: variance contribution of blood pressure; VAR_{CO2}: variance contribution of end-tidal CO_2; VAR_{STIM}: variance contribution of stimulation by manoeuvre. P-value comparing HC vs. PD, Mann-Whitney U test. *P-value comparing separate variance contributions, Friedman ANOVA.

describes a population mean ARI of 5 ± 1, derived from the thigh-cuff manoeuvre.[9] In the present study we report results of 7.5 ± 1.5 vs 6.2 ± 2.3 for HC and PD patients, respectively, which are higher than Tiecks' reference point. One interpretation of these data, at face value, may be to conclude that our populations had unusually effective autoregulation. However, existing literature demonstrates that estimates of ARMA-ARI are known to be elevated compared to Tiecks' reference values[50] and therefore direct comparison is inappropriate.

While we have demonstrated a significant difference in the dCA response between HC and PD subjects, we cannot reliably conclude that dCA is impaired in those with PD. Instead, we conclude that dCA appears to be depressed in PD patients relative to our population of HC, but whether this represents true inhibition is uncertain. Further work using a paradigm that induces large BP oscillations such as the squat-stand manoeuvre, or the thigh cuff manoeuvre, would provide a more challenging assessment of dCA and may clarify this uncertainty.[51]

VMR in PD

In the present study, we have demonstrated a significant difference in VMR between HC and PD patients. As with dCA, the existing literature on VMR in PD is conflicting. Previous studies have found VMR to be impaired[29] and intact,[37–39] and again there was considerable heterogeneity in terms of study size and measurement technique. The single study that found VMR to be impaired utilised a breath-holding paradigm in a population of fifteen PD patients, in both their medicated and unmedicated states.[29] As in our study, they found an impairment in VMR, relative to HC, which was independent of medication state.

However, the majority of studies report no evidence of impairment. Krainik et al. used a hypercapnic stimulus and BOLD-MRI to assess VMR in a population of ten PD patients and eight HC, and found no significant differences between the two study groups both in the presence and absence of dopaminergic medication.[38] Al-Bachari et al. also used a hypercapnic challenge in the context of an fMRI study and found no significant difference in cerebrovascular reactivity.[39] Interestingly, Hanby et al. used induced hyperventilation on the same study cohort as reported here, and found no evidence of impairment in VMR.[37]

The contrast between the present findings and those of Hanby is particularly interesting given the data were taken from the same study cohort, albeit performing a different manoeuvre as part of a series of recordings. On one hand, we might expect the induced hyperventilation used by Hanby to be more sensitive to differences in VMR, given the larger changes in pCO_2 as compared to our passive motor paradigm.[37] However, the analysis approach utilised did not account for the concomitant changes in BP and neural stimulation induced by the manoeuvre. Additionally, the analysis technique used was relatively simplistic; only a ratio between changes in CBFV and changes in $EtCO_2$ was calculated. This fails to consider the dynamic response of CBFV to changes in pCO_2, which are automatically accounted for in the ARMA model and expressed by the CBFV/$EtCO_2$ step response.[42]

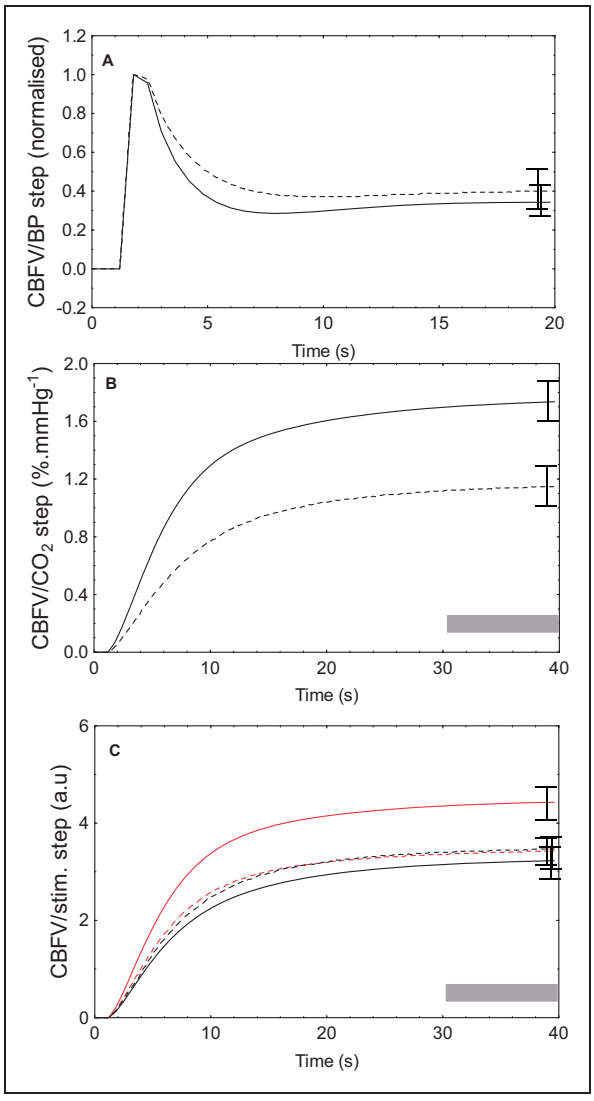

Figure 4. Mean CBFV step responses to fluctuations in blood pressure (BP, a), end-tidal CO_2 (b) and neural stimulation (c). In (a) and (b), solid line represents healthy controls (HC); dashed line, subjects with Parkinson's disease. In (c), solid red line represents healthy controls dominant hemisphere; small dashed red line, HC non-dominant hemisphere; dotted black line, Parkinson's patients non-onset hemisphere, solid black line, Parkinson's patients onset hemisphere. CBFV, cerebral blood flow velocity. Error bars represent standard error of the mean at point of maximal occurrence. Grey shading represents time interval where mean value of the step response was calculated (Table 3).

Future work utilising a hypercapnic manoeuvre in the context of ARMA modelling might be more sensitive, given evidence that haemodynamic parameters and pCO_2 demonstrate a non-linear relationship.[52] With small fluctuations, as in the present study (Figure 3), $EtCO_2$ is within the region of greater sensitivity of the logistic curve.[52] At this point on the curve, there is a comparatively linear relationship, and small changes in $EtCO_2$ induce noticeable changes in CBFV. In contrast, with a large change in PaCO2, as induced by hyperventilation, parameters enter the region of the logistic curve where sensitivity is significantly reduced and changes in $EtCO_2$ lead to a relatively small change in CBFV.

NVC in PD

To our knowledge, the existing TCD literature contains four studies that assess NVC in the PD population, none of which have demonstrated statistically significant evidence of impairment.[31,32,34,53] The only study that utilised a motor paradigm was that of Troisi et al., who used a thumb-finger opposition task to study twelve PD patients in their medicated state, seven of whom returned for a repeat visit after abstaining from medication.[31] The other studies used visual stimulation[32,34] or cognitive tasks[53] to assess NVC.

Troisi et al. found no significant effect of disease or medication state on NVC, but their analysis technique did not account for the temporal pattern of the CBFV response. Instead, they reported a single peak %change in CBFV following stimulation. By reporting a single value, the temporal relationship between both the initiation and cessation of stimulation, and the CBFV response cannot be interpreted. In contrast, Gutteridge et al. reported NVC data from 21 PD patients, and measured the latency of the CBFV response.[53] They described a non-significant trend towards an attenuated and delayed response to cognitive stimulation in the PD population.

In the present study, GLM demonstrated a significant difference in the magnitude of the CBFV/STIM step response between the dominant hemisphere in HC and the onset hemisphere in PD patients. We hypothesise that the ARMA approach has allowed us to detect this difference, which may have been present in other studies but was not statistically demonstrable. By accounting for the co-variates of BP and $EtCO_2$, we have been able to isolate the cerebrovascular response to neural stimulation with greater sensitivity and thus have identified a significant difference.

Clinical perspectives

Cerebral autoregulation is known to be impaired in a variety of disease states, including acute ischaemic stroke, traumatic brain injury and sepsis.[56–58] Our data suggest that PD may be added to this list of conditions.

In the case of acute stroke, there is a growing movement towards individualised care, whereby BP is titrated to ensure an adequate but not excessive cerebral perfusion pressure in the acute setting. This also applies to the

Table 3. CBFV step response parameters to changes in blood pressure, end-tidal CO_2 and neural stimulation.

Step response input	HC (n = 51)		PD (n = 34)		P-value
BP (ARI)	7.5 ± 1.5		6.2 ± 2.3		<0.01
CO_2 step ($cm.s^{-1}.mmHg^{-1}$)	1.8 ± 1.5		0.93 ± 0.7		<0.01
	Dominant	Non-dominant	Onset	Non-onset	
Stimulus (a.u.)	4.5 ± 2.3	3.5 ± 2.5	3.2 ± 2.0	3.4 ± 1.6	*0.02

Note: ARI describes the temporal pattern of the CBFV step response to the BP input. For the CO_2 and stimulus inputs, the CBFV step response is represented by the mean value of the plateau (Figure 4) from 30 to 40 s into the response. Values are means ± SD. Hemispheric data were averaged for ARI and the CO_2 step response, but significant differences between hemispheres in HC led to the response to stimulation being analysed separately. HC: healthy controls; PD: Parkinson's disease patients; BP: blood pressure; ARI: autoregulation index.
P-values, unpaired t-test.
*p-value from the General Linear Model. Post-hoc Tukey testing identified the difference between HC (dominant) and PD (onset), p = 0.04.

operating table, whereby recent recommendations suggest that BP should be rigidly controlled peri- and intra-operatively in the stroke patient to reduce the risk of further cerebral infarction or secondary haemorrhage as a result of impaired autoregulation.[59]

As yet there has been no such consensus on the integrity of cerebral autoregulation in PD, and so the clinical implications of our findings should be carefully considered in individual cases where patients exhibit signs and symptoms in keeping with autoregulatory dysfunction, for example in those with orthostatic hypotension. Additionally, our data suggest that measures should be taken peri- and intra-operatively to closely regulate BP in PD patients requiring general anaesthesia, thus ensuring adequate but not excessive cerebral perfusion. Further validation of our findings would be required before any definitive recommendations can be made for clinical practice.

Limitations

The key limitation associated with the use of TCD is the assumption that CBFV is a reliable reflection of CBF. We assume that the diameter of the insonated vessel does not vary significantly throughout the paradigm, despite fluctuations in $EtCO_2$. In the present study, variation in $EtCO_2$ was small throughout the paradigm (Figure 3), making significant changes in arterial diameter unlikely.[26,54]

Another limitation of this study is the proportion of participants whose data were rejected. The majority of exclusions occurred during and after the ARMA modelling process (Suppl. Table S.1). We acknowledge that the reduction in our sample size may have increased the likelihood of type II error. However, given that our findings demonstrate depression in dCA, VMR and NVC, if there is statistical error, it is likely that the error is an underestimation of differences as opposed to failing to demonstrate them.

Additionally, we acknowledge that we assessed VMR using spontaneous fluctuations in $EtCO_2$ as part of a passive motor paradigm. Using a hyperventilation manoeuvre, as employed by Hanby et al.,[37] would generate larger fluctuations in $EtCO_2$ and may provide a more robust challenge to the cerebrovasculature. However, we note previous studies have used spontaneous fluctuations in $EtCO_2$ as part of a multivariate approach and have generated physiologically relevant and plausible results.[40–42,46] Further multivariate work employing induced fluctuations in $EtCO_2$ would help clarify if the choice of paradigm has an impact our findings.

Finally, we note that our HC and PD populations were slightly mismatched in terms of age, with a mean difference of 5.4 years between the two groups (p = 0.01). Given the small magnitude of this difference, and the predominant view that there is no significant effect of ageing on autoregulatory processes,[55] it is highly unlikely that this has confounded the findings of our study.

Conclusions

In summary, our study is the first to use a multi-variate approach to assess cerebral haemodynamic regulation in a PD population. We have shown that the relative explanatory contributions of BP, $EtCO_2$ and neural stimulation into the CBFV response are comparable between HC and PD patients. Medication state in PD patients had no significant effect, and in both groups, neural stimulation was the dominant input.

Despite comparatively similar contributions of BP, EtCO2 and neural stimulation to the CBFV response, we demonstrated differences in dCA, VMR and NVC in the PD population. Therefore, we hypothesise that the disease process of PD causes alterations in cerebrovascular regulatory functions that manifest as reductions in the efficiency of dCA, VMR and NVC. Further work using different stimuli may shed light

on whether this finding is isolated to the passive elbow flexion manoeuvre.

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Authors' contributions

VJH, TGR and RBP designed research. VJH and MH performed experiments. SB, LB and RBP analysed data. SB and RBP prepared figures. SB and RBP drafted the manuscript. All authors approved the final version of the manuscript.

ORCID iDs

Sam C Barnes https://orcid.org/0000-0001-6009-406X
Ronney B Panerai https://orcid.org/0000-0001-6983-8707

Supplemental material

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