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Variability in cerebral blood flow velocity at rest and during mental stress in healthy individuals: Associations with cardiovascular parameters and cognitive performance

Running head: Cerebral blood flow velocity variability and mental stress

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Highlights

- CBFV variability in both MCA and ACA is mainly expressed in the LF and VLF ranges
- CBFV variability is greater in the MCA than in the ACA
- CBFV oscillations in the LF and VLF ranges markedly decrease during mental load
- BP variability is closely associated with CBFV variability, especially in the LF band
- LF CBFV variability negatively correlated with cognitive performance

Abstract
This study analyzed variability in cerebral blood flow velocity (CBFV) and possible underlying physiological mechanisms during rest and a mental arithmetic task. Blood flow velocities were bilaterally recorded by transcranial Doppler sonography in the anterior and middle cerebral arteries of 43 participants. Electrocardiography, continuous blood pressure (BP) and respiratory recordings were additionally obtained. Fast Fourier transformation revealed a spectral profile with two main components in CBFV, one in the very low frequency (VLF, 0.01-0.025 Hz), and the other in the low frequency band (LF, 0.075-0.11 Hz). During the task, CBFV variability decreased. While heart rate variability and respiration had only weak impacts, BP variability was closely associated with CBFV variability. LF CBFV variability correlated negatively with task performance. The findings indicate a connection between peripheral and cerebral hemodynamics, presumably mediated by the passive pressure-flow relationship and neural mechanisms. LF CBFV variability may constitute a suitable marker of mental effort load.

Key words: Cerebral blood flow variability, transcranial Doppler sonography, heart rate variability, blood pressure, respiratory rate, mental stress

Introduction

Natural physiological functioning shows intrinsic variability, indicating the existence of homeostatic regulation mechanisms which allow physiological systems to flexibly respond to physical and environmental demands and perturbations. Variability in one system can promote variability in another system or, in the opposite manner, confer physiological stability in the other system through negative feedback.

One of the fields in which analysis of physiological variability has proven most useful is the cardiovascular field. Analysis of heart rate (HR) and blood pressure (BP) variability has been successfully applied to assess autonomic cardiovascular control, the autonomic effects of physical and psychological manipulations, and for diagnostics-prognostic purposes at clinical level (e.g., Montano et al., 2009; Thayer & Lane, 2007). Variability in cardiovascular signals has been postulated to be an indicator of top-down integration of brain mechanisms that guide flexible control over behavior and peripheral physiology; as such, it can contribute to our understanding of stress and health (Berntson, Quigley, Norman & Lozano, 2016; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012).

While HR and BP variability has been comprehensively addressed in the fields of basic and clinical research, comparable research is not yet available for cerebral blood flow (CBF) variability. This research gap is important insofar as dysregulations of brain perfusion have been well-established in various diseases and some studies suggested that CBF variability may also be of clinical relevance (Montoro, Duschek, Muñóz, Ladrón de Guevara, & Reyes del Paso, 2016; Panerai, 2009; Panerai et al., 2004; Rickards & Tzeng, 2004). For example, patients with carotid artery disease showed lower spontaneous CBF oscillations than healthy individuals (Diehl, Diehl, Sitzer, & Hennerici, 1991). In contrast, in patients with epilepsy, increased CBF oscillations were seen during the interictal interval (Diehl, Diehl, Stodieck, Ringelstein, 1997). Variability of different frequencies may differentiate between specific types of headaches. While tension-type headache was associated with reduced amplitudes of oscillations in the range between 4 and 7 cycles/min (Sliwka, Harscher, Diehl, Van Schayck, Niesen, & Weiller, 2001), migraine patients showed increased amplitudes of

slower oscillations (0.5 to 3 cycles/min) (Sliwka et al., 2001; Thie, Carvajal-Lizano, Schlichting, Spitzer, & Kunze, 1992). Patients with fibromyalgia pain demonstrated a different distribution of oscillations across the power spectrum, as well as higher complexity (signal entropy) of spontaneous CBF modulations than healthy subjects (Rodríguez, Tembl, Mesa-Gresa, Muñoz, Montoya, & Rey, 2017). Another study revealed a smaller reduction of CBF complexity during painful stimulation in this patient group as compared to controls (Rodríguez, Rey, Montoya, & Duschek, 2017). In addition, CBF fluctuations have been considered as a predictor of cardiovascular and cerebral health, where the prognostic value is moderated by the time scale of variability (Rickards & Tzeng, 2004).

In the present study CBF variability was recorded through transcranial Doppler sonography (TCD). This technique allows for the continuous and non-invasive measurement of bilateral CBF velocities (CBFV) in the main basal cerebral arteries (Aaslid, Markwalder & Nornes, 1982; Duschek & Schandry, 2003). The arteries most frequently insonated by TCD are the middle cerebral artery (MCA), which supplies lateral brain areas, and the anterior cerebral artery (ACA), which supplies medial-anterior cerebral regions.

CBFV variability may be regarded in the framework of cerebral autoregulation (CA). CA refers to vasomotor processess that ensure relatively constant brain perfusion, despite the ocurrence of BP fluctuations (Claassen, Meel-van den Abeelen, Simpson, Panerai & CARNet, 2016; Mitsis, Zhang, Levine & Marmarelis, 2002). In order to ensure a stable blood flow, cerebral resistance vessels constrict during increases, and dilate during reductions, in systemic BP. CA is mediated by several physiological and biochemical processes, including metabolic, myogenic and direct neural factors

(Claassen et al., 2016; Mitsis et al., 2002). The traditional view of CA postulates virtual independence of brain perfusion from peripheral hemodynamics in a relatively large range of systemic BP (Iadecola, 2004; Paulson, 2002). According to this classic view, CBF variability may be interpreted as a sign of decompensation, and related to negative clinical outcomes (Panerai et al., 2004; Rickards & Tzeng, 2014). Although some evidence has linked long-term variations in BP and CBF with end-organ diseases, short-term beat-to-beat BP and CBF variability seems to fulfill a protective role, promoting optimal cerebral perfusion and oxygenation and preventing the negative consequences of acute challenges like hypovolemia, hypotension, hemorrhage or cardiac arrest (see Rickards & Tzeng, 2014, for a review). This is congruent with the well-established positive prognostic value of HR variability (e.g., Thayer, Yamamoto & Brosschot, 2010). In contrast to the traditional view, it may be considered that short-term CBF variability (when maintained within physiological limits) constitutes a protective feature, reflecting the functioning of a complex dynamic system that is influenced by multiple feedback and coupling mechanisms.

Analysis of short-term (in the range of minutes) beat-to-beat variability in peripheral cardiovascular signals, like HR and BP, in the frequency domain yields three main oscillatory components (Berntson et al., 1997, 2016): (a) the very low frequency (VLF) band (<0.04 Hz), which relates, among other factors, to thermoregulation, kidney functioning and myogenic activity; (b) the low frequency (LF) band (0.04 to 0.15 Hz), which represents oscillations related to changes in vasomotor tone and baroreflex regulation of BP; and (c) the high frequency (HF) band (0.15 to 0.40 Hz), which reflects the modulation of these variables due to respiration.

TCD monitoring over long periods demonstrated marked CBFV fluctuations (Lindegaard et al., 1987; Panerai, Eames & Potter, 2006). Frequency domain analysis of resting CBFV in healthy subjects has revealed spontaneous oscillations within the LF range, of around 4 to 7 cycles/min (i.e., 0.06 to 0.11 Hz, including 0.1 Hz Mayer waves) (Diehl, Diehl, Sitzer & Hennerici, 1991; Diehl, Linden, Lücke & Berlit, 1998; Mitsis et al., 2002; Vermeij, Meel-van den Abeelen, Kessels, van Beek & Claassen, 2014) and in the VLF range, of around 0.5 to 3 cycles/min (0.0008 to 0.05 Hz, also known as B-waves, associated with changes in intracranial pressure) (Diehl et al., 1991, 1998; Droste, Krauss, Berger, Schuler & Brown, 1994; Kuo, Chern, Sheng, Wong & Hu, 1998; Lundar, Lindegaard & Nornes 1990; Mautner-Huppert et al., 1989; Mitsis et al., 2002; Newell, Aaslid, Stooss & Reulen, 1992; Vermeij et al., 2014). In addition, oscillations at a HF range, of around 15 cycles/min (i.e., 0.25 Hz), have been described in some (Kuo et al., 1998; Newell et al., 1992), but not all (Diehl et al., 1991; Rickards & Tzeng, 2014) studies.

It has been suggested that CBFV variability relates to spontaneous oscillations in BP (Kuo et al., 1998) and respiration (Perlman, McMenamin & Volpe, 1983). Specifically, oscillations in the HF band have been shown to be synchronized with respiration (Newell et al., 1992), while variability at the LF range has been associated with BP variability, and suggested to originate from peripheral vasomotor activity (Hilz et al., 2013; Kuo et al., 1998). Nonetheless, the linkage between BP and CBFV variability is still under debate, with some studies indicating that these parameters are virtually independent (Diehl et al., 1991; Newell et al., 1992). Moreover, the available studies have exclusively focused on MCA recordings (e.g., Diehl et al., 1991; Kuo et al., 1998; Newell et al., 1992; van Beek, Rikkert, Pasman, Hopman & Claassen, 2010; Zhang,

Zuckerman, Giller & Levine, 1998; Zhang et al., 2002), and no data concerning the ACA are available.

Analysis of the effects of stress on variability of cardiovascular variables has been traditionally used to study autonomic reactivity, inter alia, within the framework of the cardiovascular reactivity hypothesis of cardiovascular diseases (Lovallo & Gerin, 2003; Reyes del Paso, Langewitz, Robles & Pérez, 1996; Thayer et al., 2012). Ample evidence supports the notion that HR and BP variability decreases during mental stress (e.g., Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009; Duschek, Werner, Kapan, & Reyes del Paso, 2008; Reyes del Paso, Langewitz, Mulder, Roon & Duschek, 2013; van Roon, Mulder, Althaus & Mulder, 2004). This variability reduction can be viewed as an autonomic component of the stress response and states of increased physiological activation, reflecting the efforts of the organism to successfully cope with environmental challenges. (i.e., Duschek et al., 2009; Reyes del Paso, González, Hernández, Duschek & Gutiérrez, 2009). To the best of our knowledge, no study evaluating the effects of stress on CBFV variability and processes related to CA is available.

The studies reviewed above are inconclusive concerning the specific spectral profile of CBFV variability in healthy individuals in the basal cerebral arteries, and the possible modulation of CBFV variability in the different frequency ranges by peripheral hemodynamic and respiratory activity. Therefore, complete categorization of CBFV oscillations remains to be achieved, especially regarding the ACA (for which no study is available). Furthermore, the effects of mental stress on CBFV variability and CA remain to be explored. In order to address the issues delineated above, this study

analyzed the spectral distribution of CBFV variability in the MCA and ACA of healthy young individuals, both at rest and during mental stress induced by an arithmetic task. Arithmetic processing is known to increase CBFV in both MCA and ACA (Duschek et al., 2008; Montoro, Duschek, Muñoz-Ladrón de Guevara, Fernández-Serrano & Reyes del Paso, 2015). Additionally, inter-beat interval (IBI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and respiratory rate (RR) were continuously recorded and correlated with CBFV variability. These associations would be informative regarding possible differences in CA as a function of artery and frequency range. For example, it has been suggested that lower frequency oscillations in BP are more effectively buffered by CA mechanisms than respiratory-mediated HF oscillations (Claassen, Levine & Zhang, 2009; Diehl et al., 1998; Mitsis et al., 2002; Zhang et al., 1998). Finally, possible associations between CBFV variability and performance on the arithmetic task were also evaluated.

The main hypotheses of this study were as follows: (1) A spectral profile with the three previously described variability components (i.e., the VLF, LF, and HF bands) will emerge in both pairs of arteries. (2) The perfusion territory of the MCA is larger than that of the ACA, and its diameter is greater. Therefore, greater CBFV variability in the MCA than in the ACA will arise. 3) As with the other cardiovascular variables, CBFV variability in all frequency bands will decrease during mental stress in comparison to under resting conditions. (4) Both during rest and mental stress, CBFV variability will be positively associated with SBP, DBP and IBI variability, and negatively associated with RR. Specifically, CBFV variability in the VLF and LF bands will be associated with BP variability, and oscillations in the HF band will be associated with RR and IBI variability in the HF band (i.e., respiratory sinus arrhythmia). (5) Considering that

higher levels of mental effort are associated with lower variability in cardiovascular parameters (e.g., Duschek et al., 2009; van Roon et al., 2004), an inverse association between CBFV variability during the task period and performance may be expected.

Methods

Participants

Forty-three university students (21 men and 22 women) aged between 18 and 28 years were enrolled in the study. None of the participants suffered from any cardiovascular disease (including hypertension) or was receiving pharmacological treatment affecting the cardiovascular and central nervous systems. Each participant gave written informed consent and received a course credit for participation.

Mental arithmetic task

Mental stress was induced by a 5-min mental arithmetic task presented on a computer screen using ePrime software (Psychology Software Tools, Inc., Sharpsburg, PA, USA). Two single-digit numbers appeared on the screen, which participants were instructed to add together as quickly as possible. The response had to be given by typing the last digit of the sum on the keyboard. Immediately after entering the response, the next pair of digits appeared. Performance was assessed in terms of the number of correct responses and the response time (RT). The task was preceded by six practice trials, i.e. six addition tasks.

Recording and analysis of cerebral blood flow

Blood flow velocities were recorded through the temporal bone window in the MCA and ACA of both hemispheres by means of TCD, employing a digital Multi-Dop L2

equipped with two 2-MHz transducer probes (DWL Elektronische Systeme Inc., Sipplingen, Germany). Following vessel identification, the probes were fixed via a head harness. The MCA were insonated at a depth of 48-55 mm and the ACA at a depth of 60-70 mm. The spectral envelope curves of the Doppler signal were recorded at a sample rate of 100 Hz. Mean flow velocity was taken as an index of cerebral blood flow, which is less vulnerable to artifacts than systolic or diastolic velocity peaks and demonstrates the highest correlation with blood volume through an artery per unit of time (Duschek & Schandry, 2003).

In an initial data reduction step, the 100 Hz recording was resampled at 4 Hz. Variability in CBFV (Hypothesis 1) was analyzed in the frequency domain by Fast Fourier Transformation based on the 4 Hz recording obtained using AcqKnowledge 3.9.0 software (Biopac Systems Inc., Goleta, CA, USA). A Hamming window function was applied and spectral power variability was computed in the frequency range between 0.0024 and 0.40 Hz, with a 0.0024 Hz resolution. The spectral profile was divided into the three frequency bands defined for HR variability (Berntson et al., 1997) and described in other CBFV variability studies (e.g. Diehl et al., 1991, 1998; Kuo et al., 1998; Newell et al., 1992): VLF, from 0.0024 to 0.04 Hz; LF, from 0.04 to 0. 15 Hz; and HF, from 0.15 to 0.4 Hz. Maximum peak variability values in each of these bands, expressed in absolute units (cm/s^2), were obtained.

Recording and analysis of cardiovascular and respiratory parameters

A Task Force Monitor (CNSystems, Graz, Austria) was used for non-invasive beat-to-beat cardiovascular recordings. Four electrodes were applied to the chest, two close to the shoulders, and two at the lower rib cage (Einthoven I and II) to record two bipolar

electrocardiograms (ECG). Continuous BP was taken from the first phalange of the second and third fingers of the right hand. The hand was positioned at the level of the heart. Oscillometric BP was taken from the left brachial artery. The device recalibrates continuous finger BP according to brachial artery BP every 60 s, without interrupting recording. Sample rates were 1,000 Hz for ECG and 200 Hz for continuous finger BP. Variability in IBI, SBP and DBP was calculated using adaptive autoregressive models, following algorithms described by Bianchi, Mainardi & Cerutti (2000) and using Task Force Monitor software. Variability was expressed in absolute units in the same frequency bands as CBFV variability (i.e., VLF, LF, and HF).

Respiratory activity was recorded using a Biopac TSD101 strain gauge belt placed half way up the thorax and a Biopac MP100 system (Biopac Systems Inc.) at 50 Hz. Two variables were obtained, the mean RR (mean number of breaths per minute) and peak respiratory frequency (more characteristic respiratory frequency, as the frequency with the highest power, obtained from the FFT analysis of respiratory recording). RR indicates the averaged respiratory frequency, while peak respiratory frequency indicates the mode of breathing frequency.

Procedure

After a 5-min rest baseline, participants performed the 5-min arithmetic task, followed by a 5-min recovery period. Because simultaneous blood flow assessment in the MCA and ACA cannot be achieved with sufficient precision, this procedure was conducted twice, once for each pair of arteries. The artery assessment order (MCA or ACA first) was counterbalanced across participants. The distance between the participant and the computer screen was fixed at 0.75 m. Recordings were performed in a seated position;

participants were sitting still for at least 15 min before beginning the baseline assessment. Participants were asked to avoid moving as far as possible. Testing sessions were conducted starting at 10.30 a.m. and 5 p.m. Inter-individual anatomical differences affect the possibility of successfully conducting TCD recordings (Duschek & Schandry, 2003). Therefore, the number of participants with available data was different for each artery. The sample sizes were as follows: left MCA, 41 participants; right MCA, 42 participants; left ACA, 38 participants; and right ACA, 40 participants. Complete data on all four arteries were available from 38 participants.

Participants were instructed to refrain from caffeine, alcohol, nicotine, and performance of vigorous exercise for 2 hours before the testing session. Furthermore, they were told to take their breakfast (for morning participants) or lunch (for afternoon participants) as early as possible and not take any other food prior to the study. The study protocol was approved by the Bioethics Committee of the University of Jaén.

Statistical analysis

Firstly, variables were tested with respect to deviation from normal distribution using Kolmogorov-Smirnov tests. The normality assumption was violated for variability in IBI, SBP and DBP during all the three periods, as well as VLF variability in the right MCA CBFV during the task period (all zs $\geq$ 1.37, all ps $\leq$ .047); therefore, these variables were subjected to logarithmic transformation (ln) before the statistical analysis. The tests did not reveal significant results for the remaining variables (all zs $\leq$ 1.29, all ps $\geq$ .072). Comparisons between MCA and ACA (Hypothesis 2) were performed using Student's t-tests for related samples. Effects of mental stress on CBFV and CBFV variability parameters (Hypothesis 3) were analyzed by 2 (hemisphere: right

and left) x 3 (periods: baseline, task, and recovery) repeated measures ANOVAs. Only in the case of one significant hemisphere x period interaction, one-way ANOVAs were separately computed for the left and right hemisphere. Effects of mental stress on cardiovascular variables were analyzed by repeated measures ANOVAs with period (baseline, task, and recovery) as the only factor. Results were presented as the F value associated with the multivariate test statistic Wilks' lambda. This method has no sphericity assumption and thus is more suitable for repeated measures designs. Relationships between CBFV variability, cardiovascular variability, and respiratory parameters (Hypothesis 4), as well as between physiological variables and task performance (Hypothesis 5), were quantified by Pearson correlations. Differences in correlation coefficients between CBFV, CBFV variability and cognitive performance were tested for significance using Fisher´s Z statistic. Finally, partial correlations were computed between physiological variables and task performance, controlling for the influence of respiratory parameters. Two-tailed significance tests were conducted.

Results

Cerebral blood flow velocity responses to mental arithmetic task

CBFV (absolute units, cm/s) increased during the arithmetic task and returned to baseline values during the recovery period for MCAs ($F(2,38) = 23.22$, $p < .001$, $\eta_p^2 = .550$) and ACAs ($F(2,36) = 6.74$, $p = .003$, $\eta_p^2 = .273$). A significant periods x hemisphere interaction was observed for ACAs ($F(2,36) = 3.47$, $p = .041$, $\eta_p^2 = .163$). Signifiant changes were observed for the left ACA ($F(2,36) = 8.98$, $p = .001$, $\eta_p^2 = .333$), but not for the right ACA ($F(2,38) = 1.72$, $p = .193$, $\eta_p^2 = .083$) (see Table 1).

Table 1

Means (±SD) of cerebral blood flow velocities (in cm/s) during the three experimental periods.

	Baseline	**Task**	**Recovery**
Left MCA**	63.63±14.43	65.75±14.51	62.89±13.36
Right MCA**	58.44±13.02	60.91±12.76	58.47±11.96
Left ACA**	45.71±9.97	47.50±10.45	46.24±10.30
Right ACA	44.04±11.02	44.78±11.23	44.13±11.50

***p* < .01

Note. MCA, middle cerebral artery; ACA, anterior cerebral artery. The p-value information refers to the periods effect in the repeated measures analysis.

Cerebral blood flow velocity variability

A spectral profile with three main variability components was observed in all arteries under study: (a) an initial VLF component with the highest amplitude at .005 Hz; (b) a second VLF component around 0.01 to 0.025 Hz; and (c) an LF component with the lowest overall amplitude but higher frequency extension of around 0.075 to 0.11 Hz. A clearly visually identifiable HF component did not arise in the grand averages of spectral profiles (see Figures 1 and 2). However, as shown in Table 2, variability values in the HF band, although lower than those of the VLF and LF components, were far from zero.

Our analyses were performed on the raw CBFV data, without performing any smoothing or high pass filter procedure to remove low trends in the data before computation of FFT. Under these conditions, it is known that a high amplitude component arises at lower frequency ranges of the power spectrum, i.e. below 0.01 Hz

(Claassen et al., 2016). Thus, our first VLF component (which lies below 0.01 Hz) would mainly represent low trends in the velocity series and not an actual oscillatory component. Though the amplitude of this initial VLF component showed significant correlations in some arteries with BP and IBI variability, we opted to omit it from the further description of the results. The second VLF component appeared in a frequency range higher than 0.01 Hz, i.e. outside the range in which low trends are manifested (Claassen et al., 2016). Therefore, we included this component in further analyses.

Variability in the VLF component changed as a function of periods in the ACA ($F(2, 36) = 10.28$, $p < .001$, $\eta_p^2 = .363$) and MCA ($F(2, 38) = 3.59$, $p = .037$, $\eta_p^2 = .159$). VLF variability decreased during the task and increased again during the recovery period (see Table 2). Variability in MCAs was greater than in ACAs, being significant this difference during the task period ($t(37) = -2.29$; $p = .028$, for the left, and $t(39) = -3.77$, $p < .001$, for the right).

LF variability also changed across experimental periods in the ACA ($F(2, 36) = 10.48$, $p< .001$, $\eta_p^2 = .368$) and MCA ($F(2, 38) = 10.01$, $p = < .001$, $\eta_p^2 = .345$). Variability decreased during the task and increased again during recovery (see Table 2). Variability was greater in MCA than in ACA at baseline ($t(37) = 2.37$; $p = .023$, for the left, $t(39) = 2.63$, $p = .012$, for the right), task ($t(37) = 2.99$; $p = .005$, for the left, $t(39) = 2.38$, $p = .009$, for the right) and recovery ($t(37) = 3.14$; $p = .003$, for the left, $t(39) = 3.03$, $p = .004$, for the right).

Within the HF band, no effects of task were observed for either ACA or MCA (all ps > .38). HF variability was higher in the MCAs than in the ACAs at baseline ($t(37) = 3.19$,

p = .003, for the left; t(39) = 4.55, p <.0001, for the right), task (t(37) = 3.58, p = .001, for the left; t(39) = 4.64, p < .0001, for the right), and recovery (t(37) = 3.98, p < .0001, for the left; t(39) = -4.48, p < .0001, for the right).

CBFV variability averaged across the three frequency bands correlated positively with mean CBFV. Correlations reached significance for the four arteries and each of the three experimental periods (correlations ranged from 0.41 to 0.74, all ps<.01).

Table 2

Means (±SD) of variability in blood flow velocity (cm/s^2) in the three frequency bands at baseline, task and recovery periods

		Baseline	Task	Recovery
Left MCA	**VLF***	.41±.19	.33±.18	.40±.23
	LF**	.34±.12	.28±.10	.34±.15
	HF	.19±.08	.18±.07	.18±.08
Right MCA	**VLF**	.39±.16	.34±.21	.38±.14
	LF**	.33±.14	.27±.11	.32±.16
	HF	.19±.08	.17±.06	.17±.07
Left ACA	**VLF****	.35±.18	.25±.18	.38±.22
	LF**	.29±.15	.24±.13	.28±.14
	HF	.15±.07	.14±.07	.14±.05
Right ACA	**VLF****	.35±.19	.23±.18	.36±.22
	LF*	.28±.12	.23±.11	.26±.10
	HF	.14±.05	.12±.05	.13±.05

*p < .05. **p < .01

Note: MCA = middle cerebral artery; ACA = anterior cerebral artery; VLF = very low frequency; LF = low frequency; HF = high frequency. The p-value information refers to the period effect in the repeated measures analysis.

Cardiovascular and respiratory variables

During the mental arithmetic task, IBI decreased ($F(2,41) = 16.33$, $p < .001$, $\eta_p^2 = .443$), and BP ($F(2,41) = 12.02$, $p < .001$, $\eta_p^2 = .370$ for SBP; $F(2,41) = 18.52$, $p < .001$, $\eta_p^2 = .475$, for DBP), RR ($F(2,41) = 48.72$, $p < .001$, $\eta_p^2 = .704$), and peak respiratory frequency ($F(2,41) = 6.21$, $p = .004$, $\eta_p^2 = .233$) increased (see Table 3). Variability of BP and IBI in the three frequency bands decreased during the task (all $Fs(2,41) \geq 9.86$, all $ps \leq .001$, all $\eta_p^2 \geq .324$ for SBP; all $Fs(2,41) \geq 13.91$, all $ps \leq .001$, all $\eta_p^2 \geq .404$ for DBP; all $Fs(2,41) \geq 5.57$, all $ps \leq .007$, all $\eta_p^2 \geq .214$ for IBI) (see Table 3).

Table 3

Means (±SD) of cardiovascular and respiratory variables at baseline, task and recovery periods.

	Baseline	**Task**	**Recovery**
IBI**	**808.52±121.31**	**777.47±111.38**	**812.86±115.45**
IBI VLF**	460.56±431.64	286.71±296.96	448.03±406.35
IBI LF**	1086.36±722.27	638.11±368.86	1005.96±652.78
IBI HF**	773.05±936.31	513.74±496.85	705.46±880.24
SBP**	**114.48±14.49**	**119.52±16.54**	**114.59±16.13**
SBP VLF**	4.09±3.42	3.10±2.37	2.73±1.83
SBP LF**	6.51±4.59	5.29±3.62	4.87±3.25
SBP HF**	2.30±1.77	1.90±1.34	1.74±1.19
DBP**	**67.44±8.48**	**71.63±9.82**	**66.62±8.88**
DBP VLF**	2.70±2.42	2.14±1.78	1.96±1.69
DBP LF**	5.05±3.11	4.20±2.63	3.84±2.33
DBP HF**	1.22±1.03	.99±.80	.93±.71
RR**	**18.22±3.72**	**21.83±4.31**	**17.91±3.57**

PRF**	**.26±.08**	**.30±.08**	**.27±.07**

**$p < .01$

Note. IBI = inter-beat interval (ms); SBP = systolic blood pressure (mmHg); DBP = diastolic blood pressure (mmHg); RR = respiratory rate (breaths per minute); PRF = peak respiratory frequency (Hz); VLF = very low frequency; LF = low frequency; HF = high frequency (corresponding units^2). The p-value information refers to the period effect in the repeated measures analysis.

Associations of cerebral blood flow velocity variability with cardiovascular and respiratory variables

Within the VLF band, positive associations were found between left ACA and right MCA CBFV variability and SBP and DBP variability during the task period, and between left and right ACA CBFV variability and IBI variability during recovery (see Table 4). The correlation coefficients were higher for left ACA than left MCA (Z = 1.95, p = .025), right MCA than right ACA (Z = 1.66, p = .049), and left ACA than right ACA (Z = 2.92, p = .002).

Within the LF component, positive associations were observed between CBFV variability in all arteries and SBP and DBP variability during the three experimental periods, except between the left and right ACA and SBP variability at baseline (see Table 4).

Within the HF band, right MCA CBFV variability was positively associated with variability in SBP during baseline, and with variability in DBP during the recovery period. Left ACA flow velocity variability was positively associated with variability in SBP and DBP during the task and recovery periods. The correlation with DBP

variability during the recovery period was higher for left than right ACA ($Z = 1.78$, $p = .037$).

Associations between SBP and CBFV variability were closer in the LF than in the VLF band for left MCA and right ACA (at baseline), right ACA (during the task), and right MCA and ACA (during recovery); and closer in the LF than in the HF band for left MCA (baseline), left MCA and right ACA (task), and right ACA (recovery) (all $Zs>1.64$, all $ps<.05$). Correlations between DBP and CBFV variability were higher in the LF than in the VLF bands for right MCA (baseline), right MCA and ACA (task), and right MCA and both ACAs (recovery); and higher in the LF than in the HF bands for both ACMs (baseline), both MCAs (during task), and both ACAs (recovery) (all $Zs>1.64$, all $ps<.05$).

RR (absolute values) was negatively associated with HF variability in the right MCA at baseline, while peak respiratory frequency was negatively associated with left MCA VLF variability at baseline, and with left MCA HF variability during the task and recovery periods.

Regarding associations between respiratory and cardiovascular parameters, RR correlated negatively with IBI LF variability at baseline ($r = -.35$, $p = .021$) and during the recovery period ($r = -.37$, $p = .016$), and with IBI HF variability during the recovery period ($r = -.40$, $p = .008$). During the task period, RR was positively associated with VLF variability in IBI ($r = .35$, $p = .023$) and SBP ($r = .35$, $p = .030$). Peak respiratory frequency correlated positively with VLF SBP variability during the recovery period ($r = .38$, $p = .017$).

When respiratory rate and peak respiratory frequency were statistically controlled (partial correlations), most of the above correlations remained significant (all rs > .35, all ps < .042). Only associations at baseline between SBP variability and right MCA CBFV HF variability (r = .28, p = .077), and between DBP variability and left (r = .33, p = .052) and right (r = .31, p = .054) ACA CBFV LF variability missed significance. Moreover, new significant associations arose at baseline and during the task period. During the task period, right MCA CBFV VLF variability correlated positively with DBP variability (r = .34, p = .033), left MCA CBFV LF variability correlated inversely with RRI variability (r = -.41, p = .009), and left ACA CBFV HF variability correlated positively with SBP variability (r = .40, p = .018). At baseline, left ACA CBFV HF variability correlated positively with DBP variability (r = .34, p = .044).

Table 4

Correlations between cerebral blood flow velocity variability in the three frequency bands, variability in cardiovascular variables, and respiratory parameters.

			IBIV	**SBPV**	**DBPV**	**RR**	**PRF**
VLF	Left MCA	Baseline	.08	.12	.12	-.08	**-.37***
		Task	-.16	.17	.20	-.01	-.11
		Recovery	-.05	.08	.17	.02	-.05
	Right MCA	Baseline	.20	.25	.24	.02	-.09
		Task	-.12	**.31***	.29	-.04	-.05
		Recovery	-.05	.01	.10	-.02	-.27
LF	Left MCA	Baseline	.03	**.51****	**.50****	-.03	-.21
		Task	-.30	**.45****	**.48****	-.05	-.18
		Recovery	-.03	**.34***	**.42****	.04	-.12
	Right MCA	Baseline	.11	**.41****	**.48****	-.20	-.26

		Task	-.08	**.47****	**.58****	-.20	-.02
		Recovery	-.04	**.38***	**.49****	-.01	-.24
HF	Left MCA	Baseline	.11	.20	.17	-.27	-.08
		Task	-.26	.09	.12	-.17	**-.38***
		Recovery	.24	.27	.24	-.28	**-.33***
	Right MCA	Baseline	.13	**.31***	.15	**-.39***	.21
		Task	-.22	.21	.20	-.16	-.30
		Recovery	.13	.29	**.33***	-.28	-.25
VLF	Left ACA	Baseline	.06	.05	.16	.13	-.09
		Task	.17	**.56****	**.34***	.02	-.04
		Recovery	**.39****	.02	.12	-.01	-.02
	Right ACA	Baseline	-.01	-.09	.01	.08	.16
		Task	.01	-.06	.10	-.01	.06
		Recovery	**.34***	-.07	.03	.12	.06
LF	Left ACA	Baseline	-.13	.27	**.33***	-.03	-.07
		Task	.06	**.54****	**.55****	.05	-.17
		Recovery	.11	**.63****	**.67****	-.07	-.12
	Right ACA	Baseline	.08	.31	**.32***	.10	-.08
		Task	-.03	**.52****	**.47****	.12	-.05
		Recovery	.14	**.53****	**.58****	.08	-.07
HF	Left ACA	Baseline	.04	.29	.28	-.31	-.09
		Task	.08	.32	**.36***	.06	.19
		Recovery	.18	**.44****	**.42****	-.19	-.09
	Right ACA	Baseline	.28	.10	-.02	-.26	-.15
		Task	.01	.12	.01	.02	.22
		Recovery	.05	.21	.02	-.05	.08

*$p < .05$. **$p < .01$ (two-tailed testing)

Note. IBIV = inter-beat interval variability; SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability; RR = respiratory rate; PRF = peak respiratory frequency; VLF = very low frequency; LF = low frequency; HF = high frequency; MCA = middle cerebral artery; ACA = anterior cerebral artery.

Associations between physiological variables and task performance

Table 5 displays the correlations between the CBFV response, CBFV variability during the task period in the three frequency bands, and arithmetic performance. Number of correct responses (147.28 ± 58.07 during MCA assessment; and 144.20 ± 58.19 during ACA assessment) correlated negatively with LF CBFV variability in both ACAs and the left MCA, but not with the CBFV response; differences in correlation coefficients between the CBFV response and LF CBFV variability were significant for both MCAs and ACAs (all $Z \geq -2.47$, all $p \leq .007$). RT (2235.90 ±775.66 ms for MCA; and 2262.66 ±819.12 ms for ACA) correlated positively with LF CBFV variability in both ACAs and MCAs, but not with the CBFV response; differences in correlation coefficients between the CBFV response and LF CBFV variability were significant for both MCAs and ACAs ($Z \geq 2.72$, $p \leq .003$).

LF and HF SBP and DBP variability correlated positively with RT during the task period (see Table 6). The number of correct responses correlated negatively with HF SBP variability. While no significant correlations were obtained between IBI variability and performance, peak respiratory frequency during task period was inversely associated with RT (see Table 6).

When respiratory rate and peak respiratory frequency were controlled, correlations for MCA and ACA CBFV variability remained significant (all $rs > -.38$, all $ps < .021$). For cardiovascular associations, correlations between LF SBP variability and RT ($r = .29$, $p = .073$), and between HF SBP variability and number of correct responses ($r = -.30$, $p = .064$) missed significance. However, the correlation between VLF DBP variability and RT was significant when controlling for respiratory parameters ($r = .36$, $p=.027$).

Table 5

Correlations between cerebral blood flow velocity variables during the task period and arithmetic performance parameters

		Nº correct responses	**Response time**
Left MCA	CBFV response	.25	-.18
	VLF	.13	-.12
	LF	**-.41****	**.42****
	HF	.09	.04
Right MCA	CBFV response	.28	-.23
	VLF	-.05	.10
	LF	-.27	**.36***
	HF	.09	.19
Left ACA	CBFV response	.30	-.26
	VLF	-.08	.03
	LF	**-.39***	**.44****
	HF	.07	.05
Right ACA	CBFV response	.21	-.20
	VLF	-.13	.08
	LF	**-.45****	**.42****
	HF	-.06	.09

*$p < .05$. **$p < .01$(two-tailed testing)

Note: MCA = middle cerebral artery; ACA = anterior cerebral artery; CBFV = cerebral blood flow velocity; VLF = very low frequency; LF = low frequency; HF = high frequency.

Table 6

Correlations between cardiovascular and respiratory variables during the task period and arithmetic performance parameters.

		Nº correct responses	**Response time**
IBI	Mean	.11	-.12
	VLF	.07	.06
	LF	.03	.01
	HF	-.01	.04
SBP	Mean	-.08	.02
	VLF	-.19	.27
	LF	-.14	**.32***
	HF	**-.34****	**.49****
DBP	Mean	.14	-.08
	VLF	-.22	.29
	LF	-.24	**.38****
	HF	-.29	**.44****
RR	-	.11	-.15
PRF	-	.28	**-.35***

*p < .05. **p < .01. (two-tailed testing)

Note. IBIV = inter-beat interval variability; SBPV = systolic blood pressure variability; DBPV = diastolic blood pressure variability; RR = respiratory rate; PRF = peak respiratory frequency; VLF = very low frequency; LF = low frequency; HF = high frequency.

Discussion

This TCD study aimed to analyze CBFV oscillations in the MCA and ACA, at rest and during mental stress, in young healthy individuals, as well as the possible physiological mechanisms related to these oscillations. Reflecting the arithmetical nature of the applied task, CBFV increased in both MCAs, which supply brain areas involved in mathematical cognition (Ansari, 2008). The absence of lateralization toward the left

MCA is surprising, as this might have been expected given the dominance of the left hemisphere in arithmetic processing (Dehaene, 2000; Duschek et al., 2008; Montoro et al., 2015). This may be explained by the fast arithmetic operations required during the task. Recruitment of bilateral corticothalamic circuits, such as the left and right thalamus, has been observed during rapid arithmetic processing (Menon, Rivera, White, Glover & Reiss, 2000). In addition, bilateral activation of the horizontal intraparietal sulcus during arithmetic tasks has been observed (e.g., Rosenberg-Lee, Chang, Young, Wu, & Menon, 2011). This is consistent with a TCD study by Szirmai, Amrein, Palvolgyi, Debreczeni & Kamondi (2005), which demonstrated less pronounced laterality of MCA blood flow responses during mental arithmetic than verbal fluency tasks, and with the no observation of lateralization during subtraction arithmetic tasks (Connaughton, Amiruddin, Clunies-Ross, French & Fox, 2017; Gatouillat et al., 2015). Our analysis also showed task-induced CBFV increases in the left ACA. Considering that the perfusion territory of the ACA comprises medial-anterior cerebral regions, this can be explained by the well-known interplay between superior and inferior parietal and prefrontal working memory systems during mathematical cognition (Cantlon et al., 2009; Grabner et al., 2009). No increase in CBFV was observed in the right ACA, indicating that structures in its perfusion territory play a subordinate role in arithmetic processing (c.f. Montoro et al., 2015).

Frequency domain analysis of CBFV variability in the four arteries showed a spectral profile with two main variability components, similar to those observed in previous studies (Mauntner-Huppert et al., 1989; Diehl et al., 1991; Newell et al., 1992): a VLF component ranging between 0.01 to 0.025 Hz, and a LF component between 0.075 to 0.11 Hz. Variability in the HF range was sparse and did not constitute a clearly visual identifiable peak in the grand averages of spectral profiles, as previously reported (Diehl

et al., 1991; Hu et al., 1999; Kuo et al., 1998; Rickards & Tzeng, 2014). Our finding of pronounced VLF variability in the MCA contradicts previous studies of a restriction of these oscillations to the LF band (Diehl et al., 1991). While marked CBFV oscillations were also found in the ACAs, variability in the LF and HF bands was smaller in these vessels than in the MCA (in both right and left hemispheres and during the three experimental periods); for the VLF component, these differences arose in the right and left arteries during the task period. The stronger CBFV variability in the MCAs may relate to their greater blood flow due to their larger perfusion territory and diameter. The MCA carries approximately 50% of the flow volume received by the cerebral hemisphere (Enzmann, Ross, Marks & Pelc, 1994). This view is supported by the strong correlations between mean CBFV and total CBFV variability during the three experimental periods, suggesting a close connection between mean flow and variability.

Mental effort was associated with a decrease in CBFV variability in the VLF and LF bands in all four arteries. This is in line with numerous reports of reductions in variability in peripheral cardiovascular parameters (e.g., Duschek et al., 2008, 2009: Reyes del Paso et al., 1996, 2013; van Roon et al., 2004) and CBF (Vermeij et al., 2014) during cognitive activity. However, contrary to previous reports (Vermeij et al., 2014), cognitive load not only affected VLF CBFV oscillations, but this effect was also more strongly reflected in the LF range. Consistently, reductions in variability in BP and IBI (in all three frequency bands) were presently observed during the task period, in addition to increases in peak respiratory frequency and RR.

VLF CBFV variability in the right MCA and left ACA correlated positively with SBP and DBP variability during task execution; and right and left VLF ACA variability

correlated positively with IBI variability during the recovery period. Moreover, LF CBFV variability in the MCAs and ACAs of both hemispheres correlated positively with LF BP variability during all three experimental periods. For HF variability, associations with SBP and DBP variability were limited to the right MCA (baseline and recovery) and left ACA (task and recovery). Respiratory parameters were inversely associated with CBFV HF variability in the right MCA at baseline, and with left MCA HF variability during the task and recovery periods. Finally, an inverse association arose between peak respiratory frequency and left MCA VLF variability at baseline. The statistical control of respiratory parameters did not substantially modify this set of associations. The associations between variability in BP and CBFV in the LF and HF bands are congruent with previous observations of similarities in the power spectra of BP and MCA flow velocity oscillations (Kuo et al., 1998). The finding that right MCA variability in the VLF band was associated with SBP variability during the task contradicts previous work reporting virtual independence of VLF CBFV variability in the MCA from BP variability (Diehl et al., 1991; Kuo et al., 1998; Newell et al., 1992). In contrast, the associations for respiratory parameters are consistent with previous literature showing synchronization between respiration and CBFV variability in the HF range (Newell et al., 1992).

Our analysis indicated that the influence of BP variability on CBFV variability was markedly stronger than influences of IBI variability and respiration. Furthermore, the data suggested that CA processes buffer BP oscillations in the LF range to a lesser degree than those in the VLF and HF ranges. While HF BP variability was unrelated to HF CBFV variability in both MCAs and in the right ACA, it only correlated with HF CBFV variability in the left ACA during the task and recovery periods. VLF BP

variability was unrelated to VLF variability in the MCAs and ACAs of both hemispheres under resting conditions. However, correlations were found for the right MCA and left ACA during the task period. These associations may indicate that during mental stress, although BP variability is globally reduced, VLF BP oscillations have a stronger impact on VLF CBFV variability, suggesting reduced efficacy of CA mechanisms in buffering VLF BP oscillations during stress. Altogether, these results are not consistent with the notion that slower frequency BP variability is more effectively buffered than HF variability (Zhang et al., 1998).

Mechanisms of CA are traditionally assumed to keep cerebral blood flow virtually constant during changes in peripheral hemodynamics (Iadecola, 2004; Paulson, 2002). In addition to the present findings, the traditional assumption of dissociation between cerebral and peripheral hemodynamics is also challenged by reports of substantial associations between CBFV variability and peripheral cardiovascular parameters (Diehl et al., 1991; Hilz et al., 2013; Kuo et al., 1998; Mitsis et al., 2002; Panerai, Dawson, Eames & Potter, 2001; Tzeng & Ainslie, 2014; Zhang et al., 2002). This is in line with a number of TCD studies investigating the connection between BP and CBFV. For instance, individuals with chronically low BP displayed reduced CBFV in the MCA at rest, as well as smaller CBFV increases during cognitive activity versus those with normal BP (Duschek & Schandry, 2004, 2007). Moreover, pharmacological BP elevation in individuals with low BP led to increases in baseline MCA CBFV, as well as CBFV reactivity during cognitive activity (Duschek, Hadjamu & Schandry, 2007). In several studies, increases in BP and HR during attentional and arithmetic processing predicted the magnitude of simultaneously recorded CBFV responses in the MCA (Duschek et al., 2008; Duschek, Heiss, Schmidt, Werner & Schuepbach, 2010; Duschek

& Schandry, 2006). The latter findings support the view that transient BP modulations are not fully compensated by CA, but instead have a considerable influence on CBFV, which is consistent with the presently observed dependence of oscillations in CBFV on those in BP.

The impact of peripheral hemodynamics on CBFV variability might relate to two different mechanisms: the first is a fundamental physical influence, in terms of the traditional notion of a passive pressure-flow relationship for cerebral circulation (Strandgaard & Paulson, 1984; Tiecks, Lam, Aaslid & Newell, 1995). In addition, active regulation of cerebral vasomotor tone through neural mechanisms may be important. Here, the arterial baroreflex may play a relevant role. The baroreflex is commonly regarded as the most important mechanism in short-term regulation of BP and, moreover, as a crucial source of cardiovascular variability (Duschek, Werner & Reyes del Paso, 2013; Reyes del Paso et al., 2013). It consists of a negative feedback loop, in which activity changes in arterial baroreceptors resulting from BP fluctuations are followed by compensatory changes in HR, cardiac contractility and vasomotor tone (Berntson et al., 2016; Reyes del Paso, de la Coba, Martín-Vázquez & Thayer, 2017). The first synapse of the baroreceptor afferents is located in the nucleus of the solitary tract within the medulla oblongata. This nucleus gives rise to projections to more distal brain stem structures, such as the nucleus ambiguous, dorsal motor nucleus and rostral ventrolateral medulla, which constitute the starting points of autonomic efferents transmitting cardiovascular responses (Bruehl & Chung, 2004; van Roon et al., 2004). Importantly, the cardiovascular centres of the brain stem are closely connected with higher cerebral units, particular in the prefrontal cortex and basal forebrain (Basile et al., 2013; Duschek et al., 2013). Baroreceptor influences may modulate the activity of basal

forebrain acetylcholine and brainstem serotonin neurons, which by extension directly affect vasomotor activity in cerebral arterioles, and also influence activity in the cortical GABA interneurons modulating neurovascular signaling (Fergus & Lee, 1997; Hamel, Vaucher, Tong & St-Georges, 2002). These neural pathways may mediate the effects of peripheral cardiovascular changes on those in cerebral blood flow. It has been well-established that baroreflex function is inhibited during acute mental stress (Durocher, Klein & Carter, 2011; Reyes del Paso et al., 1996, 2009, 2017), such as mental effort (c.f. Duschek et al., 2013 for an overview). On this account, it may be considered that reductions in baroreflex activity may also contribute to decreases in CBFV variability during cognition. Baroreflex influences on peripheral vasomotor tone are executed though adrenergic fibres, i.e. the sympathetic branch of the baroreflex. This is consistent with the observation of an association between impairment of sympathetic activity and lower CBFV variability in the LF band (Sliwka et al., 2001). Interestingly, in our study IBI variability, which is mainly determined by parasympathetic influences (Reyes del Paso et al., 2013), did not show a reliable association with CBFV variability.

Regarding arithmetic performance, lower CBFV variability in the LF band was associated with greater task accuracy and processing speed. Negative correlations with the number of correct responses were observed for the left MCA, and for the ACA of both hemispheres; and positive correlations with RT were significant for all four arteries under study. In these associations, interindividual differences in mental effort load may play a key role, where higher levels of effort may lead to both lower LF CBFV variability and improved task performance. The most frequently used cardiovascular index of mental effort-load is HF HR variability (Duschek et al., 2009; van Roon, et al., 2004); however, in our study it was unrelated to task performance. In contrast, HF SBP

variability, which is a far less well-established indicator of mental effort-load than HR variability, correlated negatively with performance (Vermeij et al, 2014). While SBP variability was related to performance in the HF range, the associations for CBFV variability in all four arteries emerged specifically in the LF band. This gives rise to the hypothesis that LF CBFV variability may be a strong marker of mental effort load, in addition to variability in peripheral cardiovascular parameters (Stuiver & Mulder, 2014; van Roon et al., 2004).

The reduction of CBFV variability during mental stress, and its inverse association with cognitive performance, may be viewed as inconsistent with the proposed protective role of short-term beat-to-beat CBF variability. The decrease in variability of cardiovascular variables during demanding situations is an expression of the cardiovascular autonomic stress response (Duschek et al., 2009; Reyes del Paso, Langewitz, Mulder, Roon & Duschek, 2013). This response, and the related allocation of energetic resources, would facilitate success during various tasks. As with other cardiovascular variables (e.g. HR), the adaptive CBF response during demanding situations includes increases in blood flow and decreases in its variability, which enables improved task performance. As long as these responses are restricted to acute stress episodes and involve fast recovery, they do not have negative health consequences. Several methodological limitations of the study have to be acknowledged. At first, the menstrual cycle phase was not controlled for among our female participants, which might affect autonomic control (e.g., Yazar & Yazici 2016). Furthermore, the 2 h washout period for caffeine, alcohol and nicotine was relatively short; as such, effects of these substances on the measured parameters cannot be ruled out. The same is true for the 2 h abstinence from physical exercise. Another limitation relates to the motor component of the applied task. Even though the

motor activity required therein was rather small, the CBFV signal may have been influenced by neural activity related to motor processing, in addition to cognition (Duschek & Schandry, 2003). Regarding statistical analysis, we quantified the associations between variability in peripheral hemodynamics and CBFV exclusively in the time domain using Persons correlations. However, frequency domain techniques, like transfer function (Claassen et al., 2016), may provide more detailed information about these associations (i.e., gain, phase and coherence). Unfortunately, given that our TCD recording was not time-synchronized with the cardiovascular recording, we cannot use these frequency domain techniques. Certainly, it would be beneficial to apply them in future studies in this area.

In summary, this study extended our knowledge of spontaneous variability in CBFV, and it is the first to systematically analyze ACA blood flow. Oscillations were most prominent in the LF and VLF ranges and markedly decreased during mental effort. CBFV variability was greater in the MCA than in the ACA, presumably due to the higher MCA blood flow. CBFV variability markedly decreased during mental stress, particularly in the LF and VLF bands. Our findings suggest an impact of BP oscillations on those in CBFV, supporting the notion of a close connection between peripheral and cerebral hemodynamics. This connection may be mediated by neural mechanisms, particularly related those to the baroreflex system, and by the passive pressure-flow relationship, which exists despite CA stabilization of cerebral blood flow. The marked modulations of LF CBFV during the arithmetic task, as well as its close association with task performance, may indicate the suitability of this parameter as an index of mental effort load.

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Figure legends:

Figure 1. Frequency spectra of cerebral blood flow velocity variability in the right and left middle arteries (MCAs) (grey solid line represents baseline period, black solid line represents task period and dotted line represents recovery period).

Figure 2. Frequency spectra of cerebral blood flow velocity variability in the right and left anterior arteries (ACAs) (grey solid line represents baseline period, black solid line represents task period and dotted line represents recovery period).

Figure 1.

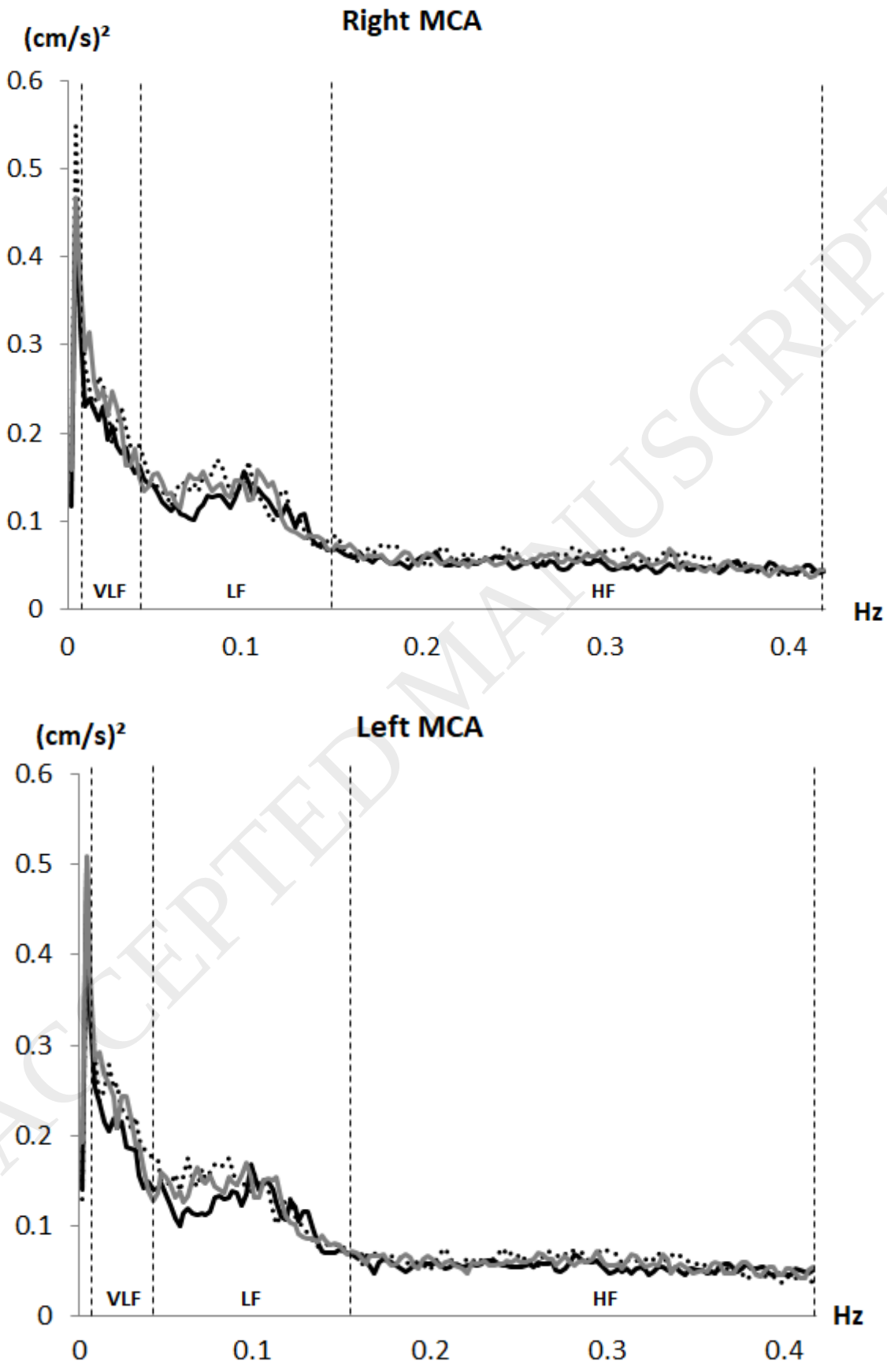
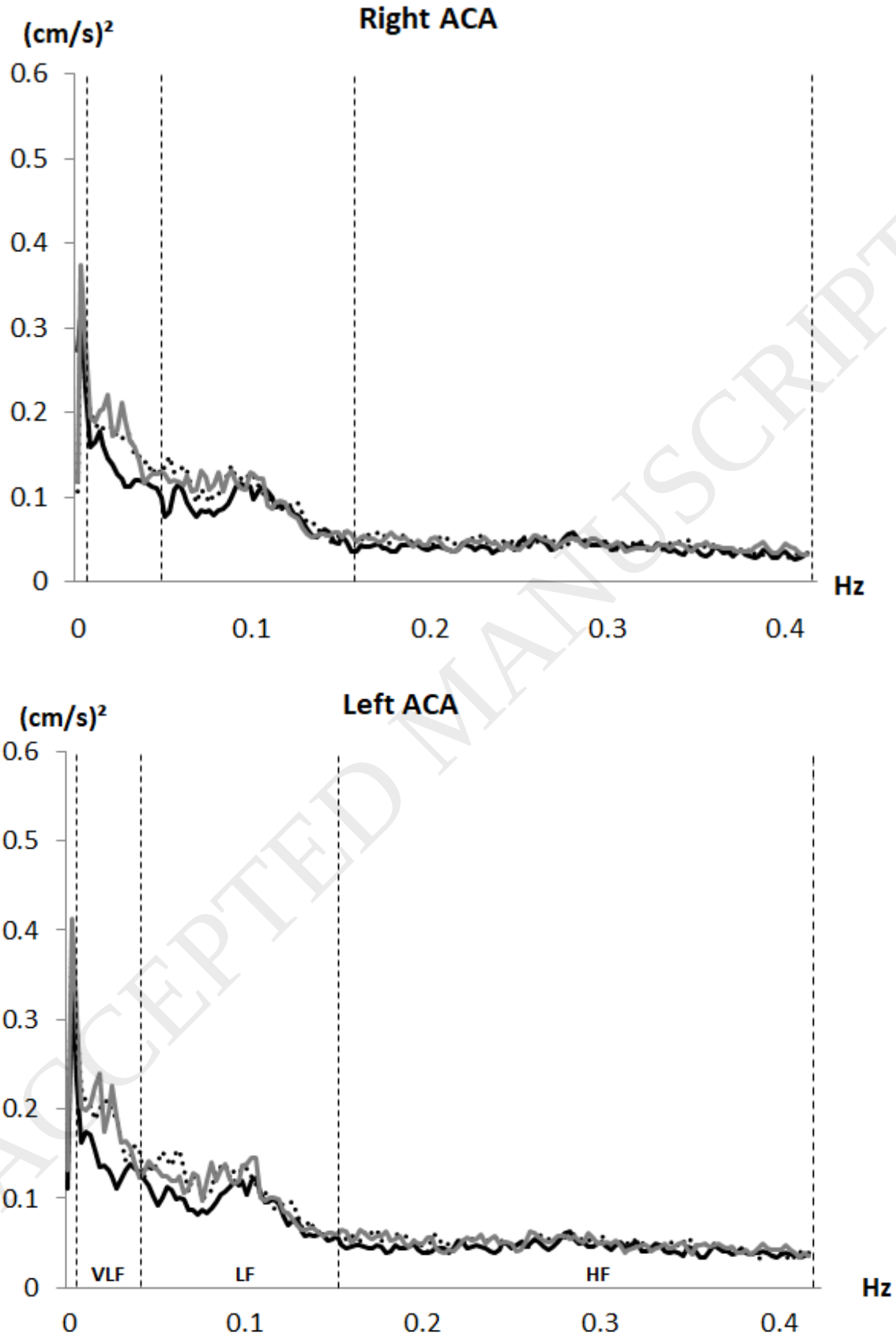


Figure 2.



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