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Interactions between systemic hemodynamics and cerebral blood flow during attentional processing

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Abstract

The study explored interactions between systemic hemodynamics and cerebral blood flow during attentional processing. Using transcranial Doppler sonography, blood flow velocities in the middle cerebral arteries (MCA) of both hemispheres were recorded while 50 subjects performed a cued reaction time task. Finger arterial pressure and heart rate were also continuously monitored. Doppler sonography revealed a right dominant blood flow response. The extent of the increase measured in second two of the interstimulus interval showed a clear positive association with reaction speed. Task-related changes in blood pressure and heart rate proved predictive of changes in MCA flow velocities in limited time windows of the response. Besides an association between cerebral blood flow and attentional performance, the results suggest a marked impact of systemic hemodynamics on the blood flow response. All observed interactions are highly dynamic in time.

Descriptors: Cerebral blood flow, Neurovascular coupling, Attention, Doppler sonography

Functional interactions between nerve-cell activity and cerebral blood perfusion were first observed more than a century ago (Mosso, 1881; Roy & Sherrington, 1890). As a result of an augmented metabolic rate of the nerve-cells, neural activation leads to dilation of cerebral arterioles and capillaries followed by increased blood flow in the active tissue (Iadecola, 2004). In addition to flow metabolism coupling, neural mechanisms are involved in blood flow modulation during cerebral activation (Szirmai, Amrein, Pálvögyi, Debreczeni, & Kamondi 2005). A fast-acting neural system is assumed to directly trigger dilation of cortical microvessels as a response to brain stem activation (Sándor, 1999; Sato, Sato, & Uchida, 2001). These mechanisms can, for instance, be observed in the enhancement of cerebral blood flow during cognition and other psychological processes (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

A recent line of research investigated relationships between cerebral blood flow modulation and mental performance. For this purpose, functional transcranial Doppler sonography (fTCD) was applied, an ultrasonic technique that enables continuous measurement of blood flow velocities in the basal cerebral arteries (Aaslid, Markwalder, & Nornes, 1982; Deppe, Ringelstein, & Knecht, 2004). Duschek and Schandry (2004, 2006) recorded flow velocities in both middle cerebral arteries (MCA) during the execution of attention and arithmetic tasks, and found correlations between the magnitudes of task-induced flow increases and task performance. Taking advantage of the high temporal resolution of fTCD, further studies focused on the time dynamics of this relationship. Schuepbach, Boeker, Duschek, and Hell (2007) conducted a component specific analysis of the hemodynamic response in the basal cerebral arteries during mental planning. They reported that the early component of the response, i.e., the change in flow velocity in the left MCA during the second second after task onset, accounted for the largest proportion of variance in planning ability. Similarly, using an attention task Duschek, Schuepbach, and Schandry (2008) obtained the closest association between modulations in bilateral MCA flow velocities and performance during the second and third seconds of task execution. In both studies, later response components were less closely associated or were unrelated to performance indices. On account of this, the authors hypothesized that the connection between the cerebral blood flow response and cognitive performance is dynamic and becomes apparent predominantly in a relatively early time window.

Modulations in systemic cardiovascular function during cognition are also well established. A large number of studies revealed, for instance, changes in heart rate, blood pressure, and cardiac contractility during various types of tasks (Bohlin & Kjellberg, 1979; Coles & Duncan-Johnson, 1975; Duschek, Muckenthaler, Werner, & Reyes del Paso, 2009; van Roon, Mulder, Althaus, & Mulder, 2004). Modulations in systemic and cerebral hemodynamics are commonly assumed to be determined by different physiological mechanisms and to occur almost independently of each other. While the increase in cerebral blood flow during neural activation relates to metabolically and neu-

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rally transmitted vasodilation, changes in systemic hemodynamics are mediated by a central autonomic network including brain stem nuclei, the basal ganglia, as well as hypothalamic, limbic, and prefrontal areas (Craig, 2002, 2003; Iadecola, 2004). In addition, processes of cerebral autoregulation usually keep brain perfusion widely constant by buffering systemic blood pressure oscillations. In order to ensure stable perfusion, cerebral resistance vessels constrict during increases and dilate during reductions in blood pressure (Paulson, 2002).

A number of observations, however, challenged the assumption of complete independence of systemic hemodynamics and cerebral blood flow (Duschek, Werner, Kapan, & Reyes del Paso, 2008). A substantial impact of fluctuations in blood pressure on brain perfusion was reported, for instance, in patients with hypertension and neurological diseases, as well as in persons experiencing posturally related syncopes (Chillon & Baumbach, 1997; Claydon & Hainsworth, 2003; Novak, Novak, Spies, & Low, 1998). In individuals with chronically low blood pressure, markedly reduced cerebral blood flow responses during mental activity were described (Duschek & Schandry, 2004; Stegagno, Patritti, Duschek, Herbert, & Schandry, 2007). In the same population, the extent of the rise in blood pressure during arithmetic processing correlated significantly with the increase in bilateral MCA blood flow velocities (Duschek & Schandry, 2006). Even though the interdependence between systemic and cerebral hemodynamics observed in these studies may be attributed to autoregulatory deficits related to the respective clinical conditions, its occurrence may not be ruled out in healthy normotensive persons either. Modulations in blood pressure and heart rate, which accompany cognitive processes, occur relatively fast, and their time courses tend to be complex, including distinct periods of increases and decreases. This is crucial since the autoregulatory response to such fluctuations is relatively inert, taking place with a delay of several seconds (Florence & Seylaz, 1992; Paulson, Strandgaard, & Edvinsson, 1990; Zhang, Zuckerman, Giller, & Levine, 1998). Thus, at least during specific phases of the cerebral hemodynamic reaction, effects of the systemic circulation may not be fully compensated, and blood flow may rise and fall with blood pressure and heart rate. This dependence of cerebral blood flow modulation during cognition on systemic hemodynamics is of particular interest given the described importance of cerebral hemodynamic adjustment for optimum performance (Duschek & Schandry, 2004, 2006; Duschek et al., 2008; Schuepbach et al., 2007). In order to gain further insight into the interaction between systemic and cerebral hemodynamics and its temporal dynamics, high time resolution analysis is required. For this purpose, fTCD combined with continuous peripheral hemodynamic recording is certainly a valuable tool.

In the present study, cerebral and systemic hemodynamics were investigated based on a cued reaction time task. Paradigms of this type focus on the arousal component of attention. In particular, they look at the short-term increase of attentiveness during the anticipation of a significant event, which enables a rapid adjustment to situational requirements. This function of "phasic arousal" is considered to be a specific component of the human attentional system that is undoubtedly of vast importance in everyday life (Johnson & Proctor, 2004; Posner & Rafal, 1987). A large part of the brain areas relevant for the control of attentional arousal, such as the dorsolateral frontal and the inferior parietal lobes, are parts of the perfusion territory of the MCA (Pardo, Fox, & Raichle, 1991; Paus, Zatorre, Hofle, Caramanos, Gorman, et al., 1997; Haines, 2007), which can easily be accessed using fTCD recordings. MCA measurements also proved suitable in previous studies based on this type of task (Duschek & Schandry, 2004, Duschek, Hadjamu, & Schandry, 2007; Duschek et al., 2008). Regarding systemic hemodynamics, the execution of a cued reaction time task is accompanied, for instance, by characteristic changes in heart rate, which are related to processes such as attentional focusing and orientation, as well as preparation of the motor response (Bohlin & Kjellberg, 1979; Hugdahl, 2001).

Blood flow velocities in the MCA and finger blood pressure were continuously monitored in the study, and changes were quantified in consecutive time windows of 1 s duration. A main research question addressed possible interactions between cognitively induced modulations in blood pressure and heart rate on the one hand and in MCA perfusion on the other. The methodological approach applied should prove particularly useful for analyzing possible differences in these interactions as a function of the time course of the hemodynamic response. Considering the reasoning presented above, we expected positive associations between modulations in systemic and cerebral hemodynamic modulations at least during limited phases of the response. A secondary question pertained to the association between cerebral blood flow modulation and attentional performance. Based on earlier results (e.g., Duschek et al., 2008; Schuepbach et al., 2007), we hypothesized that higher magnitudes of the increase in MCA blood flow velocities, especially during the first seconds of task execution, are associated with better performance.

Methods

Participants

Fifty subjects (33 women, 17 men) participated in the study. Exclusion criteria comprised severe physical diseases, psychiatric disorders, as well as the use of psychoactive drugs or medication affecting the cardiovascular system. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Forty-five of the participants were university students, 3 were employees, and 2 were self-employed. Information regarding age, Body Mass Index (BMI, kg/m^2), as well as resting blood pressure and heart rate is presented in Table 1.

Task Characteristics

The task was presented on a computer using the "Experimental Runtime System" software program (BeriSoft Cooperation, 2000). The white outline of a small cross (6 × 6 mm) was shown on the screen. After 55 s, an acoustic cue was presented (400-Hz tone of 500 ms duration). Five seconds after the cue, the image was replaced with a full white cross of the same size. This served as the imperative stimulus requiring an immediate keystroke. The task consisted of a total of 20 trials. A constant inter-trial interval may potentiate possible habituation and facilitate automatic task responses. The 55-s duration of the inter-trial interval, however, seemed long enough to prevent such processes. In order to control for laterality effects, half of the participants carried out the first 10 trials with the right hand and the remaining with the left hand. The sequence was reversed in the second half of the participants. The subjects were asked to sit still, not to speak, and to look at the cross for the entire duration of the task. Reaction times were recorded automatically and aggregated by calculating the median for each subject. Medians were used instead of means,

Table 1. *Age, Body Mass Index, Resting Blood Pressure, and Heart Rate in the Sample*

	M	*SD*	Min	Max
Age in years	24.1	4.6	20	48
Body mass index in kg/m^2	22.2	2.9	17.1	29.4
Systolic blood pressure in mmHg	111.9	12.6	91.7	145.0
Diastolic blood pressure in mmHg	74.7	8.0	61.0	95.7
Resting heart rate in beats per min	72.2	11.4	40.0	95.3

Note: Means (M), standard deviations (*SD*), minimal (Min) and maximal (Max) values.

in order to prevent distortion of the data due to outliers. Reaction times for the trials performed with the left and right hands correlated highly ($r = .75$, $p < .01$), hence only the average reaction times across all trials were included in the statistical analysis.

Recording of Cerebral Blood Flow Velocities, Blood Pressure, and Heart Rate

For the purpose of cerebral hemodynamic recording, a commercially available Doppler sonography device (Multidop L2, DWL Elektronische Systeme, Sipplingen, Germany) was employed. Blood flow velocities were monitored simultaneously in both MCA. The recordings were obtained through the temporal bone windows, using two 2-MHz transducer probes. Insonation of the MCA took place at a depth of 50 mm in all subjects. Following vessel identification, the ultrasonic probes were fixed to the head using a tight rubber band. The spectral envelope curves of the Doppler signal were stored at a rate of 28 samples per second (for insonation technique and validation of fTCD see Dahl, Russell, Nyberghansen, & Rootwelt, 1992; Duschek & Schandry, 2003; Jorgensen, Perko, & Secher, 1992; Larsen, Olsen, Hansen, Paulson, & Knudsen, 1994).

Blood pressure and heart rate were monitored continuously using a Finometer device (Model-2, Finapres Medical Systems, Amsterdam, The Netherlands). The cuff of the Finometer was applied to the mid-phalanx of the third finger of the right hand. In order to control for the influence of hydrostatic level errors, the height correction unit integrated in the device was used. To enable periodic recalibration, the "Physiocal" feature (Wesseling, De Wit, Van der Hoeven, Van Goudoever, & Settels, 1995) was put into operation. The signal was digitized at a sample rate of 200 Hz.

Procedure

The experimental sessions were conducted in a silent, dimly lit room. Prior to the experimental procedure, blood pressure and heart rate were taken using an automatic inflation blood pressure monitor (Omron M9 Premium, Omron Electronics, Schaumburg, IL). Three readings were taken, separated by 1-min rest intervals (Table 1 includes the values averaged across the three measurements.). Following this, the ultrasonic probes and the cuff of the Finometer were mounted, and the cued reaction time task was presented in the described form. Subjects were requested not to drink alcohol or beverages containing caffeine for 3 h prior to the experimental session.

Data Analysis

The envelope curves revealed by Doppler sonography were analyzed offline using the software AVERAGE (Deppe, Knecht, Henningsen, & Ringelstein, 1997). MCA blood flow velocites were represented by a time and intensity-weighted "mean flow velocity index." This score is the least susceptible to artifacts and demonstrates the highest correlation with blood volume flowing through a vessel (Duschek & Schandry, 2003). Flow velocities were integrated over each cardiac cycle and averaged, time locked to the cuing tone. The epochs were set beginning 10 s before the cuing tone and ending 25 s after the imperative stimulus. The mean flow velocity during the 10 s prior to the cuing tone served as a baseline (FV_{bas}). Relative (per cent) changes in flow velocity during task execution (dFV) were calculated for the left and right MCA using the formula $dFV = [FV(t) - FV_{bas}] \times 100/FV_{bas}$, where FV(t) is the flow velocity over the course of time. Following this, mean values of dFV were computed for 30 consecutive response intervals of 1-s duration each. The response intervals covered a period of task execution starting with the onset of the cuing tone (second 1), and ending 25 s after the imperative stimulus (second 30).

For the purpose of analyzing the data obtained by continuous blood pressure recording, the program BeatScope 1.1a (Finapres Medical Systems) was employed. Beat-to-beat values of systolic and diastolic blood pressure as well as heart rate were computed and transformed into second-by-second values (c.f. Finapres Medical Systems, 2005). These data were exported and further processed using SPSS 16.0 (SPSS Inc., Chicago, IL). Epochs were created and averaged in the same way as in the procedure concerning the MCA flow velocities. Again, the 10 s before the cuing tone served as a baseline, and percent changes were computed for each of the 30 s of the defined task period.

In the first step of the statistic analysis, possible laterality of the cerebral hemodynamic response was determined. For this purpose, *t*-tests were applied to compare the secondwise flow velocity values between both MCA. Repeated measures analyses of variance (ANOVAs) were computed for MCA flow velocities, blood pressure, and heart rate in order to evaluate intra-subject trends. Associations between task-related modulations in cerebral perfusion and such in systemic hemodynamics were quantified using regression analysis. In order to evaluate differences in the relationships over the course of time, separate models were computed for each of the 1-s response intervals of the defined task period (i.e., 30 separate regression analyses). As predictors, relative values of blood pressure and heart rate were applied. Due to high correlations between systolic and diastolic values in each of the response intervals (mean $r = .82$), mean arterial pressure was used as a single index of blood pressure. "Forced entry" was chosen as a method for entry of predictors. As there was no reason to expect specific effects for the left and right MCA, flow velocity values averaged over both vessels served as dependent variables.

Relationships between cerebral blood flow modulation and task performance were quantified by means of regression analysis with the flow velocity values for the 5 s between the cuing tone and the imperative stimulus as predictors and reaction time as dependent variable. Separate models were computed for flow velocity values from the left and right MCA. Correlations between the predictors were high, resulting in strong collinearity (tolerance values $< .1$ for all flow velocity values). Therefore, the models could be used only to determine the flow velocity value, which accounted for the largest proportion of variance in reaction time. For this purpose, a "stepwise" procedure was applied for entry and removal of predictors, in which the predictor that first enters the model explains the largest portion of criteria variance. In addition, simple Pearson correlations between flow velocity values and reaction time were computed.

Alpha-level was set at .05 in all analyses. Taking into account possible occurrence of Type I error inflation related to multiple statistical testing, the use of lower significance criteria may be considered. In the relatively small sample, this, however, would substantially reduce the power of the tests, i.e., increase the chance of Type II errors and reduce the probability of detecting any effects present. The present sample size is comparable to previous studies on interactions between systemic hemodynamics and cerebral blood flow, where between 40 and 80 subjects (e.g., Claydon & Hainsworth, 2003; Duschek & Schandry, 2004, 2006; Duschek et al., 2008), or even less (Zhang et al., 1998) were investigated. Instead of reducing alpha-level, the number of parallel tests could be limited by using longer response intervals, i.e., combining the 1-s intervals, for instance, to make 5-s intervals. This, in turn, would interfere with the aim of high time resolution analysis, which was crucial in our methodological approach.

Results

Figure 1 displays the changes in the perfusion of the left and right MCA during execution of the cued reaction time task. The data points represent the relative changes in flow velocities, which were computed for each of the 30 response intervals. A steep bilateral increase was observed after presentation of the cuing tone peaking in second 4. The imperative stimulus was again followed by a rise in flow velocity and a second maximum in second 10. The hemodynamic response was stronger in the right cerebral artery than in the contralateral vessel during a large part of the task period. The statistical analysis indicated significant differences between both MCA for the seconds 3 to 17 (all $t[49] > 2.6$, all $p < .05$).

In Figure 2, modulations in the systemic hemodynamic parameters are given. Biphasic increases in systolic and diastolic blood pressure were observed with maxima in the seconds 12 (systolic blood pressure) and 11 (diastolic blood pressure). Heart rate decreased in the first seconds. After a transient increase (second 4) it fell once again reaching its minimum in second 7. A biphasic increase occurred during the remaining period with peaks in seconds 10 and 19.

The repeated measures ANOVAs revealed significant linear, quadratic, and cubic trends for flow velocities in the left and right MCA, as well as for systolic and diastolic blood pressure (left

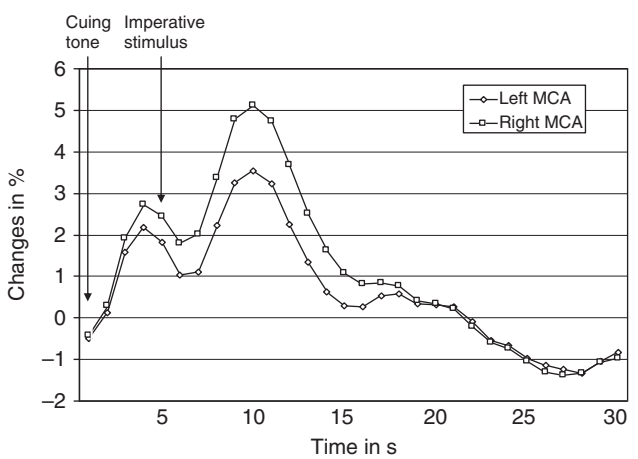

Figure 1. Relative changes in flow velocities in the left and right MCA during task execution (grand average).

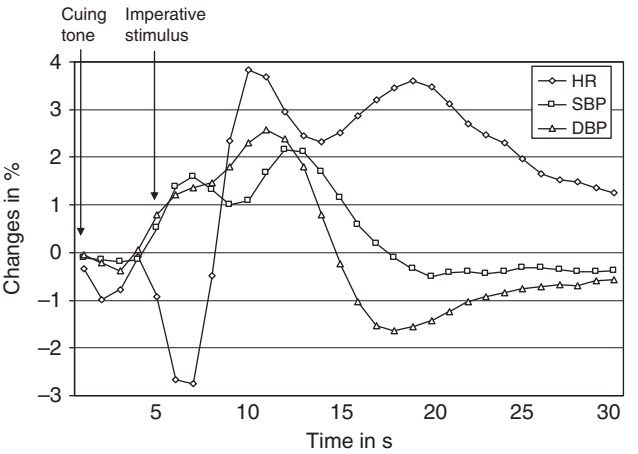

Figure 2. Relative changes in heart rate and blood pressure during task execution (grand average). HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

MCA, linear: $F[1] = 65.44$, $p < .01$, quadratic: $F[1] = 16.15$, $p < .01$, cubic: $F[1] = 46.01$, $p < .01$; right MCA, linear: $F[1] = 147.35$, $p < .01$, quadratic: $F[1] = 44.90$, $p < .01$, cubic: $F[1] = 101.24$, $p < .01$; systolic blood pressure, linear: $F[1] = 13.74$, $p < .01$, quadratic: $F[1] = 10.72$, $p < .01$, cubic: $F[1] = 34.31$, $p < .01$; diastolic blood pressure, linear: $F[1] = 26.90$, $p < .01$, quadratic: $F[1] = 7.99$, $p < .01$, cubic: $F[1] = 54.57$, $p < .01$). For heart rate, significant fourth and fifth order trends were also obtained (linear: $F[1] = 60.51$, $p < .01$, quadratic: $F[1] = 55.76$, $p < .01$, cubic: $F[1] = 7.98$, $p < .01$, fourth order: $F[1] = 54.69$, $p < .01$, fifth order: $F[1] = 7.49$, $p < .01$).

The results of the regression analyses concerning the prediction of bilateral MCA blood flow changes by modulations in mean arterial pressure and heart rate are given in Table 2. The table displays the standardized Beta weights and R values for each second of the task period. For heart rate, significant positive Beta weights were found for the initial phase, i.e., the seconds 1 to 6, as well as for the seconds 8 to 10. Significant positive Beta weights for mean arterial pressure were obtained for the seconds 4 to 9, and 14 to 23.

Mean reaction time of the participants was 309.4 ms (SD = 44.9 ms). Two stepwise regression analyses for the prediction of reaction time from flow velocity values from the left and right MCA (seconds 1 to 5) were conducted. For both vessels, the value for second 2 entered the model in the first step (left MCA: standardized Beta = $-.35$, $p < .05$; right MCA: standardized Beta = $-.41$, $p < .01$) indicating that bilateral blood flow modulations in second 2 accounted for the largest proportion of variance in reaction time. High collinearity in both models prevented further conclusions. The Pearson correlations between the flow velocity values for the seconds 1 to 5 and reaction time are given in Table 3. Significant negative correlations were obtained for flow modulations in the left MCA for second 2, and for modulations in the right MCA for the seconds 2 to 5.

Discussion

The study revealed a biphasic increase in blood flow velocities measured in the MCA during the execution of a cued reaction time task, which was more pronounced in the right than in the left vessel. The extent of the flow increase in the left MCA during

Table 2. *Regression Analyses for the Prediction of Modulations in Bilateral MCA Flow Velocities from Modulations in Mean Arterial Pressure (MAP) and Heart Rate (HR) Over the Course of the Task*

	Standardized Beta				Standardized Beta		
Time (s)	MAP	HR	R	Time (s)	MAP	HR	R
1	.10	.45**	.46	16	.32*	−.16	.35
2	.02	.36*	.36	17	.26*	.06	.27
3	.08	.32*	.33	18	.27*	.15	.28
4	.31*	.41**	.56	19	.31*	.12	.33
5	.46**	.31*	.63	20	.30*	.12	.32
6	.49**	.27*	.59	21	.30*	.19	.37
7	.34*	.17	.40	22	.33*	.22	.42
8	.26*	.28*	.37	23	.27*	.19	.33
9	.26*	.43**	.49	24	.15	.19	.24
10	.20	.39**	.45	25	.05	.16	.16
11	.19	.19	.28	26	.04	.16	.16
12	.14	.05	.15	27	.00	.23	.23
13	.19	−.12	.21	28	.06	.22	.22
14	.26*	−.23	.33	29	.22	.12	.24
15	.31*	−.24	.36	30	.21	.21	.28

Note: Standardized Beta- and R-values for each second of the task period.
*$p < .05$; **$p < .01$.

second 2 after the cuing tone was positively associated with reaction speed. Flow modulations in the right MCA during almost the entire interstimulus interval correlated with performance, the closest association being obtained for second 2. While the courses of the systolic and diastolic blood pressure responses were similar to those in MCA flow velocities, heart rate modulation showed a more complex pattern including two minima and two maxima, respectively. Task-related changes in mean arterial pressure and heart rate proved predictive of these in bilateral MCA flow velocities; the relationships were, however, limited to specific time windows of the hemodynamic response.

The task-induced increase in cerebral blood flow velocities can be ascribed to neural activation processes in structures such as the dorsolateral frontal and the inferior parietal lobes, which are relevant for the control of attentional arousal and form parts of the perfusion territory of the MCA (Haines, 2007; Pardo et al., 1991; Paus, Zatorre, Hofle, Caramanos, Gorman, Petrides, & Evans, 1997). The higher increase in the right MCA is in accordance with the assumption of a dominance of the right hemisphere for arousal regulation (Kolb & Whishaw, 2003; Posner & Petersen, 1990). One may hypothesize that the first peak, which appeared between the cuing tone and the imperative stimulus, related to neural activation associated with increase in attentiveness, anticipation of the imperative stimulus, as well as preparation of the response. This response component may relate to the contingent negative variation (CNV) and the readiness potential (''Bereitschaftspotential'') known from electroencephalography (EEG) research (Andreassi, 2000). Also, the assessment of cerebral blood flow by means of near infrared spectroscopy revealed a similar phenomenon during response preparation (Weber, Lutschg, & Fahnenstich, 2004). The second maximum was observed after the imperative stimulus and the ensuing keystroke, and may be attributed to cortical activation associated with a second increase in alertness due to concentration on the imperative stimulus, as well as activation related to the execution of the motor reaction. The time window of the closest association between MCA blood flow modulation and performance (second 2) fits well with previous studies from the field of attention and executive functions (Duschek et al., 2008; Schuepbach et al., 2007). This underlines the specific relationship between early cerebral hemodynamic modulation and cognition. Flow velocity changes in the right MCA were more closely related to reaction time than those in the left vessel, which again emphasizes the specific role of the right hemisphere for attentional arousal.

Table 3. *Correlations Between Modulations in MCA Blood Flow Velocities During the Seconds 1 to 5 and Reaction Time*

Time (s)	Left MCA	Right MCA
1	−.19	−.27
2	−.35*	−.41**
3	−.26	−.34*
4	−.23	−.29*
5	−.26	−.31*

*$p < .05$; **$p < .01$.

Given the rapid onset of the cerebral hemodynamic response, one may hypothesize that, in addition to neurovascular coupling, fast-acting neurogenic blood flow regulation was involved in its occurrence. Innervation of the cortical arterioles by fibers originating from the brain stem has been well documented (Hamel, Vaucher, Tong, & St-Georges, 2002; Sándor, 1999). These fibres form part of an intracranial neural vasodilative system consisting of cholinergic and serotonergic neurons that project from the ascending reticular activating system to cortical areas (Sato et al., 2001, Szirmai et al., 2005). In animals, the stimulation of brain stem nuclei was shown to be accompanied by cortical blood flow increase (Biesold, Inanami, Sato, & Sato, 1989). Activation of brain stem areas constitutes an integral part of the cerebral processes related to the increase of attentiveness occurring in a cued reaction time task (Posner & Petersen, 1990; Sturm, de Simone, Krause, Specht, Hesselmann, et al., 1999). Thus, also brain stem activity may have contributed to the modulation of flow velocities registered in the MCA.

Although the biphasic blood pressure response was presumably related to the same cognitive and motor processes, the beginning of the rise as well as both maxima were observed 1 to 3 s after the increases in cerebral blood flow velocities. Blood pressure modulations during mental activity result from cardiac and vasomotor adjustment, which are initiated by the central autonomic network and transmitted to the cardiovascular system by autonomic nervous and hormonal pathways (Craig, 2002, 2003; Loewy, 1990). As suggested by the present data, these processes are markedly slower than metabolically mediated cerebral blood flow adjustment.

According to classic theories, a variety of psychological processes contribute to heart rate responses during attention and reaction time tasks (Hugdahl, 2001; Lacey & Lacey, 1970). The beginning of the present response was characterized by heart rate deceleration. This is a common observation, which is usually ascribed to cognitive processes of orienting and attentional focusing (Coles & Duncan-Johnson, 1975; Venables, 1991). After a transient return to baseline level, heart rate decreased once again. Given that this decline occurred exactly when blood pressure started to increase, it is plausible to attribute it to the cardiac baroreflex. The baroreflex consists of a negative feedback loop, in which blood pressure fluctuations are responded to by com-

pensatory adjustment of heart rate (Levy & Pappano, 2007; Reyes del Paso, Vila, & Garcia, 1994). After the second decline, heart rate increased by a large amount. This accelerative component of the cardiac response is commonly ascribed to internal cognitive processing as well as emotional and motivational aspects of the task (Coles & Duncan-Johnson, 1975; Hugdahl, 2001). A second and smaller acceleration appeared right after the start of the blood pressure decrease, and thus may again be best explained by counter-regulatory activity of the baroreflex.

The most interesting result of the study may be the interactions between peripheral and cerebral hemodynamic modulations and their courses across the task. Changes in mean arterial pressure yielded substantial positive Beta weights in the prediction of modulations in MCA blood flow velocities during a large part of the response (seconds 4 to 23) suggesting a considerable impact of systemic arterial pressure on cerebral perfusion. One may hypothesize that the blood pressure increase facilitated the rise in flow velocities, whereas its subsequent decline supported the return of blood flow toward the initial level. In the seconds 10 to 13, the Beta weights did not reach significance, which may be explained by the specific course of the blood pressure response. The named period included the maximum of the response and therefore only slight changes that were apparently without significant impact on cerebral perfusion. The same holds true for the final part of the task period, during which blood pressure was virtually stable. One should, however, not overlook that, in the present correlative design, the interpretation of a causal effect of systemic hemodynamics on cerebral blood flow may not be drawn with complete certainty. This is underlined by the observation that the peaks of the cerebral blood flow response appeared earlier than the maxima of the heart rate and blood pressure responses. One may thus suppose that, in addition to a causal influence of systemic on cerebral hemodynamics, third variable effects may in part account for the correlations. Here, one may consider central nervous regulatory processes, which affect both cerebral blood flow and peripheral cardiovascular processes.

A previous study by Zhang et al. (1998) supports the notion that rapid changes in blood pressure are not fully compensated by cerebral autoregulation. The study explored the link between spontaneous fluctuations in arterial pressure and MCA blood flow velocities. Data obtained by Doppler sonography and finger blood pressure measurement were processed in the frequency domain based on transfer function analysis. Oscillations in MCA perfusion occurring in a relatively high frequency range (0.07–0.30 Hz) were closely associated with oscillations in blood pressure. This was not the case for lower frequencies. The authors therefore characterized autoregulation as a frequency dependent phenomenon. While it is effective in dampening slower fluctuations, changes in the high frequency range are widely transferred to cerebral blood flow. Cerebral autoregulation is mediated by a number of physiological mechanisms including metabolic, myogenic, and endothelium-related factors (Iadecola, 2004; Paulson, 2002). Though the exact response times of these processes are still unknown, it would appear that the dynamics of the autoregulatory system do not allow the full compensation of either spontaneous or psychologically triggered fast blood pressure modulations.

Cerebral autoregulation is considered a protective mechanism preventing brain ischemia during phasic blood pressure decrease, and capillary damage, edema formation, and disruption of the blood brain barrier during blood pressure increase (Paulson, 2002). The mechanism most efficiently operates in the normotensive range (Chillon & Baumbach, 1997). Hence, one may assume that rapid blood pressure fluctuations are even more strongly transferred to cerebral blood flow in the extremes of the tonic blood pressure spectrum, i.e., hypotension and hypertension. In chronically low blood pressure, reduced mental performance has repeatedly been documented (Duschek, Matthias, & Schandry, 2005; Duschek & Schandry, 2007), and there is evidence linking these deficits to insufficient cerebral autoregulation (Duschek & Schandry, 2004, 2006). Impaired autoregulation is furthermore involved in the genesis of symptoms occurring in patients with orthostatic failure (Novak et al., 1998). Also, in the case of chronically elevated blood pressure, cerebral autoregulation does not operate at its optimum (Chillon & Baumbach, 1997). A number of observations suggested blunted vascular reactivity and diminished cerebral blood flow in hypertension, which among other factors may underlie the reduced cognitive performance related to the condition (Jennings, 2003; Waldstein, Ryan, Manuck, Parkinson, & Bromet, 1991). Dependence of cerebral blood flow on systemic blood pressure may be of special importance in individuals with increased blood pressure variability, a group that is well known to be at risk of cerebrovascular disease (Sloan, Shapiro, Bagiella, Myers, & Gorman, 1999). Here, fluctuations in systemic hemodynamics may result in pronounced destabilization of brain perfusion and reduced protection of the neural tissue interfering with optimal cerebral functioning. On account of this, it would certainly be worthwhile to more intensely study the interaction between systemic and cerebral hemodynamic modulation and possible clinical implications in the named populations.

In our study, heart rate modulation was also positively associated with that in MCA blood flow. The link was particularly pronounced in the period between the cuing tone and the imperative stimulus, where an overall slight heart rate reduction occurred. This indicates lower amplitudes of the initial component of the cerebral blood flow response in individuals who experienced stronger heart deceleration than in such in which the decline was less pronounced. Like blood pressure, the predictive value of heart rate modulation for changes in MCA blood flow was reduced while at extreme values, i.e., the phase around the heart rate minimum (seconds 6 to 8). It seems notable that modulations in mean arterial pressure and heart rate were associated with changes in cerebral blood flow velocities during different time windows of the response. In this regard, it is important to bear in mind that heart rate and blood pressure are determined by different physiological factors. Heart rate modulation is a product of rather direct autonomic and hormonal influences on sinus node activity, while changes in mean arterial pressure relate to alterations in multiple cardiac and vascular factors such as vasomotor tone, stroke volume, and peripheral resistance (Levy & Pappano, 2007).

Classic psychophysiological models view the decrease in heart rate during attentional processing as an adaptive mechanism (Hugdahl, 2001; Porges, 1992; Thayer & Lane, 2009). According to the "intake rejection hypothesis," for instance, phasic heart deceleration is associated with a state of reduced sensory thresholds and improved conditions for the detection of external stimuli (Lacey & Lacey, 1970). The present findings propose a somewhat different perspective. Considering the positive association between modulations in heart rate and MCA blood flow, one may hypothesize that pronounced heart rate deceleration interferes with efficient cerebral hemodynamic adjustment. As suggested

by the link between initial cerebral blood flow modulation and reaction time, lower degrees of blood flow increase may in turn impede attentional performance. The latter association, however, can certainly not be interpreted unambiguously. It is generally believed that modulations in cerebral blood flow during cognitive activity reflect a perpetual adjustment to the changing metabolic demands of neural activation. In particular, the high rate of aerobic metabolism in the neural tissue requires a constant and sufficient supply of oxygen and glucose (Paulson, 2002). It therefore seems reasonable to assume that a stronger increase in cerebral perfusion is accompanied by improved functional conditions, resulting in enhanced cognitive performance (Duschek & Schandry, 2004). An alternative explanation could emphasize a possible association between levels of neural activation and attentional performance. According to this view, stronger blood flow increase in case of better performance would only constitute an epiphenomenon of enhanced nerve-cell activity. The present data do not make it possible to decide between these interpretations. Recent research, however, suggested that differences in cerebral blood flow may indeed causally modulate cognitive function. It could be demonstrated that experimental increase in brain perfusion induced by pharmacological blood pressure elevation is followed by significant enhancement of attentional performance (Duschek et al., 2007). Facilitation of cognitive functioning as a consequence of efficient cerebral blood flow adjustment thus seems a plausible consideration.

A limitation of the study is due to the use of a relatively easy reaction time task with complete predictability of the imperative stimulus. Different types of cognitive paradigms with varying levels of difficulty may evoke hemodynamic reactions differing in time course and magnitude. Also, the generalizability of the association between cerebral hemodynamic modulation and task performance is limited. In more difficult tasks, non-linear, for instance inverted U-shaped, relationships may also occur. The major limitation of fTCD concerns its low spatial resolution, which is determined by the size of the brain area supplied by the artery under study (Duschek & Schandry, 2003). The perfusion territory of the MCA is relatively large, thus our conclusion about task-related modulations in regional blood flow in specific cortical structures must remain hypothetical. In future studies, flow velocities in cerebral arteries other than the MCA should also be assessed. In this regard, the anterior cerebral arteries are of particular interest since they supply medial regions of the cortex including the anterior cingulate, which is of great importance for attentional processes. Regarding data analysis, possible restrictions arise from multiple statistical testing. The use of separate regression models for each of the 30 response intervals is related to the aim of hemodynamic analysis with high time resolution. Even though in principle this approach constitutes a strength of the study, multiple testing inevitably increases the risk of Type I errors, i.e., false rejection of the null hypothesis. A final methodological limitation is due to the imbalance of the sexes in the sample. This prevented the efficient analysis of possible gender effects on hemodynamic responses, which have recently been proposed (Schuepbach, Huizinga, Duschek, Grimm, Boeker, & Hell, 2009).

In conclusion, the present study revealed evidence for pronounced interactions between cognitively induced modulations in systemic hemodynamics and such in cerebral blood flow. Like the connection between cerebral blood flow adjustment and cognitive performance, these interactions are highly dynamic in time. The findings underline the importance of the temporal aspect in the investigation of relationships between cardiovascular and central nervous processes and emphasize the suitability of research techniques enabling high time resolution analyses.

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