Cerebral and systemic hemodynamic changes during cognitive and motor activation paradigms

Michelle Moody, Ronney B. Panerai, Penelope J. Eames, and John F. Potter. Cerebral and systemic hemodynamic changes during cognitive and motor activation paradigms. Am J Physiol Regul Integr Comp Physiol 288: R1581–R1588, 2005. First published January 27, 2005; doi:10.1152/ajpregu.00837.2004.—Cognitive and/or sensorimotor stimulation of the brain induces increases in cerebral blood flow that are usually associated with increased metabolic demand. We tested the hypothesis that changes in arterial blood pressure (ABP) and arterial PCO2 also take place during brain activation protocols designed to induce hemispheric lateralization, leading to a pressure-autoregulatory response in addition to the metabolic-driven changes usually assumed by brain stimulation paradigms. Continuous recordings of cerebral blood flow velocity (CBFV; bilateral, middle cerebral artery (MCA)), ABP, ECG, and end-tidal PCO2 (PetCO2) were performed in 15 right-handed healthy subjects (aged 21–43 yr), in the seated position, at rest and during 10 repeated presentations of a word generation and a constructional puzzle paradigm that are known to induce differential cortical activation. Derived variables included heart rate, cerebrovascular resistance, critical closing pressure, resistance area product, and the difference between the right and left MCA recordings (CBFVR-L). No adaptation of the CBFVR-L difference was detected for the repeated presentation of 10 activation tasks, for either paradigm. During activation with the word generation tasks, CBFV changed by (mean ± SD) 9.0 ± 3.7% (right MCA, P = 0.0007) and by 12.3 ± 7.6% (left MCA, P = 0.0007); ABP by 7.7 ± 6.0 mmHg (P = 0.0007); heart rate by 7.1 ± 5.3 beats/min (P = 0.0008); and PetCO2 by −2.32 ± 2.23 Torr (P = 0.002). For the puzzle paradigm, CBFV changed by 13.9 ± 6.6% (right MCA, P = 0.0007) and by 11.5 ± 6.2% (left MCA, P = 0.0007); ABP by 7.1 ± 8.4 mmHg (P = 0.0005); heart rate by 7.9 ± 4.6 beats/min (P = 0.0008); and PetCO2 by −2.42 ± 2.59 Torr (P = 0.001). The word paradigm led to greater left hemispheric dominance than the right hemispheric dominance observed with the puzzle paradigm (P = 0.004). We concluded that significant changes in ABP and PetCO2 levels occur during brain activation protocols, and these contribute to the evoked change in CBFV. A pressure-autoregulatory response can be observed in addition to the hemodynamic changes induced by increases in metabolic demand. Simultaneous changes in PCO2 and heart rate add to the complexity of the response, indicating the need for more detailed modeling and better understanding of brain activation paradigms.

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induced by a Valsalva maneuver, cold stress test, hand grip, or other maneuvers (21). Moreover, the CBFV dynamic autoregulatory response can also be identified in spontaneous ABP transients (21). From this, it can be expected that even small changes in ABP, taking place during mental activation tasks, will provoke a dynamic autoregulatory response of CBF. In addition to testing this hypothesis, we have also studied the short-term adaptation effects of repeated activation tasks presented within a 10-min time interval.

Although the present study was based on recordings of CBFV with TCD, it is important to emphasize that its hypotheses and some of the main conclusions should also apply to similar studies using different techniques to record CBF.

METHODS

**Subjects and measurements.** Fifteen young healthy subjects (7 men) were recruited mainly from department staff. Their age distribution is given in [Table 1](#). The local research ethics committee approved the study, and fully informed, written consent was obtained from each subject. Acceptance into the study required a score of ≥70% for right-handedness as assessed by the Edinburgh handedness inventory (19). No subject had any indication of cerebrovascular disease.

Subjects avoided alcohol, nicotine, and caffeine-containing products for 24 h before they reported to a temperature- (23°C) and lighting-controlled laboratory. Measurements were performed with subjects in the seated position with the legs placed under a bench and the hand used to perform the tasks (“active hand”) resting on the bench. The other hand was kept at heart level and was used to record ABP noninvasively with an arterial volume-clamping device (Finapres 2300, Ohmeda). PETCO2 was measured via a closely fitting mask and an infrared capnograph (Capnogard, Novametrix). We monitored ECG signals using three surface chest leads. The middle temporal bone window and locked in position with a specially designed head frame. All physiological signals were continuously recorded onto digital audiotape (DAT, Sony PC-108M). The heart-MCA distance was measured to obtain estimates of MCA pressure.

**Activation paradigms.** Two different paradigms were adopted involving the use of the right or left hand, to activate the contralateral hemisphere (32). After random assignment, the ABP transducer was placed on the middle finger of the nonactive hand, the servo-corrected head frame. All physiological signals were continuously recorded onto digital audiotape (DAT, Sony PC-108M). The heart-MCA distance was measured to obtain estimates of MCA pressure.

**Data analysis.** Data recorded on tape were downloaded onto a microcomputer in real time. A fast Fourier transform was used to extract the maximum frequency velocity envelope with temporal resolution of 5 ms. The ABP, ECG, PETCO2, and stimulus marker signals were sampled at a rate of 200 samples/s, and ABP was calibrated at the start of each recording. All signals were visually inspected to identify artifacts or noise, and narrow spikes were removed by linear interpolation. The two CBFV signals were subjected to a median filter with a window width of five samples, and all signals were low-pass filtered by a zero-phase Butterworth filter with a cutoff frequency of 20 Hz.

The beginning and end of each cardiac cycle were detected on the ECG, and mean beat-to-beat values were calculated for the two CBFV channels, ABP, and heart rate. The CBFV signals were normalized by their baseline values and expressed in percent. The heart-MCA distance was used to obtain estimates of ABP in the MCA (ABP-MCA).

The end-tidal position was detected in the capnographic signal, and linear interpolation was used to obtain estimates of PETCO2 synchronized to the end of each cardiac cycle. An index of cerebrovascular resistance (CVRi) was estimated by the ratio of mean ABP to mean CBFV for each heartbeat, for both MCAs (12). The instantaneous

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline 1</th>
<th>Baseline 2</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>28.7 ± 6.2 (21–43)</td>
<td>81.8 ± 6.8 (70–92)</td>
<td>0.10</td>
</tr>
<tr>
<td>Edinburgh inventory score, %</td>
<td>68.9 ± 11.8 (54.5–94.4)</td>
<td>69.0 ± 7.2 (49.3–74.1)</td>
<td>0.010</td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>57.6 ± 13.4 (37.0–85.1)</td>
<td>55.7 ± 12.9 (35.9–81.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>CBFV, cm/s</td>
<td>55.4 ± 9.9 (35.8–70.1)</td>
<td>53.7 ± 8.0 (39.9–65.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>68.8 ± 7.5 (58.1–84.2)</td>
<td>68.6 ± 8.6 (56.3–89.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>PETCO2, mmHg</td>
<td>40.6 ± 5.2 (29.8–46.6)</td>
<td>39.5 ± 4.5 (30.2–45.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>CBFV, mmHg</td>
<td>8.1 ± 13.4 (–12.3–39.8)</td>
<td>16.1 ± 19.3 (–21.3–42.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>CBFV, mmHg</td>
<td>8.3 ± 14.8 (–15.9–40.6)</td>
<td>16.0 ± 20.2 (–19.4–41.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>RAP, mmHg/s•cm−1</td>
<td>1.11 ± 0.32 (0.57–1.70)</td>
<td>0.86 ± 0.39 (0.34–1.69)</td>
<td>0.001</td>
</tr>
<tr>
<td>RAP, mmHg/s•cm−1</td>
<td>1.13 ± 0.33 (0.72–2.1)</td>
<td>0.87 ± 0.34 (0.36–1.37)</td>
<td>0.037</td>
</tr>
<tr>
<td>CVRi, mmHg/s•cm−1</td>
<td>1.22 ± 0.27 (0.69–1.56)</td>
<td>1.17 ± 0.29 (0.59–1.62)</td>
<td>0.46</td>
</tr>
<tr>
<td>CVRi, mmHg/s•cm−1</td>
<td>1.25 ± 0.25 (0.84–1.61)</td>
<td>1.18 ± 0.22 (0.79–1.55)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Values are means ± SD, with range in parentheses. ABP, arterial blood pressure; CBFV, cerebral blood flow velocity; CrCP, critical closing pressure; CVR, cerebrovascular resistance; MCA, middle cerebral artery; PETCO2, end-tidal PCO2; RAP, resistance area product. Subscripts R and L indicate right and left, respectively.
CBFVR = \text{cerebral blood flow velocity (CBFV; right middle cerebral artery (MCA))},

CBFVL = \text{cerebral blood flow velocity (CBFV; left middle cerebral artery (MCA))},

ABP = \text{arterial blood pressure (ABP)},

\text{end-tidal CO}_2 = \text{end-tidal value}.

The inverse of the linear regression slope was also obtained for each cardiac cycle, and it is referred to as “resistance area product” (RAP = 1/a) to differentiate it from CVRi (10, 20). The CrCP can then be obtained from the value of ABP where CBFV = 0, that is, CrCP = \(-b/a\). All beat-to-beat estimates were interpolated with a third-order polynomial and resampled at 0.2-s intervals to generate a time series with a uniform time base. R and L are used with abbreviations to denote right-side and left-side variables, respectively.

Averages were performed for each variable synchronized by the beginning of each activation task. To study the effects of adaptation, 10 separate averages included all subjects for each repetition of the activation task. Averages adding the 10 repetitions for each subject were used to assess changes in ABP, heart rate, \textit{PETCO}_2, and other variables induced by the two different activation paradigms.

Statistical analysis. Paired Student’s \(t\)-tests were used to assess changes in baseline parameters between the two recordings performed at rest before each activation paradigm. To test for the presence of adaptation, the CBFV right-left difference (CBFVR-L) was calculated for each of the 10 presentations of the word or puzzle paradigms for each subject. The parameter \(\Delta V_{R-L}\) was extracted as the difference of the mean value during the plateau phase (middle 20 s during the 30-s activation period) and the baseline (10-s average ending 2 s before beginning of task). Repeated-measures ANOVA was used (10 levels) to test for changes in \(\Delta V_{R-L}\) that could be indicative of adaptation. The Mann-Whitney test was used to test for differences in \(\Delta V_{R-L}\) between the word and puzzle paradigms.

Change from rest to activation was tested with Wilcoxon’s matched pairs test. From the population task synchronized averages, the positions of the minimum and/or maximum values were located and their time differences, in relation to the beginning of activation, were expressed as \(T_R\) and \(T_A\), respectively. The mean values for each subject \((n = 10)\) at these instants of time were then used to test the hypothesis that activation leads to changes in the 12 variables that were measured (ABP-MCA, \textit{PETCO}_2, heart rate, CBFV\(_R\), CBFV\(_L\), CBFV\(_{R-L}\)) or derived (CrCP\(_R\), CrCP\(_L\), RAP\(_R\), RAP\(_L\), CVRi\(_R\), CVRi\(_L\)). Statistical significance was set at \(P < 0.05\).

RESULTS

All 15 right-handed subjects (7 men) completed the word and puzzle paradigms. On average, subjects wrote 7 words for each of the 10 initials presented on the screen. The puzzle was seldom completed within the 30 s available for each task. Table 1 provides subject characteristics and mean \((\pm SD)\) values of the recorded and derived variables for the two baseline recordings preceding each activation paradigm. Due to a technical fault, recordings were lost for the first baseline of one subject, and for this reason only 14 values are shown in Table 1. Baseline recordings were similar for all variables, except for RAP estimates whose second baseline values, for both right and left sides, were lower \((P < 0.05)\). All other variables indicate a complete recovery to rest conditions after the first paradigm.

Figure 1 shows a representative recording of the off-on transition during one task of the word paradigm. As soon as the task is presented (gray bar), ABP and the two CBFV channels start to rise, showing a peak \(\sim 5\) s into the task. More gradually, the capnographic tracing also shows a slight reduction of the end-tidal value.

Adaptation of the CBFV response to successive presentations was not significant, as assessed by repeated-measures ANOVA of the parameter \(\Delta V_{R-L}\) (see METHODS). Figure 2 shows that \(\Delta V_{R-L}\) was consistently negative for the word paradigm, indicating the presence of lateralization resulting from larger changes in CBFV\(_L\) compared with CBFV\(_R\). Conversely, \(\Delta V_{R-L}\) was consistently positive during the puzzle paradigm, again confirming the occurrence of right hemispheric lateralization (Fig. 2). Left hemispheric dominance for the word paradigm was stronger than the right hemispheric dominance elicited by the puzzle (Mann-Whitney \(P = 0.004\)).
Task-synchronized averages for the whole population for the word paradigm are given in Fig. 3 for the 12 variables considered. The initial peaks observed in the raw data (Fig. 1) are clearly visible in the right and left CBFV channels and the ABP-MCA; these were followed by a gradual rise in CBFV and a plateau in ABP-MCA. Heart rate also rose continuously during the task, and PETCO2 reached a nadir ~10 s into the task. The average CBFV_R−L difference shows a relatively rapid reduction, reaching a negative plateau, which was used to derive the ΔVR−L parameter as described above. Highly significant differences for the change from rest to activation (P < 0.01) were obtained for all variables, as indicated in Table 2, with the exception of CrCP_R (P = 0.031) and CVRi_L (P = 0.015). Values of TR and TA in Table 2 indicate the position of the minimum and/or maximum points during rest and activation, detected on the population averages (Fig. 3). With the exception of CBFV_R−L, whose nadir occurs approximately in the middle of the 30-s window of activation, for all other variables, TA was either at the beginning of activation or nearer the end of activation, as observed for CBFV_L, heart rate, and CrCP for both sides.

Figure 4 represents the corresponding averages for the puzzle paradigm. Although the initial peak in CBFV is less pronounced than the corresponding changes during the word tasks (Fig. 3A), the marked peak in ABP-MCA is again observed, as well as the dip in PETCO2. For the CBFV_R−L difference, there is a more gradual change, but a plateau is also established, and the difference is maintained for at least 10 s...
after the puzzle is removed from the screen (Fig. 4B). The profiles of heart rate and CrCP are similar to those observed from Fig. 3, but the changes in RAP (Fig. 4F) and CVRi (Fig. 4H) are less pronounced. The puzzle also led to highly significant \( P < 0.01 \) results for the change from rest to activation for the majority of variables (Table 3), with the exception of CRCPr \( (P = 0.036) \) and RAPr \( (P = 0.02) \). Similarly to the word paradigm, the puzzle led to maximum (or minimum) mean population values either at the beginning or nearer the end of the 30-s activation window, as shown by the values of \( T_A \) in Table 3.

In summary, both the word and puzzle paradigms induced significant changes in CBFV right, left, and R-L difference; ABP-MCA; heart rate; \( \text{PETCO}_2 \); and derived values of CVRi, RAP, and CrCP for both sides.

**DISCUSSION**

Despite differences in the type of cognitive and/or sensorimotor stimulation adopted, the changes in bilateral CBFV and CBFVR-L difference in this study are in very good agreement with values previously recorded by others (4, 5, 7, 11, 15–17, 23, 24, 27–35, 37). The latency of the response, as represented by the position of the initial peak in CBFV, was also similar to results found by previous investigators (16, 23, 24, 31, 32, 35, 36), and the entire temporal pattern of the CBFV response resembled the results reported in a small number of studies (8, 23, 31, 35, 36).

The occurrence of adaptation due to task repetition has received little attention in functional TCD studies, probably due to poor signal-to-noise ratio of measurements performed without task-synchronized averaging. Although we extracted the parameter \( \Delta V_{R-L} \) for separate tasks in each subject, the resulting sequential changes show a relatively stable behavior (Fig. 2) with no evidence of accommodation. This result agrees with the previous findings of Rosengarten et al. (24) who used an on-off reading stimulation paradigm. Lack of adaptation is an important requisite to use task synchronized averaging, as in Figs. 3 and 4, or other analytical procedures, such as spectral analyses, which require the assumption of stationarity for repeated activation tasks at 60-s intervals. As a word of caution however, it is still possible that individual responses might show well-defined patterns of neural habituation or sensitization, but with canceling effects in the grand average.

The main findings of our study can be grouped as 1) evidence of significant dynamic changes in ABP, heart rate, \( \text{PETCO}_2 \), and other variables (RAP, CrCP, CVRi) during mental activation tasks; and 2) indications that cerebral vasodilation, reflecting the neurovascular coupling to increased metabolic demand, is preceded by cerebral vasocostriction, probably due to a myogenic dynamic autoregulatory response elicited by the transient increase in ABP in the first 10 s of the activation phase (Figs. 3 and 4). These two main findings will be discussed below.

The main difference between our study and previous investigations of the potential contributions of ABP, \( \text{PETCO}_2 \), and heart rate to evoked CBF responses is that we recorded and analyzed these variables continuously, without performing time averages. Although some previous studies have also recorded ABP, heart rate, and \( \text{PETCO}_2 \) continuously (5, 14–16, 24, 25, 27–31, 34, 35), in most cases these values were either averaged over periods of 30–60 s (5, 14, 16, 27, 29–31) or were restricted to comparing values before and after the complete activation sequence (15, 24, 25, 28). From the results shown in Figs. 3 and 4, it is clear that averaging along time would have a major effect in dampening the dynamic changes that we observed. Despite the reduced sensitivity of time-averaged results, several studies reported changes in these covariates. A few studies explicitly mentioned significant increases in ABP (5, 14, 29, 30) and heart rate (5, 14, 29–31). Other investigations did not find statistically significant differences but reported increases in ABP of 2.2 \( \pm 1.8 \% \) (16), 3–6 mmHg (28), and \( \sim 12\% \) (27). For heart rate, the same studies mentioned increases of 3.0 \( \pm 2.6\% \) (16), 2–6 beats/min (28), and 5–7% (27). Despite being attenuated by time averaging, these values are similar, or even higher, than those that we obtained (Tables 2 and 3; Figs. 3 and 4). \( \text{PETCO}_2 \) was recorded in many cases, but we found only one study reporting a significant decrease in \( \text{PETCO}_2 \) (14). Nonsignificant reductions in \( \text{PETCO}_2 \) were noted, however, of the order of 1 Torr (28) and heart rate (5, 14, 29–31). Other investigations did not find statistically significant differences but reported increases in ABP of 2.2 \( \pm 1.8 \% \) (16), 3–6 mmHg (28), and \( \sim 12\% \) (27). For heart rate, the same studies mentioned increases of 3.0 \( \pm 2.6\% \) (16), 2–6 beats/min (28), and 5–7% (27). Despite being attenuated by time averaging, these values are similar, or even higher, than those that we obtained (Tables 2 and 3; Figs. 3 and 4). \( \text{PETCO}_2 \) was recorded in many cases, but we found only one study reporting a significant decrease in \( \text{PETCO}_2 \) (14). Nonsignificant reductions in \( \text{PETCO}_2 \) were noted, however, of the order of 1 Torr (28) and heart rate (5, 14, 29–31). Another study concluded that \( \text{PETCO}_2 \) was stable, “oscillating between 38 to 42 mmHg throughout each recording” (5). Again, these averaged changes compare well and even surpass the differences in \( \text{PETCO}_2 \) that we observed in breath-by-breath values (Tables 2 and 3; Figs. 3 and 4). We are not aware of any other studies providing the temporal evolution of changes in ABP, \( \text{PETCO}_2 \), and heart rate as displayed in Figs. 3 and 4. However, Tiecks et al. (35) monitored ABP continuously by radial tonometry in one subject and observed a significant peak occurring simultaneously with the first peak value in CBFV, \( \sim 3\mathrm{s} \) after the beginning of activation. This observation is in close agreement with our results in Figs. 3 and 4. Although changes in ABP, \( \text{PETCO}_2 \), and heart rate are better evidenced by the population averages in Figs. 3 and 4, it is important to add that similar changes could be detected in intrasubject averages or even in the raw data as exemplified by Fig. 1.

The above discussion has not taken into account the influence of the different cognitive and/or sensorimotor stimulation paradigms adopted to induce mental activation, but this factor is obviously of key importance to assess concomitant changes in ABP, \( \text{PETCO}_2 \), heart rate, and other variables. The use of two
particular paradigms means that our results cannot be generalized to all mental activation protocols. It is likely that less demanding paradigms will lead to smaller changes in ABP, PETCO₂, and heart rate. The choice of paradigms in our study was not guided by the intention of inducing stress or anxiety but mainly resulted from a detailed review of the literature searching for the most common activation protocols with demonstrated hemispherical specificity. We decided against pure visual stimulation to avoid simultaneous recordings in the posterior cerebral artery. For the MCA, the most common paradigms, by far, involve the use of word generation (32), and we opted for written confirmation to be able to check for compliance and effort, as well as to add the motor component to the left hemispherical response to improve signal-to-noise ratio. Searching for a second paradigm, more specific to right hemispherical stimulation, we followed the detailed study of Vingerhoets and Stroobant (37), who indicated greater reliability with the use of a three-dimensional puzzle. We had to adapt the puzzle concept to a two-dimensional representation to allow the active use of the left hand while keeping the right hand immobilized with the Finapres cuff. In both cases, the premises of lateralization were confirmed, as shown by the results in Figs. 2–4. Nevertheless, it is essential that further work is performed to assess the extent to which alternative paradigms will also lead to changes in ABP, PETCO₂, and heart rate.

Turning now to the influences of changes in ABP, heart rate, and PETCO₂ on the CBFV response to activation, some authors have admitted the possibility that increases in ABP and heart rate might enhance the CBFV response and that cerebral
autoregulation might play a role as well (14, 16, 32, 35). The possibility that the reduction in PETCO2 could restrict the CBFV response was also acknowledged (14, 31, 32). In other studies, recorded changes in ABP and heart rate (averaged over 30 or 60 s) were taken into account in the statistical analyses but were not found to influence the main results (5, 27, 29). The demonstration that the transient or dynamic response of cerebral pressure-autoregulation operates with time constants of a few seconds (3, 9, 12, 21) indicates that it is not appropriate to study the influences of any covariates of CBFV by averaging values over 30 s or more. To determine whether a vasoconstrictive autoregulatory response was superimposed on the expected cerebral vasodilation, we calculated well-known indexes of vasomotor activity, as expressed by CVRi, RAP, and CrCP (9, 12, 20). Our results provide evidence of cerebral vasoconstriction in the early phase of mental activation, and the most likely explanation is that increases in CVRi and RAP express the dynamic autoregulatory response to the ABP peak, ~5 s after the beginning of activation (Tables 2 and 3; Figs. 3 and 4) (9, 12, 20).

In addition to the observed changes in ABP-MCA, the significant reduction in PETCO2 also needs to be taken into account regarding its contribution to hemodynamic changes during activation. In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation. In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation. In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation. In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation. In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation. In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation. 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In the absence of other influences, the fall in PCO2 would be responsible for a corresponding reduction in CrCP during activation.

If our initial observations, of significant dynamic changes in CBFV covariates and the interference of dynamic cerebral autoregulation in the early phase of mental activation, are confirmed by further investigations, then this raises the question of how to progress with studies of neurovascular coupling in humans. Additional research might find ways to unscramble the myogenic from the metabolic components of the CBFV response, which would have the additional benefit of enriching the amount of physiological information derived from mental activation tests. On the other hand, most previous studies of dynamic cerebral autoregulation, based on CBFV measurements in the MCA, have not shown hemispheric differences (9, 21). Therefore, by subtracting the right from the left side CBFV response (CBFVR), Figs. 3 and 4), we can assume that the contribution of dynamic autoregulation is removed, thus yielding some estimate of the differential metabolic response. Nevertheless, for advancing our understanding of neurovascular coupling in humans, both in health and disease, it is important to improve the accuracy of estimates from each hemisphere, and for this purpose it is essential to take into account the possibility that the CBF response includes a complex interaction of vasoconstriction and vasodilatation.

The limitations of the study are mainly related to the use of noninvasive measurements. Changes in CBFV will reflect changes in CBF as long as the cross-sectional area of the MCA remains constant. Hitherto, significant changes in MCA diameter have not been found, even in situations where large changes in ABP and PCO2 are taking place (18, 26). Nevertheless, it is important to keep in mind that diameter changes resulting from sympathetic stimulation would lead to overestimation of CBFV and could thus explain some of the increases in CBFV observed during activation. Having the subjects seated during recordings, similarly to the majority of other brain activation studies using TCD (4, 5, 7, 8, 15–17, 23–25, 33, 35–37), limits the generalization of our results to studies employing other methods of recording CBF, such as fMRI, where subjects are normally supine. Peripheral ABP measurements also need careful consideration because of the different ABP waveforms recorded in the finger, compared with what is normally measured in large central arteries. As mentioned previously, there is good evidence that changes in mean ABP recorded in the finger provide a reliable indication of changes in central mean ABP (13). The main problem however is the use of the finger ABP waveform to obtain estimates of CrCP and RAP. Due to the amplification of systolic pressure taking place with wave propagation along the arm, finger ABP recordings tend to underestimate CrCP, often yielding negative values (2, 20). However, this potential problem can be countered by careful data analyses, mainly by averaging across subjects and tasks and by checking for consistency of temporal patterns, as demonstrated in Figs. 3 and 4. Notably, none of the 30 sets of data analyzed (15 word + 15 puzzle) presented negative values of CrCP at heart level, but some values became negative when CrCP was corrected to MCA height. Systolic ABP distortion in the finger might have been a minor problem in our study due to the young age of the population. The questionable accuracy of CrCP and RAP estimates based on
finger ABP, however, led us to also calculate a CVR index as an adjunct to the interpretation of our findings. Despite being less informative than the separate analysis of RAP and CrCP, CVRi has also signaled the presence of rapid vasconstriction, during activation with the word paradigm (Fig. 3). Peaks of smaller amplitude were also observed for activation with the puzzle, although in this case the statistical significance of CVRi changes had more to do with the reduced values observed at the end of activation.

In summary, we have demonstrated that two different paradigms stimulating left and right cortex with a 30-s on-off cycle do not lead to adaptation of the CBFV differential response. Additionally, we found that significant changes in ABP, PETCO2, and heart rate, as well as in indicators of vasomotor activity, can take place during activation, indicating a complex interaction of hemodynamic changes during mental activation tasks. Further investigation is required to quantify these interactions and to allow a better understanding and interpretation of mental stimulation tests, as well as a more rigorous standardization of activation paradigms.

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