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Hemodynamic and metabolic responses to neuronal inhibition

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Functional magnetic resonance imaging (fMRI) was used to investigate the changes in blood oxygenation level dependent (BOLD) signal, cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption (CMR_{O_2}) accompanying neuronal inhibition. Eight healthy volunteers performed a periodic right-hand pinch grip every second using 5% of their maximum voluntary contraction (MVC), a paradigm previously shown to produce robust ipsilateral neuronal inhibition. To simultaneously quantify CBF and BOLD signals, an interleaved multislice pulsed arterial spin labeling (PASL) and T_2*-weighted gradient echo sequence was employed. The CMR_{O_2} was calculated using the deoxyhemoglobin dilution model, calibrated by data measured during graded hypercapnia. In all subjects, BOLD, CBF and CMR_{O_2} signals increased in the contralateral and decreased in the ipsilateral primary motor (M1) cortex. The relative changes in CMR_{O_2} and CBF were linearly related, with a slope of ~0.4. The coupling ratio thus established for both positive and negative CMR_{O_2} and CBF changes is in close agreement with the ones observed by earlier studies investigating M1 perfusion and oxygen consumption increases. These findings characterize the hemodynamic and metabolic downregulation accompanying neuronal inhibition and thereby establish the sustained negative BOLD response as a marker of neuronal deactivation.

Keywords: fMRI; Negative BOLD; Perfusion; Oxygen consumption; Inhibition

Introduction

Functional magnetic resonance imaging (fMRI) using BOLD effect (Ogawa et al., 1990) has become a prominent tool for examining brain function. Despite a wealth of BOLD-based neuroscientific studies and a growing use of BOLD fMRI in clinical applications, the physiological mechanisms modulating the blood oxygen saturation in the context of neuronal activation remain incompletely understood. While many aspects of the steady state positive BOLD response have been investigated, attention has only recently been given to sustained decreases in the BOLD signal.

In both animal (Harel et al., 2002; Shmuel et al., 2003a,b) and human visual stimulation studies (Cotillon-Williams et al., 2003; Dojat et al., 2003; Shmuel et al., 2002), decreased BOLD signal has been observed in the nonstimulated areas of the visual cortex upon partial visual field stimulation as well as areas corresponding to regions in the visual field not receiving the subject's attention (Tootell et al., 1998). Several theories have been put forth by the investigators to explain these observations: from the purely hemodynamic effect of ''blood stealing'' to neuronal inhibition, or some combination of these (Cotillon-Williams et al., 2003; Dojat et al., 2003; Shmuel et al., 2002). During an acoustically triggered saccade paradigm, a bilateral negative BOLD response has been reported in the visual cortex; simultaneously, near-infrared spectroscopy revealed decreased oxy- and increased deoxy-hemoglobin concentration with an overall decrease in total hemoglobin (Wenzel et al., 2000). These findings have been attributed to decreased blood flow resulting from the inhibition of background activity in the visual cortex during saccades, as described in psychophysiological studies (Duffy and Burchfiel, 1975).

A sustained negative BOLD response has also been observed in the motor cortex. A steady state decrease in BOLD signal has been documented in the ipsilateral primary sensorimotor cortex of normal volunteers during sequential finger apposition (Allison et al., 2000; Nirkko et al., 2001). A PET study reported ipsilateral CBF decreases during low-force, right index finger flexion (Dettmers et al., 1995). In contrast, ipsilateral CBF increases were measured during high force finger flexion (Dettmers et al., 1995) and positive ipsilateral BOLD responses documented during circling shoulder movements (Nirkko et al., 2001). Finally, a decreased BOLD signal has been documented in the ipsilateral primary sensorimotor cortex of normal volunteers performing a low force, phasic pinch grip task (Hamzei et al., 2002), accompanied by a decrease in blood flow (Hopt et al., 2003). Transcallosal inhibition, reported in a plethora of transcranial magnetic stimulation (TMS) studies (Boroojerdi et al., 1996; Ferbert et al., 1992; Gerloff et al., 1998; Liepert et al., 2001; Netz et al., 1995), has been suggested as the likely origin of these changes (Hamzei et al., 2002).

Determining the origins of sustained negative BOLD responses accompanying neuronal inhibition is important not only for understanding the BOLD mechanism, but also for probing the extent and nature of neurovascular coupling,

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thereby establishing the applicability of BOLD as a marker of upregulation as well as downregulation of neuronal activity. We thus set out to investigate the hemodynamic and metabolic processes concomitant to the negative BOLD response in a low-force, phasic pinch grip of the right index finger and thumb in right-handed healthy volunteers. We hypothesized that this steady-state negative BOLD response results from sustained decreases in both perfusion and oxygen consumption and, furthermore, that the same relationship between CMR_{O_2} and CBF underlies both positive and negative steady state BOLD signal changes. The variations in BOLD, CBF, and CMR_{O_2} were measured by interleaved T_2*-weighted and PASL acquisitions, with hypercapnic calibration for CMR_{O_2} quantification. Here we report on the relationship between blood flow and oxygen consumption in regions of sustained BOLD and CBF signal increases, in the contralateral M1, and their decreases, in the ipsilateral M1. Since the paradigm employed induces ipsilateral neuronal inhibition, these findings have direct implications for the use of negative BOLD response as a marker of neuronal deactivation.

Methods

Motor task

Before scanning, the maximum voluntary contraction of the right-handed pinch grip was measured for each subject. The subjects were then trained to perform the pinch grip task at a frequency of 1 Hz, as cued by a metronome. On each grip, subjects pressed a water-filled ball with the thumb and the index finger of the right hand. The ball was connected to a pressure transducer (Ashcroft, Stratford, CT), in turn linked to a data acquisition card (National Instruments, Austin, TX). The real-time recording and analysis of the exerted pressure was done using MATLAB's data acquisition toolbox (Mathworks, Natick, MA). An auditory feedback was provided to the subject: a low-frequency tone indicated that the force applied was in the desired range, namely within 15% of the target level; a high-frequency tone accompanied too strong a force; and no tone was played out when insufficient force was exerted. To minimize habituation, the target level was randomized on each pinch grip and varied between 4% and 7% of the subject's MVC. A metronome, set at 60 beats per minute was on during the anatomical scan for accustomization and then switched off for the functional scan, the subjects having been instructed to maintain a pinch grip frequency of 1 Hz.

Hypercapnic modulation

Mild hypercapnia was induced through administration of mixtures of carbon dioxide and air through a nonrebreathing face mask (Hudson RCI, Model 1069, Temecula, CA). At baseline, the subjects were inhaling medical air, supplied at 16 l/min. During hypercapnic perturbations, a premixed preparation of 10% CO_2, 21% O_2 and balance N_2 (BOC Canada Ltd., Montreal, Quebec, Canada) was combined with medical air in a Y-connector. The CO_2 concentration in the mixture varied between 2.5% and 10%. At each level, the flow rates were adjusted to maintain a total flow rate of 16 l/min. End-tidal CO_2 was measured via a nasal cannula with monitoring aspirator (Normocap 200, Datex Inc., Plymouth, ME) and increased an average 23 $\pm$ 2 mm Hg (or 54 $\pm$ 4%) during inhalation of the highest concentration CO_2 mixture. Subjects were asked to breathe at a constant rate, and their respiratory rate was monitored via a respiratory belt.

Experiment

Eight healthy adults (two females and six males; average age 28 $\pm$ 3 years) participated in the study. All the subjects were right-handed, with an average Edinburgh inventory laterality quotient (Oldfield, 1971) of 87 $\pm$ 18. The scanning protocol consisted of a high-resolution 3D RF-spoiled T_1-weighted gradient echo ($1 \times 1 \times 2$ mm^3) sequence for anatomical reference, followed by interleaved multislice PASL and T_2*-weighted gradient echo sequence for CBF and BOLD signal measurements. The high-resolution gradient echo sequence employed a TR of 22 ms, a TE of 10 ms, and nonselective 30° RF-spoiled excitation. The CBF and BOLD acquisitions covered seven slices ($4 \times 4 \times 7$ mm^3; interslice gap of 0.7 mm) parallel to the AC–PC line, with the seventh slice grazing the top of the brain. The CBF data were acquired using a proximal inversion with a control for off-resonance effects (PICORE) labeling scheme (Wong et al., 1997) with two presaturation pulses in the imaging region followed by an adiabatic FOCI inversion pulse (Ordidge et al., 1996) (β = 1172 s^{-1}, μ = 8, T_p = 10.24 ms, $B_{1,max}$ = 0.28 G, FOCI factor 9) in the labeling region (thickness of 100 mm, gap of 5 mm) and a postlabel delay of TI = 1200 ms. An EPI readout (2232 Hz/pixel) was employed, with an echo time of 22 ms for CBF and 50 ms for BOLD. In both cases, the repetition time was 2.5 s. The functional paradigm involved 12 sessions of 20/60/40 s off/on/off blocks, rest alternating with the low-force, phasic, right-handed pinch grip, the beginning of each block being indicated by auditory cues. Following the functional scan, medical air alternating with graded hypercapnia was administered in 1/3/2 min blocks. Subjects were immobilized using a vacuum bag and a head holder assembly. The RF body coil was used for transmission and a quadrature head coil for signal reception. All the examinations were performed on a Siemens 1.5-T Magnetom Sonata system. Informed consent was obtained from each subject before the scanning session, the experimental protocol having been approved by the Research Ethics Board of the Montreal Neurological Institute.

Data analysis

The motion correction parameters of the functional data set were estimated using AFNI's 3dvolreg software (Cox, 1996) and the frames with estimated translation exceeding 1 mm or rotation greater than 1° excluded from the analysis. The data were spatially smoothed using a three-dimensional Gaussian filter with full-width at half maximum of 6 mm. Drift was removed by subtracting from each voxel's time course the first components of its discrete cosine transform, with a cutoff frequency of one half of the stimulation paradigm frequency. The generalized linear model (Worsley et al., 2002) was used to identify areas of statistically significant task correlation at the omnibus significance level

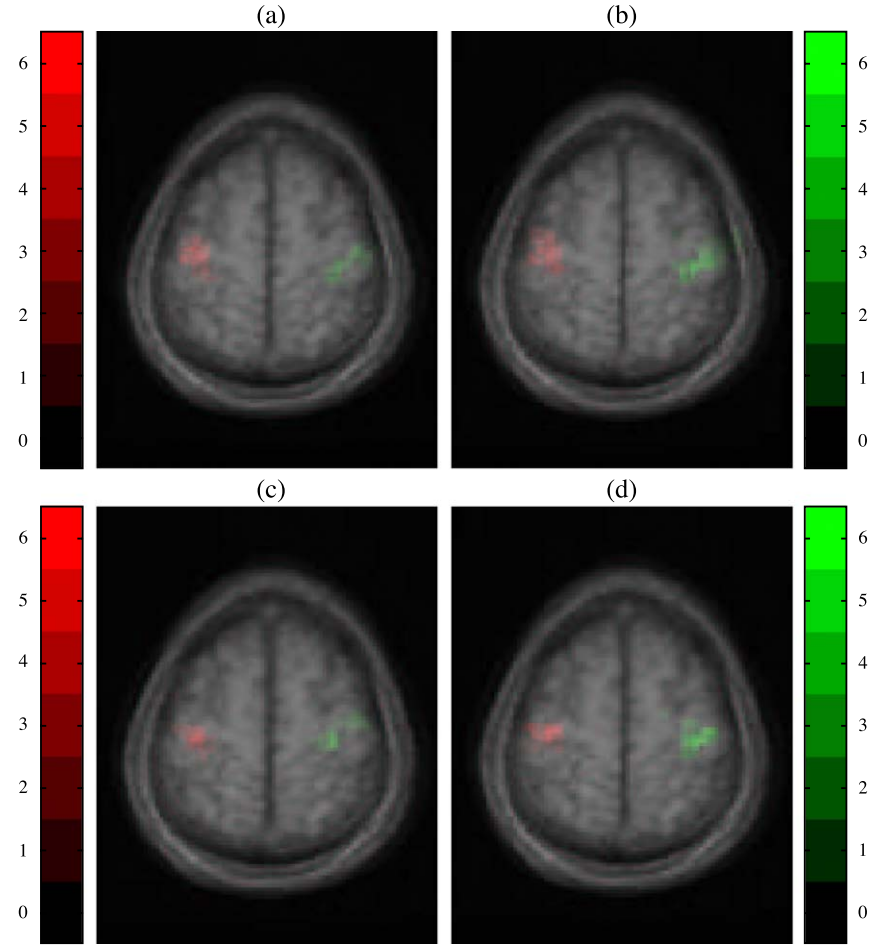

Fig. 1. Regions of interest based on percent difference changes (left column) and *t* values (right column), transformed into the Talaraich space and summed over all subjects, are overlaid on the average of all subjects' anatomical scans in the Talaraich space. The top row shows BOLD and the bottom row CBF ROIs, the contralateral ROIs being displayed in red and the ipsilateral in green.

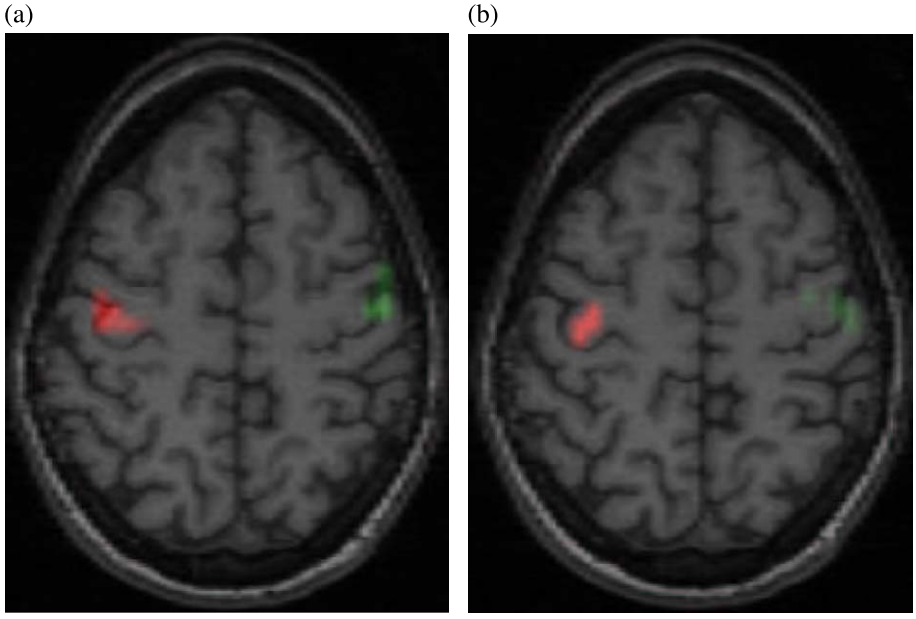

Fig. 2. The regions of interest for BOLD (a) and CBF (b) based on respective percent difference changes in a subject. The contralateral ROIs are displayed in red and the ipsilateral in green.

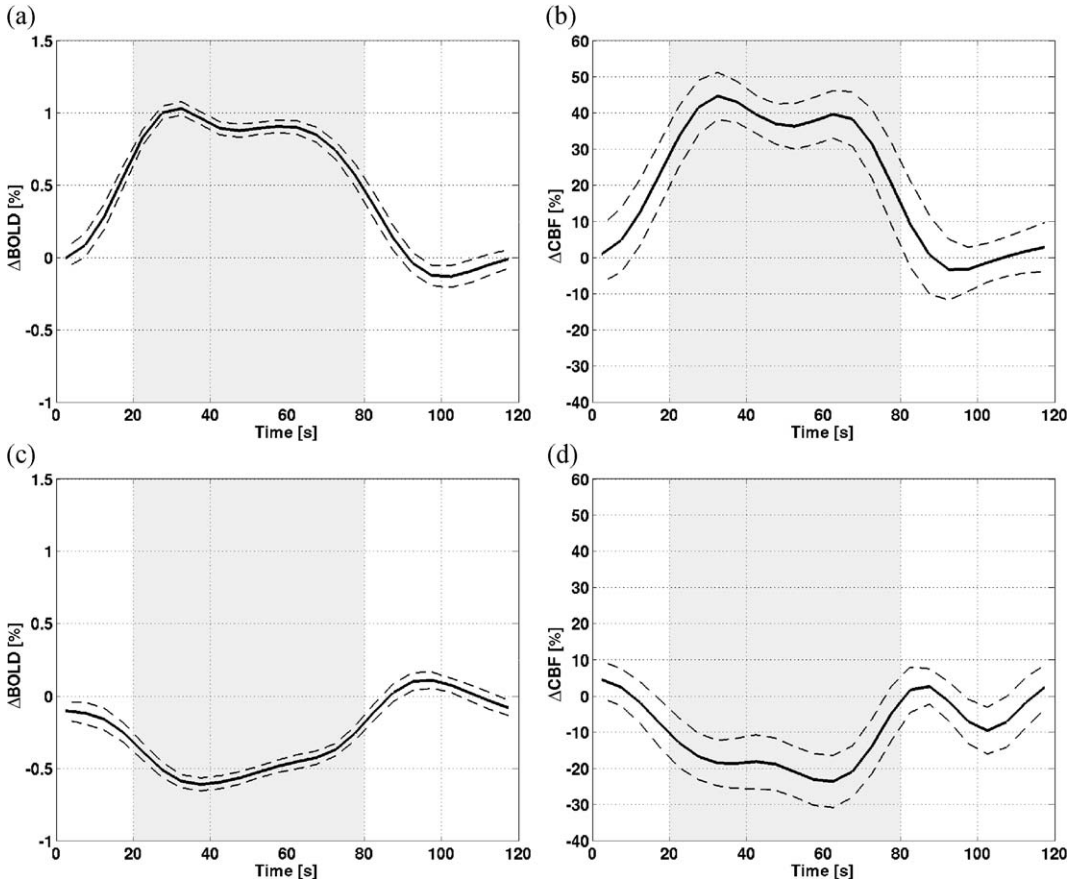

Fig. 3. Time courses of contralateral (positive) BOLD (a) and CBF (b), as well as ipsilateral (negative) BOLD (c) and CBF (d) percent changes in a subject. The standard errors are shown as dashed lines. All time course data have been low-pass-filtered with a Hanning window (FWHM = 20 s) before averaging across the 12 sessions.

of 0.05 in BOLD and CBF data, respectively. Upon establishing statistical significance of both BOLD and CBF responses in both hemispheres of every subject, regions of interest were defined on BOLD and CBF percent signal change maps, respectively, by selecting the M1 voxels showing at least 30% of the peak signal change in the primary motor cortex. This selection strategy maximized the dynamic range of sampled CBF variations and thereby improved the robustness of the coupling ratio estimation. To allow for establishment of a physiological steady state, the hypercapnic data acquired within half a minute following a change in the concentration of the inspired CO_2 was excluded from the analysis. The hypercapnic data were averaged across all subjects, at each level of hypercapnia, and a common maximum achievable BOLD signal change (M) was estimated by linear fitting of the transformed and averaged CBF data vs. averaged BOLD data to the deoxyhemoglobin dilution model (Davis et al., 1998; Hoge et al., 1999):

$$\frac{\Delta BOLD}{\mathrm{BOLD}_0} = M\left(1 - \left(\frac{\mathrm{CBF}}{\mathrm{CBF}_0}\right)^{\alpha-\beta}\right). \quad (1)$$

We thus assumed no effect of the mild hypercapnia elicited in this experiment on the rate of oxygen consumption. The α and β were set to 0.38 and 1.5, respectively (Boxerman et al., 1995; Grubb et al., 1974). The individual task-induced CMR_{O_2} changes were next calculated using the estimated M (and its associated standard error) in combination with the measured BOLD and CBF data during the functional run, as follows (Davis et al., 1998; Hoge et al., 1999):

$$\frac{\mathrm{CMR}_{O_2}}{\mathrm{CMR}_{O_2|0}} = \left(1 - \left(\frac{\Delta BOLD}{\mathrm{BOLD}_0}\right)M\right)^{\frac{1}{\beta}}\left(\frac{\mathrm{CBF}}{\mathrm{CBF}_0}\right)^{1-\frac{\alpha}{\beta}}. \quad (2)$$

Therefore, the errors in the M estimate from the linear fitting of the transformed and averaged CBF hypercapnia data to averaged BOLD hypercapnia data have been propagated into the errors on the calculated activation-induced CMR_{O_2} changes. Finally, a single straight line was fit to the noisy CMR_{O_2}, noisy CBF data pairs from both contralateral and ipsilateral ROIs of all subjects to obtain an optimal estimate of the CMR_{O_2}/CBF coupling ratio. The quality of the fit was assessed by χ^2 analysis, with the χ^2 probability reported as q (Press et al., 1992).

Results

Task-induced increases in BOLD signal were observed, contralaterally, in the primary sensorimotor cortex (SM1), premotor cortex (PMC), supplementary motor area (SMA), as well as part of the posterior parietal association cortex (PPC) flanking the postcentral sulcus. Ipsilaterally, BOLD signal increased in the secondary areas (namely, PMC, SMA, and PPC), but decreased in the primary sensorimotor cortex. Fig. 1 shows a slice of BOLD and CBF ROIs, summed over all subjects after registration (Collins et al., 1994) with the Montreal Neurological Institute template brain (Evans et al., 1993). The world coordinates (x, y, z) of the center of mass of the percent difference based M1 ROIs transformed into the Talaraich space and summed over all subjects were (−39, −19, 54) for contralateral BOLD, (41, −22, 54) for ipsilateral BOLD, (−37, −20, 56) for contralateral CBF, and (37, −22, 56) for ipsilateral CBF. The BOLD and CBF regions of interest for a sample subject are displayed in Fig. 2.

A typical set of BOLD signal and CBF time courses, in both contralateral and ipsilateral M1 ROIs of a subject, is shown in Fig. 3. Fig. 4 displays the measured BOLD and CBF data pairs, for hypercapnic perturbation and motor task, as well as the calculated iso-CMR_{O_2} contours. In seven out of eight subjects, the magnitude of CBF and BOLD signal changes were significantly larger in the contralateral than in the ipsilateral ROI. The maximum achievable BOLD signal increase (M), obtained by linear fitting of the average hypercapnia data across all subjects, was 0.072 ± 0.010, corresponding to a ΔR_2^* of −1.4 ± 0.2 s^{-1}. The χ^2 analysis indicated a good fit (q = 0.37) (Press et al., 1992). Finally, the calculated CMR_{O_2} and the corresponding measured CBF changes, for each subject, are displayed in Fig. 5. The slope of the straight line fit to these data yielded a CMR_{O_2}/CBF coupling ratio of 0.44 ± 0.04 (with q of 0.98 indicating an excellent χ^2 fit (Press et al., 1992)).

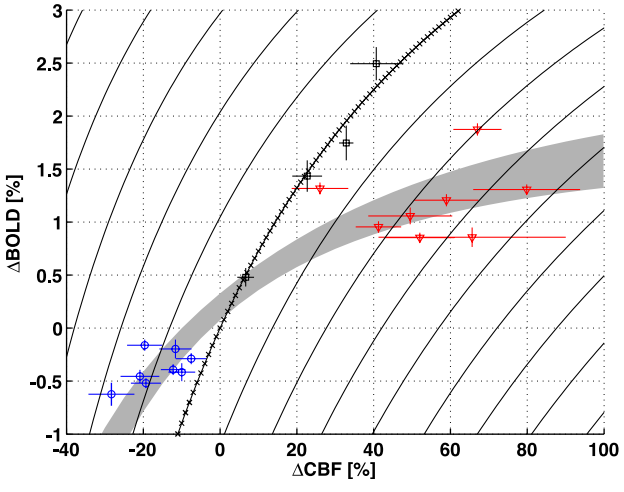

Fig. 4. The percent changes in BOLD and CBF signals in the ipsilateral ROIs (blue circles) and contralateral ROIs (red triangles) for each subject. The average hypercapnia data (black squares) are displayed along with the corresponding fit, representing the baseline iso-CMR_{O_2} contour, and providing the estimate of the maximum achievable BOLD signal change. The estimated M was substituted into the equation (13) of the deoxyhemoglobin dilution model (Hoge et al., 1999) to generate nonbaseline iso-CMR_{O_2} contours, at 10% intervals. The shaded area corresponds to the shaded region of Fig. 5.

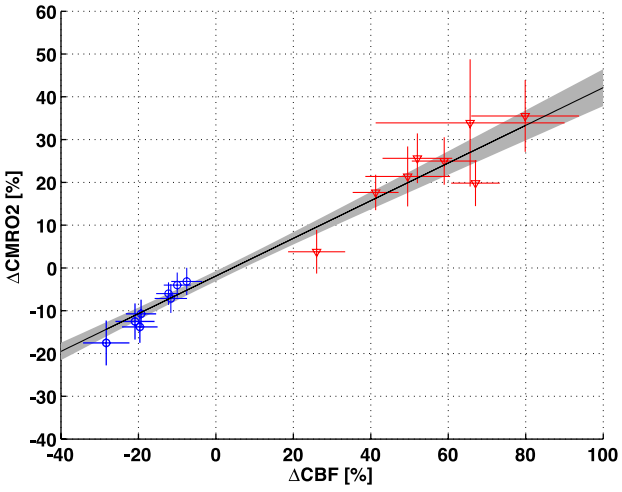

Fig. 5. The oxygen consumption variations corresponding to each subject's perfusion changes induced by the motor task in ipsilateral ROIs (blue circles) and contralateral ROIs (red triangles). The optimal straight line fit (q = 0.98) to these data is shown superimposed, providing the coupling ratio of 0.44 ± 0.04. The shaded region represents the standard error in the linear fit.

Discussion

The present findings demonstrate a consistent coupling between perfusion and oxygen consumption governing both positive and negative BOLD responses. While no other results exist on the ipsilateral CBF and independently measured CMR_{O_2} changes in the context of this or an equivalent paradigm, similar data on the contralateral steady state BOLD signal increases are available. Specifically, Kastrup et al. (2002) report the maximum achievable BOLD signal change (M), averaged over all subjects, at 1.5 T and TE of 40 ms to be 9 ± 3%; that is, ΔR_2^* of −2.2 ± 0.7 s^{-1}, for bilateral finger tapping in healthy volunteers. The M estimated from our average graded hypercapnia data, of 7.2 ± 1.0% (with q of 0.37) or ΔR_2^* of −1.4 ± 0.2 s^{-1}, is thus in good agreement. Our M estimate also agrees with the average 9 ± 1% or ΔR_2^* of −1.8 ± 0.2 s^{-1} obtained in earlier 1.5 T motor cortex studies in our lab, using TE of 50 ms (Atkinson et al., 2000).

The slope of 0.44 ± 0.04 of the best line fit to both contra- and ipsilateral CMR_{O_2} vs. CBF percent signal changes is only slightly larger than the average of 0.33 ± 0.06 reported by Kastrup and 0.35 ± 0.03 found in this lab (Atkinson et al., 2000). The quality of the single linear fit to both ipsilateral and contralateral CBF and CMR_{O_2} changes is excellent (q = 0.98). Treating the data from each hemisphere separately produces slope estimates that are within one standard error of each other (results not shown). It is also instructive to note that fitting a separate M value for each subject, as was done by Kastrup et al., does not influence the linear relationship between CMR_{O_2} and CBF data, but results in a small increase of the estimated coupling ratio and the corresponding error, to 0.53 ± 0.06. In view of the uncertainty in the value of the exponent α, describing the flow/volume coupling in the deoxyhemoglobin

dilution model, we have investigated the dependence of the present findings on variation of α. Specifically, over the range of reported α values from 0.38 (the presently selected value) to 0.18 (Grubb et al., 1974; Jones et al., 2002; Mandeville et al., 1999), we observed a linear decrease in the estimated M value, from 7.2 ± 1.0% to 6.3 ± 0.9% (accompanied by a small drop in the quality of the fit, q decreasing from 0.37 to 0.35). Correspondingly, the estimated CMR_{O_2}/CBF coupling ratio increased, roughly linearly, from 0.44 ± 0.04 to 0.53 ± 0.05 (with negligible effect to the quality of the linear fit). We also note that both M and coupling ratio estimates may be affected by systematic bias in the flow measurement of the presently employed PICORE tagging method. However, paralleling the low sensitivity of the coupling ratio estimate to variations in α over a physiologically relevant range, a bias in the flow measurement—as high as 30% underestimation for hypercapnia or 15% overestimation for motor activation—does not affect the finding of linear coupling between oxygen consumption and flow. Moreover, based on ASL kinetic signal model simulations (not shown), impact of such a bias on M and coupling ratio estimates is on the order of the random measurement error.

While the lack of independent oxygen metabolism measurements by Shmuel et al. (2002) precludes a CMR_{O_2}/CBF coupling ratio comparison, the present findings certainly agree with their qualitative conclusion of smaller relative changes in CMR_{O_2} than CBF in the regions of negative BOLD response. We conclude that there is a consistent coupling between oxygen consumption and blood flow for sustained positive and negative BOLD responses.

Our ROI definition was carried out using the percent difference maps, combined with anatomical constraints. While the details of ROI delineation do not affect the linearity of the relationship between CMR_{O_2} and CBF, they do influence the coupling ratio estimate. Specifically, the present choice of ROIs maximizes the dynamic range of sampled data and hence the estimation power. Moreover, while incomplete overlap between the BOLD and CBF ROIs may introduce bias, only partial spatial congruency of the CBF and BOLD responses has been documented in many studies (Lipton et al., 2000; Luh et al., 2000; Mandeville and Marota, 1999). Finally, the CBF and BOLD ROIs employed are largely overlapping, as shown in Figs. 1 and 2. Ideally, the regions of interest would be defined through a method that is independent of any metabolic and hemodynamic processes and, instead, probes the neuronal activity directly.

While no direct measurements of neuronal activity have been made in this experiment, numerous electrophysiological studies using transcranial magnetic stimulation (TMS) have documented that unihemispheric magnetic stimulation of the primary motor cortex can induce inhibition in the M1 of the other hemisphere (Boroojerdi et al., 1996; Ferbert et al., 1992; Gerloff et al., 1998; Liepert et al., 2001; Netz et al., 1995). This interhemispheric inhibition phenomenon also arises with voluntary manual tasks: the study by Liepert et al. has reported a significant decrease in the TMS-induced, motor-evoked potentials in the relaxed contralateral first dorsal interosseous muscle, while the subjects were performing the current motor task with the ipsilateral hand (Liepert et al., 2001).

The paradigm used in this study was chosen to ensure distinct blood supplies to the positive and negative BOLD response regions. Therefore, a purely hemodynamic effect involving a redirection of flow from the unactivated areas surrounding the activated ones, or blood stealing, is a highly improbable origin of the observed decreases in BOLD and CBF. Moreover, the right-hand task in strictly right-handed individuals maximized the degree of the inhibition: the dominant motor cortex have been shown to exhibit more inhibitory control over the nondominant one than vice versa (Chen et al., 1997; Leocani et al., 2000; Liepert et al., 2001; Netz et al., 1995; Nirkko et al., 2001; Ziemann and Hallett, 2001).

Notwithstanding relatively sparse interhemispheric connections of the cortical motor areas representing the most distal parts of the extremities (Cusick and Kaas, 1986; Gould et al., 1986; Matsunami and Hamada, 1984), the ipsilateral neuronal inhibition is likely mediated via activation (by excitatory axons crossing the corpus callosum) of local ipsilateral $GABA_B$ergic interneurons (Allison et al., 2000; Berlucci, 1990; Daskalakis et al., 2002; Dettmers et al., 1995; Hamzei et al., 2002; Krnjevic et al., 1966; Nirkko et al., 2001). Other investigators have suggested that subcallosal routes may, in part, relay the inhibitory effect (Boroojerdi et al., 1996; Gerloff et al., 1998). Disfacilitation of the excitatory drive onto the α-motorneurons has also been proposed (Gerloff et al., 1998) (TMS not affording means of discerning between the two phenomena).

The underlying purpose of these interhemispheric inhibitory interaction is still not clear. On the basis of EMG recordings of bilateral muscle activation during complex unilateral motor tasks (Kristeva et al., 1991), the proposition has been made that the movements of distal extremities are prepared bilaterally, the late transcallosal inhibition then ensuring unilateral movement (Britton et al., 1991; Rossini et al., 1988). In addition to the suppression of mirror movements, the ipsilateral inhibition may be aimed at reducing interference, aiding focus and thereby achieving high manual dexterity in complex unilateral tasks (Geffen et al., 1994).

Irrespective of the exact purpose of the inhibitory effect in this paradigm, local changes in metabolic and hemodynamic processes most likely reflect net variations in focal energy requirements, in turn arising from the overall level of neuronal firing, BOLD signal changes thus being determined by a balance between increased and decreased neuronal activity. The present findings extend the range of applicability of BOLD signal as a marker of neuronal state and hence brain function over a normal physiological range. Furthermore, the consistency of the coupling ratio for positive and negative BOLD response domains establishes a unique relationship between blood flow and oxygen consumption in the healthy human brain. However, careful investigations, simultaneously quantifying hemodynamic and metabolic changes, are necessary to establish the role of BOLD in determining functional deficits and plasticity under pathological conditions.

Conclusion

We have found a consistent linear relationship between oxygen consumption and perfusion in regions of sustained positive as well as negative BOLD response under normal physiological conditions. The slope of the linear fit to CMR_{O_2} vs. CBF changes from both ipsilateral and contralateral ROIs was 0.44 ± 0.04, in agreement with earlier motor studies investigating steady state BOLD signal increases. The current findings on the coupling between metabolic and hemodynamic processes underlying sustained BOLD decreases, in combination with extensive evidence on the accompanying neuronal inhibition from TMS experiments,

provide support for steady state negative BOLD response as a marker of neuronal deactivation.

Acknowledgments

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