Dissociation of CBF responses corresponding to negative BOLD activity

Y-C. L. Ho[1,2], E. T. Petersen[1,2], and X. Golay[1,3]

[1]Neuroradiology, National Neuroscience Institute, Singapore, Singapore, [2]CFIN, University of Aarhus, Denmark, [3]Singapore Bioimaging Consortium, A*STAR, Singapore

INTRODUCTION: Like its positive counterpart, the sustained negative BOLD signal is an ambiguous marker of underlying neurophysiological processes. Experimentally, such negative signals have been elicited in the visual cortex [1,2] and in the motor cortex [3,4]. It is thought that the generation of a negative BOLD signal could be due to: neuronal/synaptic inhibitory activity [2,4] or vascular 'steal' effects [5]. CBF activity could be differentiated for these two situations. This preliminary study utilised a novel motor task, which was expected to elicit both positive and negative BOLD responses in brain regions associated with motor control. The use of a dual echo PASL sequence, with and without crushers, allowed us to measure BOLD and CBF responses simultaneously, as well as bolus arrival times. We aimed to assess the CBF changes and timing characteristics associated with the positive and negative BOLD responses generated.

METHODS: Five healthy volunteers (2 males, 3 females, 19-34 yrs, 1 left-handed) were scanned on a Philips Achieva 3.0T imager. A QUASAR sequence was used for CBF measurement [6]: Venc=[∞, 4 cm/s], TR/TE_1/TE_2=3000/20/35 ms, ΔTI=250 ms, time points=10, α=35°, SENSE factor=3, labeling slab=150 mm, inversion gap=20 mm, slices=3, thickness=6 mm, gap=1 mm. Slices were positioned at the level of the motor cortex for hand function. Inside the scanner, volunteers were asked to focus on a screen with a small, central circle that flashed at 2Hz during stimulus blocks. The task was to clench the dominant fist out of sync with the flashing circle. Stimulus conditions were alternated with a rest condition: 15 volumes per rest block and 10 volumes per stimulus block. Total volumes = 165. BOLD responses were measured by adding the control and labeled data of the 2nd echo. T-tests ($p<0.001$, uncorrected) on the crushed data determined the regions with significant BOLD activity in either direction. Using the BOLD thresholded masks as ROIs, we assessed CBF responses in those ROIs, focusing on the sensorimotor cortex. CBF calculation using both crushed and non-crushed data was done as follows: (a) Linear interpolation before subtraction was done to avoid BOLD effects [7]; (b) ΔM curves were derived with pair-wise subtraction using first echo data; (c) ASL arrival times of the averaged baseline and stimulation blocks were detected using an edge detection algorithm [6]; and (d) CBF changes were quantified using Buxton's 3-parameter fit [8].

RESULTS: Consistent negative BOLD responses (NBR) were found in the ipsilateral sensorimotor cortex, as well as in the bilateral frontal cortex. In 3 (of 5) subjects, there were also NBRs in the contralateral sensorimotor cortex surrounding that of the positive BOLD response (PBR), similar to what we would expect from 'vascular steal'. PBRs were found, as expected, mainly in the contralateral primary sensorimotor area, the secondary motor areas (PMC, SMA) and the posterior parietal cortex. See Figs. 1 and 2. Using only the thresholded ROIs in the sensorimotor cortex, the detected ASL bolus arrival times for the PBR region were generally quicker during the task activation (420±50 msec), as compared to baseline (450±70 msec), although it was short of statistical significance ($p=0.07$). The ASL bolus arrival times for the ipsilateral and contralateral NBR regions did not significantly differ between baseline and task (ipsilateral – baseline: 570±200 msec, task: 500±150 msec; and contralateral – base: 390±60 msec, task: 480±190 msec). There was no significant difference between the ΔM curves derived from the crushed and non-crushed data, in terms of arrival times and amplitudes. Using Buxton et al's fit [8] on the crushed data alone, we saw an increase in CBF (25-30%, $p<0.05$, mean baseline=72ml/100g/min) in the region of the PBR. However for the NBRs, there was a dissociation of CBF responses – the ipsilateral side showed CBF decrease of ~ 10% ($p<0.05$), while there was no significant change on the contralateral side ($p>0.05$).

DISCUSSION: The BOLD signal reflects the ratio between CBF and $CMRO_2$ changes. With the load imposed by the motor task and the assumption that energy demand drives CBF, we would expect coupling of CBF increase with the PBR in the contralateral sensorimotor cortex, indeed as seen in this study. At the same time, we see NBR and corresponding negative CBF changes on the ipsilateral side. While we did not measure neuronal activity, several TMS studies have shown M1 inhibition in the ipsilateral hemisphere using uni-hemispheric stimulation [9,10]. Such interhemispheric inhibition could be effected via GABA interneurons through transcallosal fibres [3]. The vascular steal theory does not hold in this case, because of distance to the PBR and a separate blood supply [4]; neither can it explain the contrasting finding of a lack of CBF change associated with the contralateral NBR surrounding the PBR in the sensorimotor cortex, although we note that only 3 of 5 subjects demonstrated this latter phenomenon. Our detection of ASL bolus arrival times between baseline and task duration for the PBRs and NBRs did not show significant differences. This could be due to relatively low temporal resolution that we used (ΔTI=250 ms) in order to acquire more slices. The crushed and non-crushed ΔM curves were similar in shape and amplitude, indicating that the ROIs were distant from large arteries and in almost pure gray matter. This has implications for model-free estimates of CBF using locally derived arterial input functions [6] in such anatomical regions. Overall, there appears to be a dissociation of CBF responses with NBRs in different sensorimotor areas. Further work clarifying the findings should aim for better temporal resolution and possible measurement of $CMRO_2$.

REFERENCES:

[1] Wenzel et al (1996), Brain 119:101
[2] Shmuel et al (2002), Neuron 36:1195
[3] Allison et al (2000), Neurol. 54:135
[4] Stefanovic et al (2004), NeuroImg. 22:771
[5] Raichle (1998), PNAS 95:765
[6] Petersen et al (2006), MRM 55:219
[7] Lu H. et al (2005), ISMRM 35.
[8] Buxton et al (1998), MRM 40:383
[9] Ferbert et al (1992), J. Physiol. 453:525
[10] Liepert et al (2001), Clin. Neurophysiol. 112:114

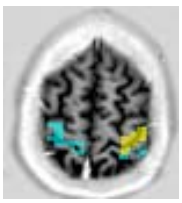

Fig. 1: Thresholded PBR (yellow) and NBR (blue) activity shown for the contralateral (R) and ipsilateral (L) motor cortex. The NBR surrounds the PBR on the contralateral side.

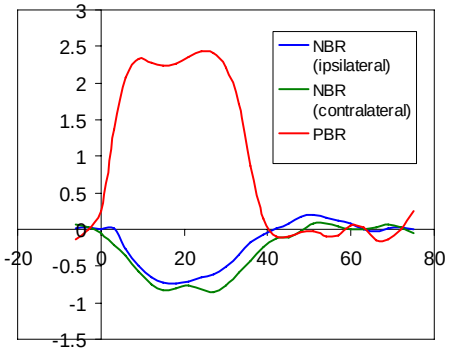

Fig. 2: Averaged BOLD timecourses. Red – PBR; blue – NBR-ipsilateral; green – NBR-contralateral. The negative amplitudes are about 20% of the positive.

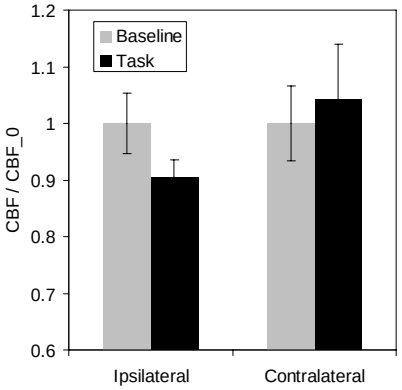

Fig. 3: Normalized CBF responses during baseline and task, corresponding to the ipsilateral and contralateral NBRs seen in Fig. 2. While the amplitudes of the NBRs are similar, the corresponding CBF changes are different. The ipsilateral CBF decrease was significant ($p<0.05$).

Acknowledgements: The SMF and NMRC/0919/04.