BOLD, Blood Flow and Hypercapnic Challenge Reveals Cerebrovascular Decoupling in Multiple Sclerosis

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Target audience: This information will be of interest to researchers using fMRI to study multiple sclerosis.
Purpose: It is known that multiple sclerosis results in decreased cerebral metabolic rate of oxygen and blood flow(1, 2). Both of these are critical elements in cerebrovascular reactivity (CR) to neuronal activation. Using simultaneous BOLD/ASL, we measured BOLD activation during a visual task and cerebrovascular reactivity using a hypercapnia challenge in a cohort of multiple sclerosis (MS) patients and matched control subjects. We show that the cerebrovascular coupling is significantly different in MS.
Methods: Nine paired MS patients and gender-/age-matched healthy controls (HC) were recruited for the study. After excluding one paired subjects due to the poor performance, 8 paired age-/gender- matched MS and HC were employed in the analysis (2 males, MS: 53±3 years, HC: , 54±4 years). Calibrated fMRI data was collected using visual/motor task and hypercapnia condition. MR images were acquired using dual-echo ASL sequence, which provides perfusion weighted signal form the first echo and BOLD weighted signal form the second echo (3). In 7:30 of scan time, 4 cycles of 32 sec ON/OFF flashing checkboard block design paradigm of visual stimulus were delivered (n = 16), and 4 cycles of 32 sec ON/OFF unilateral complex finger tapping were performed (n = 8). Hypercapnia condition was delivered using non-rebreathing mask (Hans Rudolph, St. Louis, MO) and 100 L non-diffusible Douglas bag, which contained 5% CO2. Hypercapnia fMRI study was conducted with 2 mins of normal air breathing followed by 3 mins of 5% CO2 mixed air inhalation and 3 and half mins of normal air breathing.
Data Analysis
BOLD-ASL:Briefly, the first 4 volumes from each ASL and BOLD time series are discarded. Perfusion-weighted images are constructed by performing a running subtraction of consecutive control and tagged images using the first acquired echo in each volume. BOLD-weighted images are constructed by performing a running average of the BOLD-weighted second echo. The data were retrospectively motion corrected. BOLD data were analyzed for activation by least-squares fitting the time series for each pixel to a boxcar reference function plus a slope. Following the methods of Leontiev et al.(4), we selected the voxels from these maps that exceed a Student's t of 3.45 ($p<0.01$, one-sided) for ASL and 4.0 ($p < 0.0001$, one-sided) for BOLD. These voxels were used to calculate %CBF and %BOLD from the activation study. The hypercapnia study is used to calculate M, using the fact that %BOLD=0 during that scan, but otherwise Eq. 1 holds. $CMRO_2$ can be calculated using the value of M, and %CBF and %BOLD from the visual stimulation study.

$$\frac{\Delta BOLD}{BOLD} = M\left(1-\left(\frac{CMRO_2'}{CMRO_2}\right)^{\alpha-\beta}\cdot\left(\frac{CBF'}{CBF}\right)^{\beta}\right) \qquad \text{Eq1}$$

Results: From the defined activated voxels, average ASL and BOLD signal changes were calculated in visual and hypercapnia tasks. M, Δ CMRO2, and N coupling ratio (ΔCBF:ΔCMRO2) were calculated. We found there was no significant difference of baseline cerebral blood flow between MS and HC groups in either whole gray matter mask (MS: 53.8 ± 17.2 vs HC: 54.1 ±32.2 ml/100g/min), BOLD (MS: 70.0 ± 30.0 ml/100g/min vs HC: 73.8 ± 34.3 ml/100g/min) or ASL activated ROI (MS: 70.4 ± 25.3ml/100g/min vs HC: 75.9 ± 39.8 ml/100/min)
We have not observed significantly different ASL or BOLD activated volume in the visual study. The BOLD activation volume in response to visual stimuli was with 69 ± 38 cm^3 and 69 ± 26 cm^3 MS and HC, showing no significant difference. **This is contrary to prior findings that MS patients showing that MS patients have larger BOLD activation volume than controls.**
BOLD-ASL Results: It has been reported in several studies of the hypercapnic BOLD response, that the BOLD response to activation is highly correlated to the BOLD response to hypercapnia(5, 6). In HC, the correlation is highly significant ($r=0.8$, $p<0.02$, see Figure 1). In our MS population, however, we observed no significant correlation ($r=0.15$, $p<0.7$). In addition, the blood flow response to activation has been widely reported to be correlated to that from hypercapnic challenge(5, 6). In our control population, the correlation is trending significant ($r=0.5$, $p<0.1$). However, in our MS population, the correlation is not ($r=-0.2$).

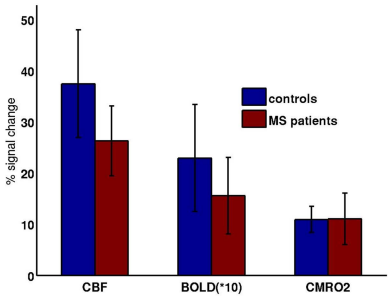

Fig 1: Observed changes in CBF, BOLD and CMRO2 during a visual task in MS patients and controls

We measured the blood flow response to activation to be significantly higher in control subjects than MS patients (paired t-test, $p<0.04$). In addition, the BOLD response to activation trended higher (paired t-test, $p<0.1$) in controls than patients. There was no difference observed in CMRO2 between MS patients and controls (Figure 1).

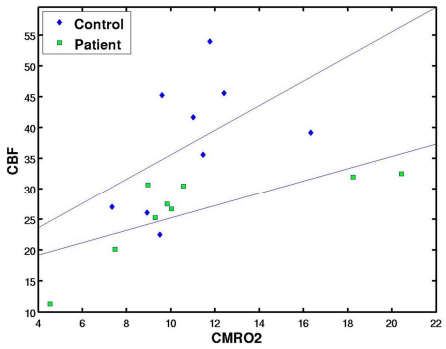

Fig. 2

An important hemodynamic parameter in understanding BOLD functional neuroimaging, is the cerebrovascular coupling ratio, the ratio of change in blood flow to change in CMRO2 in response to neuronal activation. In our preliminary data, we measure a significant difference in the ratio between MS patients and controls ($p<0.004$) (see Fig 2).
Discussion: These results have important consequences for interpreting the widely reported differences in BOLD activation between MS patients and healthy controls subjects. It seems unlikely that the CMRO2 demands of an MS patient is different for a given amount of neuronal activation. Thus, we observe a lower BOLD signal in a visual task in MS for what appears to be the same amount of neuronal activation. Without directly measuring the underlying neuronal activation, it is difficult to conclude exactly what the differences are in cerebrovascular coupling.
Conclusion: We present evidence that supports the notion that cerebrovascular coupling relating BOLD signal change and neuronal activation is altered in MS compared to age and gender-matched controls. This has important consequences for any fMRI study of MS as a population.
Acknowledgements:
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