Caffeine induced uncoupling of cerebral blood flow and metabolism: a calibrated-BOLD study

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Introduction

The calibrated-BOLD technique, in which cerebral blood flow (CBF) and BOLD responses to mild hypercapnia in addition to neural activation are measured, can be used to calculate changes in the cerebral metabolic rate of oxygen (CMRO2) and the flow/metabolism coupling *n* (the ratio of the fractional CBF change to the fractional $CMRO_2$ change). The flow/metabolism coupling in visual cortex in response to visual stimuli has been previously reported, and typically *n*~2-3 [1,2]. Caffeine has been shown to significantly decrease cerebral blood flow (CBF) [3,4], and animal studies [5] have shown increases in glucose metabolism, suggesting a significant *uncoupling* of CBF and energy metabolism, in contrast to the observed coupled responses to visual stimulation. However, measurements of changes in the cerebral metabolic rate of oxygen (CMRO2) associated with caffeine ingestion have not been reported. In this study we used a calibrated-BOLD approach to measure the CBF and BOLD responses from a defined baseline state to three conditions: mild hypercapnia, caffeine consumption and visual stimulation. The CBF and BOLD responses were compared between the three conditions, and by application of the Davis model [2], CMRO2 changes due to ingestion of caffeine were calculated and compared to those due to visual stimulation.

Methods

Data were acquired on four healthy adults, (2 male; ages 27 to 41 years), on a GE Signa Excite 3 Tesla whole body system. All subjects had a moderate daily caffeine intake (>150 to <300 mg) and abstained from caffeine consumption for at least 12 hours prior to the scan. Each imaging protocol consisted of two sessions, between which the subject ingested an over-the-counter tablet containing 200mg caffeine and remained outside the scanner for 30 mins to allow the caffeine to take effect before the post-dose session [3]. During both the pre and post-dose sessions, a dual echo arterial spin labeling (ASL) PICORE QUIPSS II sequence [6] with spiral readout was used to acquire data during one baseline and two visual stimulus runs. The subjects fixated on a stationary point during the baseline scan (8 min), and during the visual stimulus scans, viewed a flickering checkerboard at 8Hz (4 cycles of 20 s 'on' alternating with 60s 'off'). In addition, during the pre-dose session only, two hypercapnia scans were acquired (2 min room air-3 min 5% CO_2-2 min room air). Full ASL sequence parameters were: six contiguous 5mm slices through the calcarine sulcus, TR=2.5s, TI1/TI2=600/1500ms, TE1=2.9ms, TE2=24 ms, flip angle 90, FOV 240mm, 64x64 matrix. A high resolution structural image was also acquired in each session. Perfusion and BOLD time series were obtained from the running difference and average of tag and control images, respectively. Physiological noise was removed from the perfusion data using an extension of RETROICOR for perfusion-based fMRI [7,8]. The pre and post-dose data were aligned in AFNI, using the high-resolution structural data to determine the rotation matrices required. For each subject, a visual cortex region of interest (ROI) was defined by choosing voxels that were active (R>0.3 on the perfusion timeseries) on both the pre and post-dose visual stimulus runs, with at least 2 active neighbors. The changes in CBF and BOLD due to caffeine administration were calculated using the pre and post-dose baseline scans; CBF was quantified using CSF as a signal intensity reference [9], and R2* values were calculated and converted to BOLD signals. The CBF and BOLD changes in response to visual stimulation were measured from the pre-dose functional scans. The BOLD scaling factor (M) was calculated using the BOLD and CBF responses to hypercapnia, assuming no CMRO2 changes. The Davis model [2] was then used to calculate the CMRO2 changes associated with caffeine consumption and visual stimulation. All measures were averaged over the functional ROI.

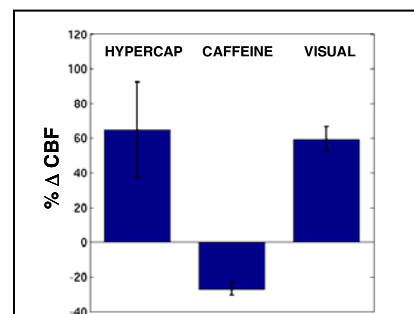

Fig 1a. Measured CBF responses to hypercapnia, caffeine and visual stimulus. Error bars show +/- 1SE.

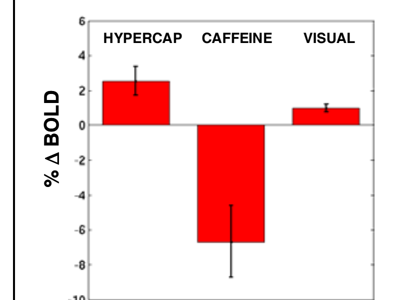

Fig 1b. Measured BOLD responses

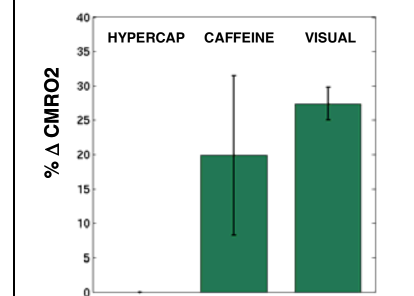

Fig 1c. Calculated CMRO2 responses, assuming hypercapnia induces no CMRO2 change.

Results

The calculated M ranged from 5-8%, and is similar to previously reported values [2,10,11]. Figure 1 shows the measured CBF (a), BOLD (b) and calculated CMRO2 (c) responses to hypercapnia, caffeine and visual stimulation. The CMRO2 response to hypercapnia is necessarily zero (Davis model). As expected, the visual stimulation led to CBF and BOLD increases, and a CMRO2 increase. However, the predicted decrease in CBF due to caffeine was accompanied by a substantial decrease in the BOLD signal, also resulting in a mean CMRO2 *increase* of 20%.

Discussion

The current study suggests that decreases in CBF induced by caffeine consumption are accompanied by an increase in CMRO2. This represents a significant uncoupling of flow and metabolism, and must be accompanied by a large increase in the oxygen extraction fraction. The study described demonstrates the feasibility of using a calibrated-BOLD approach for comparing longitudinal within-subject data, and may be utilized in other studies of medication affects.

References

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