

Caffeine Tightens the Coupling Between Resting-State Blood Flow and Metabolic Fluctuations

A. L. Rack-Gomer¹, and T. T. Liu¹

¹Bioengineering and Center for Functional MRI, UC San Diego, La Jolla, CA, United States

INTRODUCTION

Caffeine has been found to decrease the amplitude and correlation of resting-state blood oxygenation level dependent (BOLD) fluctuations [1], and hence is an important factor to consider in functional connectivity studies. This widely used stimulant affects both neural activity and cerebral blood flow (CBF) through adenosine antagonism [2]. However, because the BOLD signal is sensitive to neural and vascular factors, the physiological mechanisms by which caffeine alters spontaneous BOLD fluctuations remain unclear. In this study, we analyzed simultaneous measures of BOLD and CBF resting-state fluctuations to determine if caffeine-induced changes in CBF fluctuations can explain the reduction found in BOLD fluctuations in the motor cortex.

METHODS

Following a 12-hour period of caffeine abstinence, 9 healthy subjects were scanned on a GE Signa 3T system. The imaging procedure consisted of a pre-dose session and a post-dose session, in between which subjects were removed from the scanner and given a tablet containing 200 mg of caffeine. Both scan sessions included a bilateral finger-tapping block design paradigm and a 5-minute resting-state scan with visual fixation. Functional data were collected over 6 oblique slices through the primary motor cortex with resolution = 3.75×3.75×6mm. A PICORE QUIPSS II arterial spin labeling (ASL) sequence was used with dual echo spiral readout (TR = 2s, T11/T12 = 600/1500ms, TE1/TE2 = 9.2/30ms, $\theta = 90^\circ$).

Data from the post-dose session was aligned to that of the pre-dose session using AFNI. Activation maps were generated from the finger-tapping data, and a region of interest was defined for the motor cortex using the intersection of the BOLD and CBF activation maps (pre-dose and post-dose). Nuisance terms were regressed from the resting data, including: linear trends, 6 motion terms, physiological noise terms calculated using cardiac and respiratory data collected during image acquisition, and the mean signal extracted from the anterior portion of the brain. Resting time courses were low pass filtered with a cutoff frequency of 0.08 Hz. Percent signal changes were calculated as the standard deviation of the resting BOLD and CBF time courses, normalized by their means. Average values of % Δ BOLD and % Δ CBF were extracted from each subject's motor cortex and the ratio of % Δ BOLD to % Δ CBF was calculated. Differences between the pre-dose and post-dose sessions were assessed using paired t-tests.

RESULTS AND DISCUSSION

In contrast to % Δ BOLD, which was found to decrease with caffeine [1], we found that caffeine significantly ($p = 0.004$) increased % Δ CBF across subjects (Fig 1a). These disparate changes indicate that the relationship between BOLD and CBF fluctuations is altered by caffeine, which can be seen as the significant ($p = 9.4\text{e-}5$) decrease in the % Δ BOLD to % Δ CBF ratio (Fig 1b). BOLD signal dependence on CBF can be approximated using a mathematical model proposed by Davis et al. (1998) [3]:

$$\% \Delta \text{BOLD} = M \left[1 - \left(\frac{\% \Delta \text{CMRO}_2}{100} + 1 \right)^\beta \left(\frac{\% \Delta \text{CBF}}{100} + 1 \right)^{\alpha - \beta} \right],$$

where CMRO₂ represents oxygen metabolism, M is the maximal BOLD response, and the exponents α and β were taken to be 0.38 and 1.5, respectively [3]. Caffeine-induced decreases in % Δ BOLD fluctuations cannot be explained by the increase in % Δ CBF fluctuations, as the model predicts that an increase in % Δ CBF will lead to an increase in % Δ BOLD. In addition, it is unlikely that the factor M , which reflects baseline physiology and scan parameters caused the reduction in BOLD signal fluctuations as recent work has shown that caffeine increases M in the motor cortex [3]. Instead, a change in flow-metabolism coupling ($n = \% \Delta \text{CBF} / \% \Delta \text{CMRO}_2$) may be responsible for the diminished BOLD fluctuations. We used the % Δ BOLD and % Δ CBF values and previously determined estimates of M (pre-dose = 3.7%, post-dose = 4.5%) [4] to calculate n for each subject. We found that n was significantly ($p = 0.0011$) decreased by caffeine (Fig 1c). The decrease in n remained significant even if $M = 3.7\%$ was used for both the pre-dose and post-dose sessions.

CONCLUSION

We have shown that caffeine tightens flow-metabolism coupling in the motor cortex during the resting state. This result is similar to the recent finding that caffeine decreases the flow-metabolism coupling ratio n for a finger-tapping task [4]. Tighter flow-metabolism coupling can explain the decreased amplitude of spontaneous BOLD fluctuations. Reduced resting-state BOLD connectivity may reflect the change in coupling, which would tend to reduce the signal to noise ratio of the BOLD signal. It is interesting to note that the smaller n and larger % Δ CBF values found in this study imply that fluctuations in oxygen metabolism have increased, possibly indicating that resting-state neural fluctuations are also increased by caffeine. Future experiments with simultaneous electroencephalography (EEG) and fMRI would be helpful in elucidating the relationship between caffeine-induced changes in resting BOLD measures and the underlying coherence of intrinsic neural activity.

REFERENCES

[1] Rack-Gomer et al., NIMG 46:56-63, 2009. [2] Fredholm et al., Pharm Rev 51:83-133, 1999. [3] Davis et al., PNAS 95:1834-39, 1998. [4] Chen et al., NIMG 44:647-52, 2009.

