

# Caffeine reduces resting-state BOLD functional connectivity

W-C. Wu<sup>1</sup>

<sup>1</sup>Graduate Institute of Oncology, National Taiwan University, Taipei, Taiwan

## Introduction

Temporal correlation of BOLD signal has been observed between remote cerebral areas even in the absence of task performing (1). Such correlation is commonly believed to be neuronal and reflect the functional connectivity or default mode of the brain. Known as a vessel contractor, caffeine has been found effective in modulating the hemodynamic response in task-based BOLD fMRI (2). A recent study showed that caffeine significantly reduced resting-state BOLD connectivity in the motor cortex (3), although the underlying mechanism and whether the effect is global remain unanswered. In the present study, we further investigated the effect of caffeine on resting-state BOLD connectivity by performing measurements at different anatomic areas (primary motor cortex, primary visual cortex, and thalamus) in combination with multiple TE's. The results were also correlated with local perfusion.

## Materials and Methods

The Institutional Review Board approved this study. Five healthy volunteers (age = 23-30 yrs) were scanned and all gave informed written consent. MR imaging was conducted on a 3T whole-body system (Tim Trio, Siemens, Erlangen, Germany) using the body coil for transmission and a 32-channel phased-array head coil for reception. The subject underwent two imaging sessions (pre- and post-dose), each of which included a 3D high-resolution T1-weighted MPRAGE, a BOLD-fMRI (TR/TE = 2s/30ms, matrix = 64x64, voxel size = 3.75x3.75x5 mm<sup>3</sup>), three runs of resting-state BOLD imaging (TE = 20, 30, and 40 ms, respectively), a 2D phase-contrast imaging, and a pseudocontinuous arterial spin-labeling imaging (pCASL (4,5)) (TR/TE/tagging duration/post-labeling delay = 4s/18ms/1s/1.2s, 40 pairs of tag and control acquisitions). A single-shot gradient-echo echo-planar (EPI) readout was used for both BOLD and ASL scans. Physiological signals were prospectively recorded using the system's built-in pulse oximeter and respiratory belt. After the pre-dose session, the subject was removed from the magnet to ingest a 200mg caffeine pill, and rested outside for about 30min before re-entering the scanner. A whole-field black-white flashing checkerboard was used for visual stimulation (5 cycles of 20s ON and 40s OFF, preceded by a 40s OFF). The subject was also instructed via the intercom to perform self-paced finger tapping (all right-handed; five 20s ON epochs with semi-random overlaps with the visual stimulation). Complex data were reconstructed into magnitude images and then exported to a workstation for off-line processing. After realignment, BOLD series were corrected for physiological noise using the RETROICOR algorithm (6). For ASL series, the tag and control images were processed separately. Surround subtraction and signal calibration were applied to the corrected images to generate quantitative flow maps. The activated area detected from the fMRI scan ( $p_{FWE} < 0.05$  and cluster size  $\geq 10$ ) served as the seed for connectivity calculation on the resting-state images. The region of right thalamus was manually defined on the high-resolution anatomic image coregistered to the EPI images. Correlation coefficient was computed on a voxel-wise basis. Off-line analysis was performed using homemade MATLAB (<http://www.mathworks.com>) program and SPM2 (<http://www.fil.ion.ucl.ac.uk/spm/>).

## Results

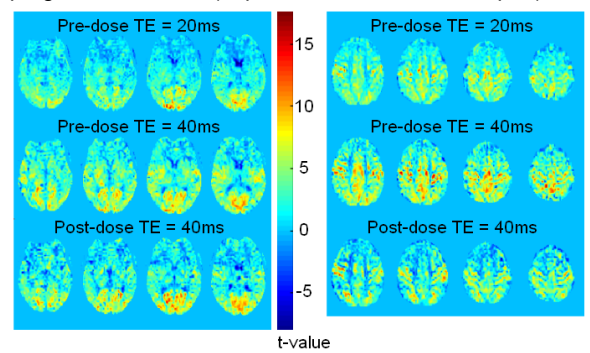
The caffeine dose used in this study did not cause significant difference in the pulse and respiratory periods, and the flow velocity in the carotid arteries. Figs 1 and 2 show the connectivity maps obtained from a representative subject (for  $p_{corrected} < 0.01$ ,  $t > 7$ ). For the seed regions investigated, the connectivity is more significant when data was collected with a longer TE, and noticeably drops after caffeine intake. For TE = 40ms, the voxels connected in the pre-dose map ( $t > 7$ , cluster size  $\geq 10$ ) were then sorted according to the post-dose t-value decrease. The 200 voxels where t-value drops the most were divided into 10 bins and compared to their resting-state perfusion as measured by pCASL. As shown in Fig 3, the t-value drop is larger in the region where caffeine causes more flow decrease.

## Conclusion

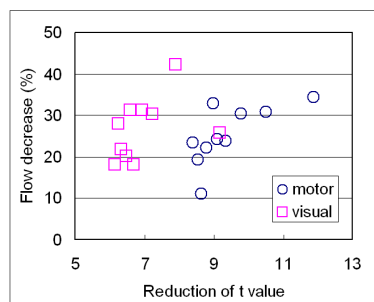
Both TE and resting-state perfusion affect the measurement of BOLD connectivity. We have demonstrated in multiple functional regions that caffeine reduces BOLD connectivity. The degree of reduction is associated with flow decrease, which suggests the role of vascular regulation in the functional connectivity measured by BOLD.

## References

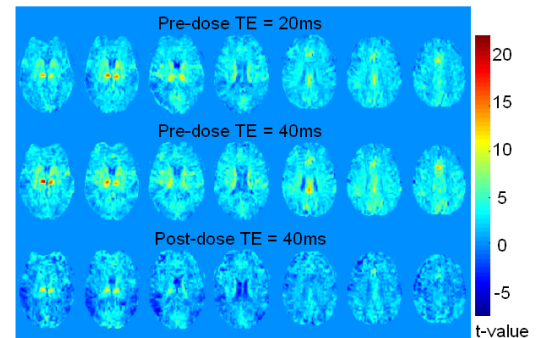
1. Biswal B, et al, MRM 1995;34:537.
2. Gack-Gomer AL, et al, Neuroimage 2009; 46:56.
3. Liu TT, et al, Neuroimage 2004;23:1402.
4. Garcia DM, et al, ISMRM 2005, #37.
5. Wu WC, et al, MRM 2007;58:1020.
6. Glover GH, et al, MRM 2000;44:162.



**Fig 1.** Connectivity maps. The functional seed was placed at the primary visual cortex (left panel) and the primary motor cortex (right panel), respectively.



**Fig 3.** Scatter plot of the t-value drop and flow decrease. A mild positive correlation is revealed.



**Fig 2.** Connectivity maps before (top and middle rows) and after (bottom row) caffeine intake. The functional seed was placed at the right thalamus.