Caffeine alters connectivity measured by BOLD: A resting-state fMRI study

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Introduction: Caffeine is a popular stimulant that is present in a number of beverages and foods consumed everyday. Caffeine is an antagonist for adenosine which causes global vasoconstriction and increased vascular tone in the cerebrovasculature. The effect is decreased resting blood flow with reduced physiologic noise when monitoring the BOLD signal. Caffeine also has the effect of being a neurostimulant which increases neuronal activity and alertness. Previous work had demonstrated an effect of caffeine on the connectivity between motor cortices only [1]. In this study, we investigated the effect of an optimized caffeine dose [2] on the resting state connectivity in the whole human brain.

Methods: Three healthy, normal, right-handed subjects were scanned on a 3T scanner (Siemens TIM Trio B15 software, Erlangen, Germany) using the 32 channel head coil to maximize the signal to noise. The subjects were instructed to abstain from caffeine 12-24 hours prior to the study which took place in the morning to facilitate compliance. The protocol collected resting state BOLD data (EPI sequence with TR/TE=2500ms/20ms, 128 matrix, 220 FOV, forty 3mm slices using GRAPPA) for 10 minutes followed by a PASL acquisition (Picore Q2TIPS with TR=2500ms, TE=11ms, TI1/TI1s/TI2=700/1600/1800ms, 4mm inplane resolution, nine 5mm thick slices with a 1mm gap, 70 control and tag volumes collected) to measure the resting blood flow level. A 10 minute injection of caffeine (dose of 2.5mg/kg) was given to each subject during the acquisition of the T1 anatomic volume (MPRAGE with TR/TI/TE=2300/900/2.9, 9 degree flip angle, 1mm isotropic resoltuion). Another PASL acquisition was run to measure the change in the resting blood flow and the final resting state BOLD sequence was run. During the acquisition heart rate, skin conductance, end tidal CO2, and respiratory rate were monitored and physiologic data were collected to use in the data analysis.

Data analysis: Using SPM5, functional images were realigned to the first image of each session, slice timing corrected, and normalized to the MNI template and spatially smoothed with an 8-mm Gaussian kernel. Resting-State fMRI Data Analysis Toolkit (REST, by SONG Xiaowei et al., http://resting-fmri.sourceforge.net) was then used to remove the linear trend of time series and temporally band-pass filtering (0.01-0.08 Hz). Before the correlation analysis, several sources of spurious variance were then removed from the data through linear regression: (i) six parameters obtained by rigid body correction of head motion, (ii) the whole-brain signal averaged over a fixed region in atlas space,(iii) signal from a ventricular region of interest, and (iv) signal from a region centered in the white matter. Seed time series were chosen as averaged time series within a sphere (radius=6mm) in left motor cortex and posterior Cingulate. Individual correlation coefficients were converted to z-scores by using Fisher's r-to-z transformation to improve the normality.

Results: There were no significant changes in heart rate, end tidal CO2, or respiratory rate after the injection of caffeine. All three subjects demonstrated a large decrease in resting blood flow (25-30%) following the injection of caffeine. When the left motor cortex was used as the seed region in the REST analysis, the correlations from left to the right motor cortex decreased (Fig. 1A: r=0.22 pre and r=0.10 post). Similar results were seen in the supplementary motor area. The overall amplitude of the low frequency fluctuations was also decreased after the injection of caffeine. This is evidence that the increased vascular tone has altered the compliance of the vessels which in turn has altered the resistance to the low frequency oscillations. The correlation analysis results in decreased connectivity globally.

When the seed region was placed in the posterior cingulate cortex (a key node in the default mode network, DFN), a much larger decrease in the connectivity was also demonstrated (Fig 1B: r=0.4 pre and r=0.12 post).

Discussion: Changes in the DFN are a result of an altered level of alertness and physiologic changes to the injection of caffeine. As alertness increases the DFN disengages. The connectivity is further decreased due to the presence of caffeine as demonstrated in other networks. This study demonstrates that caffeine can decrease apparent connectivity in the normal resting brain indicating that the BOLD resting state signal contains a mixture of neural and physiologic signals. Caution needs to be used when interpreting the connectivity results given the nature of the BOLD signal. The differences seen between groups can be a result of alterations of vascular tone or physiologic noise.

References: **1**. Rack-Gomer AL, Liau J, Liu TT. Caffeine reduces resting-state BOLD functional connectivity in the motor cortex. Neuroimage 46(1):56-63, 2009. **2**. Chen Y, Parrish TB. Caffeine dose effect on activation-induced BOLD and CBF responses. Neuroimage 46(3):577-83, 2009.

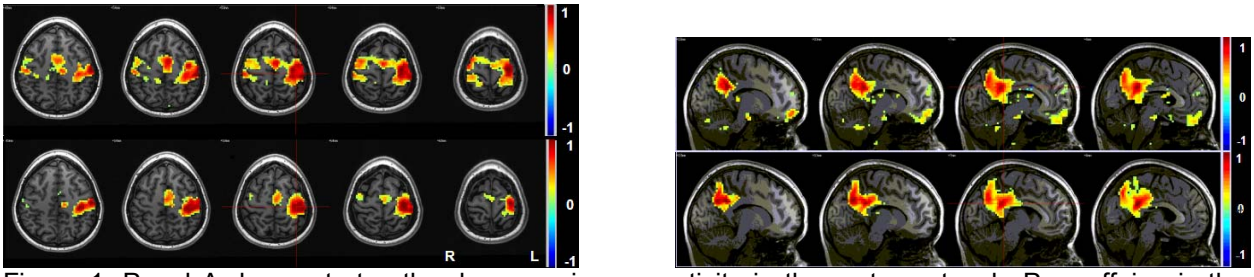

Figure 1: Panel A demonstrates the decrease in connectivity in the motor network. Pre-caffeine is the row on top and post-caffeine at the same threshold is the bottom row. Note the decrease across hemispheres and the SAM. Panel B shows the DFN and the dramatic decrease in connectivity between the Posterior cingulate the medial frontal lobe, top row=pre-caffeine, bottom=post-caffeine, same threshold).