Caffeine causes widespread decreases in resting-state BOLD connectivity and energy

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INTRODUCTION

In the absence of an explicit task, temporal synchrony is maintained across brain regions. Taking advantage of this synchrony, resting-state fMRI has been used to study resting-state brain connectivity in both health and disease [1]. Changes in resting-state BOLD connectivity measures are typically interpreted as changes in coherent neural activity across spatially distinct brain regions. However, this interpretation can be complicated by the complex dependence of the BOLD signal on both neural and vascular factors. Previous studies have shown that caffeine (a potent vasoconstrictor) reduces resting state BOLD connectivity in the motor cortex [2], the Default Mode Network (DMN) [3], and the thalamus [4]. In this study, we show that the caffeine-induced reductions in BOLD connectivity and energy are widespread, spanning multiple brain regions.

METHOD

Following a minimum of 30 days of caffeine abstinence, nine healthy subjects with low caffeine intake (4 males and 5 females) were scanned using a 3 Tesla GE MR750 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 an over the counter tablet containing 200mg of caffeine. The functional scan in the post-dose session began 40 mins. after the caffeine intake. A 5-min resting state scan (eyes open with fixation) was conducted in each session. The BOLD data were acquired with the following parameters: echo planar imaging with 166 volumes, 30 slices, 3.438x3.438x5mm^3 voxel size, 64x64 matrix size, TR=1.8s, TE=30ms. Nuisance regressors (0^{th}+1^{st}+2^{nd} order Legendre, 6 motion time courses, BOLD signal from the cerebral spinal fluid and white matter) were removed from the raw data through linear regression, and the data were then low-pass filtered (0.08Hz). For each session, high resolution anatomical data were acquired using a magnetization prepared 3D fast spoiled gradient (FSPGR) sequence. Each anatomical volume was first registered with the functional data. The registered anatomical volume was then warped to Talairach space. ROIs from the Brodmann atlas were then identified and warped back to the functional data space using an inverse affine transformation [5]. An average BOLD signal was computed for each ROI and used to calculate the average energy for each ROI and pairwise correlations between all pairs of ROIs. The correlation maps were thresholded at different levels (0.1 to 0.9 in steps of 0.05) to generate network connectivity matrices. At each threshold level, we computed the mean network degree (or density) of the network, defined as the average number of links between ROIs [6]. The pre-dose and post-dose mean degree measures were then compared with a paired t-test.

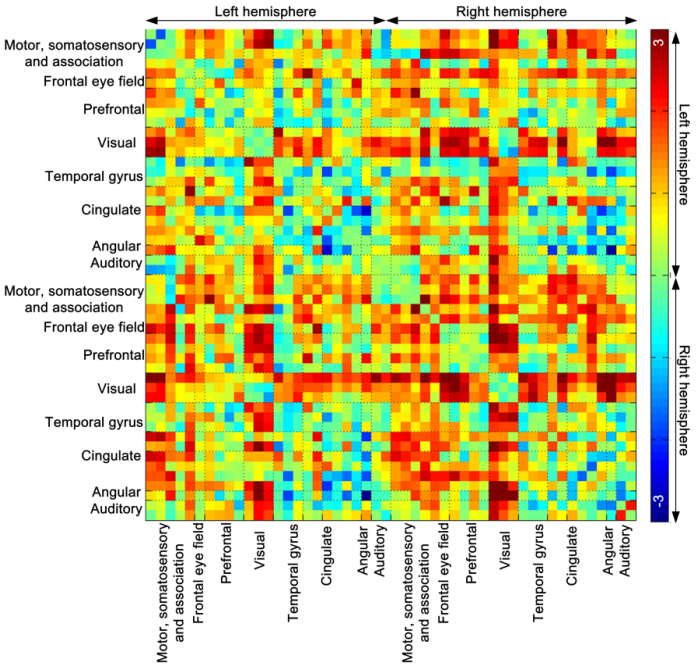

Fig. 1 Map of t-values from paired test showing wide-spread reduction of BOLD connectivity between various Brodmann areas after caffeine intake

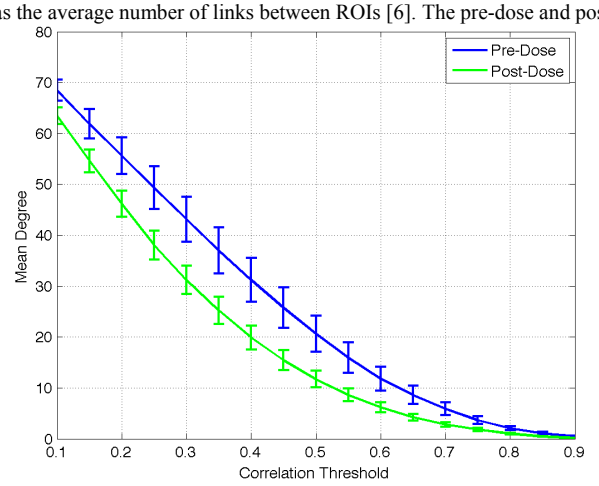

Fig. 2 Mean network degree measures for pre-dose and post-dose conditions

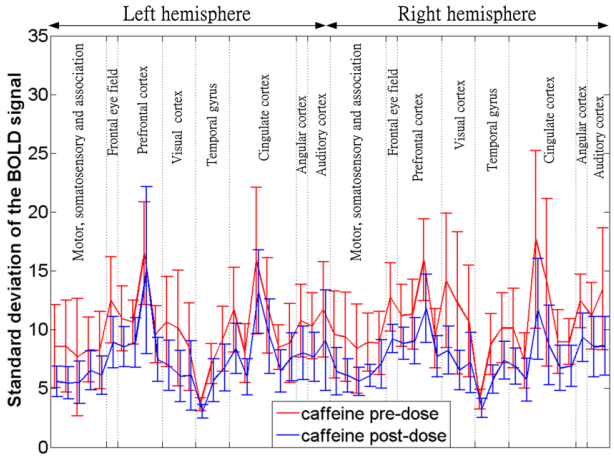

Fig. 3 Reduction of average energy below 0.08Hz after caffeine intake

RESULTS AND DISCUSSION

Fig. 1 displays a map of t-values (paired test) summarizing the comparison of pre-dose and post-dose correlation values, with a positive t-value (in red) corresponding to a decrease in BOLD connectivity after caffeine intake. Decreases in connectivity are widely distributed across the ROIs. As a quantitative assessment of the decrease in connectivity, Fig. 2 shows the mean network degree measures (group mean +/- standard error) for the pre-dose (blue) and post-dose (green) conditions versus the correlation threshold. For thresholds above 0.15, the caffeine-related decrease in mean network degree is significant at $p<0.05$; below 0.15, the decrease is significant at $p<0.07$. Fig. 3 shows that the caffeine-induced reduction in average energy below 0.08Hz occurs in multiple regions, with significant decreases in primary somatosensory and motor cortex, the frontal eye field, part of the prefrontal cortex, the primary visual cortex, the inferior and superior temporal gyrus, the posterior and anterior cingulate cortex, angular cortex and the primary auditory cortex ($p<0.05$). In summary, our results demonstrate a global effect of caffeine on BOLD connectivity and energy.

[1] Fox et. al., PNAS 2005, 102: 9673-9678. **[2]** Rack-Gomer et al., Neuroimage 2009, 46:56-63. **[3]** Wang et. al., ISMRM 2010, 3426. **[4]** Wu et. al., ISMRM 2010, 3430. **[5]** Lancaster et. al., HBM 2000, 10:120-131. **[6]** Rubinov and Sporns, Neuroimage 2010, 52:1059-1069.