Differentiating neural and vascular effects of caffeine in resting state connectivity study

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Introduction:

It is well known that caffeine constricts the vascular system and decreases CBF by antagonizing adenosine A2 receptors [1] and stimulates the neural system through antagonism of adenosine A1 receptors [2]. According to the neurovascular coupling model for BOLD fMRI, these two mechanisms of caffeine can have opposite effects and can cancel each other out in terms of BOLD response. On one hand, the reduction in baseline CBF and increased CMRO2 can increase BOLD response, while on the other the enhanced coupling between CBF and CMRO2 tends to reduce BOLD sensitivity. At the field strength of 3T, the BOLD signal contributions from intravascular (IV) and extravascular (EV) components are roughly equal, and if the IV blood signal can be largely removed, then the contribution from blood flow and blood volume to the BOLD signal can be reduced or even removed. This creates a similar scenario of caffeine's CBF reduction, but not its neural stimulation effects. By comparing the results between caffeine and blood signal nulling, it is possible to provide further understanding to caffeine's effect on BOLD fMRI signals. In this study, we use two approaches to modify the intravascular signal component, i.e. using caffeine to modify the CBF baseline and remove blood signal via flow dephasing [3], in order to unravel caffeine's vascular and neural stimulating effects to resting state BOLD analysis.

Methods:

Five healthy volunteers (3 males, age 26±6 years) participated in the study with written consents. The total scan was divided into pre- and post-caffeine intake sections, and each section comprised the same scans: GE-EPI with and without flow dephasing for resting state data (TR/TE = 2000/30 ms, FA = 80°, voxel size = 2.3×2.3×3.5 mm^3), pASL for rCBF and SWI for blood oxygen saturation levels. In order to reduce the IV blood signals in major draining veins, we inserted a pair of bipolar gradients into the GE-EPI sequence, between the excitation RF pulse and the readout. With total duration of 10ms and amplitude of 24mT/m, the VENC value is 0.98cm/s, which can effectively dephase the blood signal in most of the draining veins [3]. After the pre-caffeine section (~30 min), the subject came out and ingest one 200mg caffeine pill (NoDoz), and waited outside the scanner about 30 min for the caffeine to take effect, and then underwent the post-caffeine section scan.

For preprocessing, all RS EPI data were normalized to the MNI template. After regressing out the motion, low passed filtering with a 0.01~0.08Hz filter and spatially smoothing with a 6mm kernel, the maps fractional amplitude of low frequency fluctuation (fALFF) and coherence regional homogeneity (cReHo) [2] were calculated. Cardiac pulsatility signal was recorded using an oxymeter clipped to the left index finger, and was removed from the data using linear regression. Seeding ROIs were selected from the AAL template to determine the functional connectivity of various networks, and correlation coefficient (cc) matrices were calculated for all 90 AAL ROIs of the brain. All data were collected on a Siemens Verio 3T system with 32-channel head coil, and processed using REST and SPM8 algorithms.

Results:

Figure 1 shows the results of a representative subject, including rCBF obtained with pASL, fALFF and cReHo maps. The V1 ('4,-81,8' in MNI coordinate) and DMN ('4,-53,26') networks are selected for display considering the fact that the seeding regions (i.e. V1 and precuneus) are rich in vasculature and thus blood flow, as shown in rCBF maps. All shown images are of the same slice position, and have the same display window settings within each group. The resting state data results correspond to four conditions, i.e. pre-/post-caffeine × with/without blood signal. The results from other volunteers are of similar pattern. The subject averaged cc matrices of 90 ROIs extracted from the MNI AAL template are shown for all conditions in Fig.2.

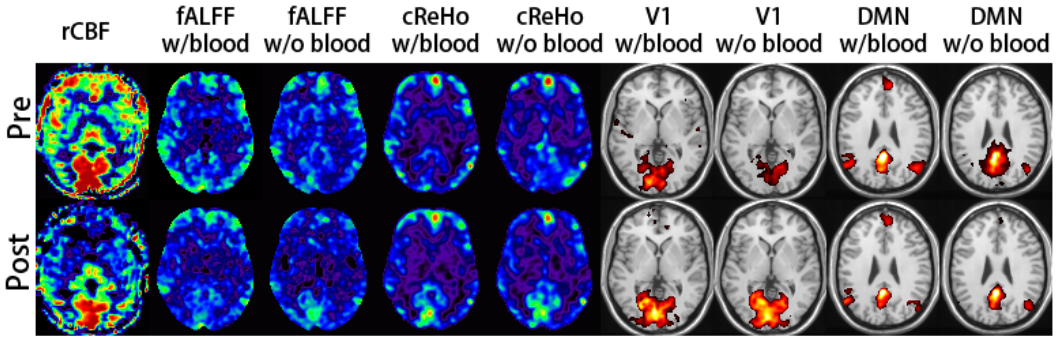

Figure 1. rCBF, fALFF, cReHo maps and V1/DMN networks of one representative subject, as well as the cc matrices between 90 AAL regions of the same subject.

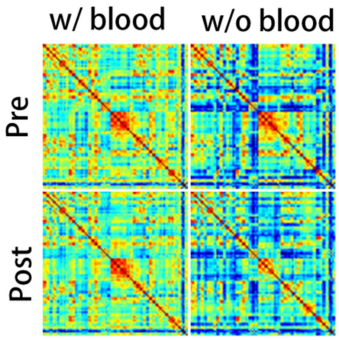

Figure 2. Averaged correlation matrices across all subjects.

Discussion:

As expected, cerebral perfusion is significantly reduced after caffeine intake, as evidenced by the significant drops in ASL rCBF maps, mostly in grey matters (GM) except the cuneus/precuneus regions which is rich in both macro and micro vasculatures. The post-caffeine fALFF also drops in certain GM regions, and the pattern of such drops is subject dependent; for other GM regions fALFF remains largely unchanged. On the other hand, post-caffeine increase in cReHo can be seen in cuneus/precuneus regions in most of the subjects. Comparing between fALFF and cReHo results with and without blood, one can see the trends of the above changes induced by caffeine are quite similar, and that they are very similar in both pre- and post-caffeine groups. This suggests that IV component of the resting state BOLD signal may not play a significant role in affecting the regional spectral characteristics of the signal time series, thus showing similar cReHo patterns. However, although IV signal components are being affected by both caffeine and flow dephasing, their effects are different. In the cc matrices with blood signal, the post caffeine case shows slight decrease in certain regions, but generally retains high cc values for most connections. But in the cc matrices without blood signal, the post caffeine case instead shows a significant and global trend of decrease. If the perfusion reduction caused by caffeine intake had similar effects as that caused by flow dephasing, this suggest that the neural simulation effect of caffeine is indeed of opposite direction, so that the post caffeine, with blood case remains high cc values (Fig.2). The V1 and DMN networks, on the other hand, indicates that the flow dephasing may reduce long distance connectivity, but enhance local connectivity, possible caused of this may be due to the fact that physiological effects conveyed through vascular system can play a role in long distance connection.

In summary, caffeine indeed modifies the functional connectivity more via neuro-vascular coupling than via blood flow, and these two mechanisms may have opposite effects on connectivity outcomes. To better confirm this and understand the underlying mechanism of the caffeine's effect in affecting resting state signal characteristics and connectivity, a larger cohort of subjects including different age groups will be enrolled for better statistical evaluation. On the other hand, although caffeine's vascular constriction and neural stimulation effects are global, the results suggest such effects may be brain region specific. Therefore a finer ROI parcellating algorithm [4] will be adopted for a more accurate estimation of caffeine's effect in those brain regions that have been widely reported in resting state functional networks, such as precuneous, frontal/motor/temporal cortices; this can also help exclude regions that are being affected by physiological noise.

Reference:

[1] Fredholm *et al*, 1999; Pharmacol.Rev. [2] Dunwiddie *et al*, 2001; Annu.Rev.Neurosci. [3] Ye *et al*, 2013; JMRI. [4] Nelson et,al. 2010; Neuron.