Does caffeine ingestion alter brain metabolism?

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TARGET AUDIENCE: Researchers interested in using caffeine as a physiological challenge or investigating neural physiological effects of caffeine.

PURPOSE: Caffeine, as a common substance in beverage, effectively alters the alertness via inhibiting inhibitory neurons. There are also on-going studies of investigating therapeutic effect of caffeine on Alzheimer's and diabetes (1,2). However, the exact effect of caffeine on neural activity and metabolism in vivo has not been examined. The primary reason is that caffeine has a vasoconstriction effect on brain blood vessels, independent of its neural effect (3-5). As a result, conventional hemodynamic based method such as fMRI is not able to correctly depict the neuro-metabolic effect. Therefore, advanced methods that can separately evaluate vascular and metabolic parameters are needed. The scope of the present work is two-fold. In Study 1, we used a recently developed MRI technique to examine the effect of caffeine ingestion on whole-brain cerebral metabolic rate of oxygen ($CMRO_2$). We are cognizant that a lack of change in whole-brain $CMRO_2$ does not necessarily indicate the absence of regional metabolic changes (6). Therefore, in Study 2, we used the whole-brain finding as a benchmark and examined regional heterogeneities in CBF changes following caffeine ingestion. The rationale is that, if a particular brain region manifests a CBF decline faster than the whole-brain rate, it may indicate a neuro-metabolic effect in this region in addition to the vascular effect.

METHODS: *Study 1: whole-brain $CMRO_2$:* Ten healthy caffeine naïve (not a regular caffeine beverage consumer) adults (age 28±5yrd, 5F, 5M) were scanned after caffeine ingestion; another ten healthy adults (age 28±4yrd, 5F 5M) were scanned without caffeine ingestion as controls. Study was performed on a 3T Philips System. The caffeine group subject took 200mg caffeine tablet immediately before MRI scans, after he/she was positioned on the table. Following intake of caffeine tablet, the subject was quickly positioned inside the scanner and the physiological scans started promptly. A total of 40min MRI was performed, consisting of 9 continuous measurements of $CMRO_2$. Each CMRO2 measurement consisted of a venous blood oxygenation (Y_v) scan using TRUST MRI (7) and a CBF scan using phase-contrast (PC) MRI, from which $CMRO_2=C_h$xCBFxOEF, $OEF=Y_a - Y_v$. Arterial oxygenation, Y_a, was measured by a Pulse Oximetry. A blood draw was done immediately after MRI to measure hematocrit and caffeine content. A battery of running memory test provided by the Automated Neuropsychological Assessment Metrics (ANAM, Center for the Study of Human Operator Performance, University of Oklahoma) was performed on caffeine group outside MRI at 10min before and 1 hour after the caffeine ingestion. *Study 2: regional CBF:* 10 healthy caffeine naïve adults (27±3yrd, 6F, 4M) were scanned for 40min immediately after taking the 200mg caffeine tablet. Regional CBF was measured using pseudo-continuous ASL with background suppression and GRASE acquisition. The acquisition parameters were: acquired voxel size =4x4x5 mm^3, TR=3803ms, SENSE factor =1.5/1.1 (RL/AP), four shots, volume TR=15sec. ASL parameters were: label duration (τ)=1650ms, label delay=1525ms, and background suppression with TI=1701ms and 2750ms. This data set results in 40 dynamic CBF maps at 1min temporal resolution. *Statistics:* The time dependence of physiological parameters was examined by mixed linear model with subject as the random effect, time and group as the fixed effects. For the $CMRO_2$ study, two-group (caffeine and sham control) difference was determined by the p value of group effect in the mixed linear model. For regional CBF study, the map were normalized by grey matter mean at each time point for each subject; then mixed-effect linear fitting for normalized CBF with time was performed on all subject data at each voxel to assess the variance of grey matter CBF decay rate. The p values for the linear slope at each voxel were threshold by $p<0.005$ and cluster size of 100 voxels.

RESULTS and DISCUSSION: *Study 1*: The blood test showed that caffeine concentration is elevated to a level of 2.0±1.3mg/L at 1-hour after ingestion. Baseline (1st dynamic value) $CMRO_2$ was 164.0±23.5 μmol/min/100g (mean±STD) and 168.8±27.1 μmol/min/100g for caffeine and control respectively; CBF was 57.8±6.2 ml/min/100g and 55.9±8.1 ml/min/100g; Y_v was 62.8±5.3 % and 60.8±6.8 %. No difference was found in these baseline parameters between groups ($p>0.05$ for all). The time courses in Figure 1 shows that global CBF, Y_v and OEF were significantly changed by caffeine ingestion (Figure 1 black) while no change was present in control group (Figure 1 red) (mixed effect model for group difference, $p<0.0001$ for all). However, global $CMRO_2$ did not show any change with time (mixed model $p=0.38$). Although no $CMRO_2$ change was observed for the whole group, there were individual variations. An interesting observation is that individual changes in $CMRO_2$ seem to be correlated with changes in cognitive scores ($p=0.03$). That is, an individual exhibiting an increase in $CMRO_2$ tends to show an improvement in cognition, and vice versa. *Study 2*: Since whole-brain $CMRO_2$ did not show a change with caffeine ingestion, we reason that the amount of whole-brain CBF reduction observed is entirely attributed to vascular effect of caffeine. Thus, if a particular region shows a CBF reduction rate faster than whole-brain rate, it may indicate the presence of an additional effect of metabolic suppression. Voxel-wise analysis on normalized CBF suggests that several regions showed a decreased metabolic rate (Figure 3 red) due to caffeine ingestion, which were located primarily in the frontal lobe (red in Figure 3). A few other regions showed an increased metabolic rate (yellow in Figure 3), which were located in the parietal and occipital regions including posterior cingulate cortex.

In summary, the present study revealed that, despite a pronounced CBF reduction with caffeine ingestion, oxygen extraction fraction was increased reciprocally, resulting in an unaltered whole-brain $CMRO_2$. However, this does not rule out the possibility of regional changes in $CMRO_2$ that could have cancelled each other out in the whole-brain measure. Indeed, voxel-by-voxel analysis of CBF changes following caffeine ingestion suggest that there exist certain degrees of heterogeneity in CBF decline rate, which may suggest differential alteration of neural activity across the brain.

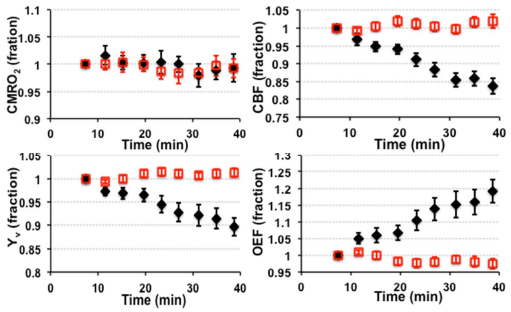

Figure 1 The time courses of cerebral metabolic rate of oxygen ($CMRO_2$), CBF, venous oxygenation (Y_v), and oxygen extraction fraction (OEF) for caffeine ingestion experiment (black) and sham control experiment (red). The error bar is standard error.

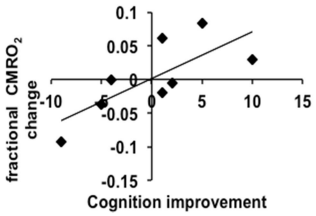

Figure 2 The scatter plot between memory score change and fractional $CMRO_2$ change.

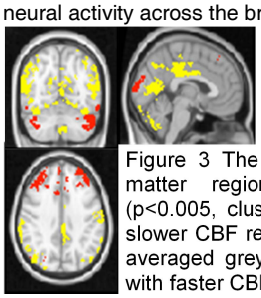

Figure 3 The color maps of grey matter regions with significant ($p<0.005$, cluster size=100 voxels) slower CBF reduction (yellow) than averaged grey matter and regions with faster CBF reduction (red).

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