# Caffeine alters the integration of relay and attention-associated areas in the functional connectivity of the visual cortex

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## Introduction

Caffeine has been known to increase neuronal activity and decrease local cerebral blood flow (1). Several recent studies (2-5) showed that caffeine altered BOLD signals and some (4,5) examined the effect from a perspective of signal processing and global contrast modulation. Since caffeine has known pharmacological effects on human behavior, we hypothesized that in addition to the reported global effect, caffeine's influence on resting-state BOLD signals might be spatially differential and could be detected. In this study, the hypothesis was tested in the visual cortex under the eyes-open condition.

## Materials and Methods

The Institutional Research Ethics Committee approved this single-blind caffeine-placebo study. Twenty healthy volunteers (10 females, 10 males; age = 21-35 years) were recruited. All subjects provided written informed consent before participation. MR imaging was conducted on a 3T Siemens scanner (body coil transmission and 12-channel phased-array reception). The experiment comprised two identical sessions (pre-dose and post-dose). After the pre-dose session, the subjects were removed from the scanner to ingest an over-the-counter caffeine pill (200mg dose). Post-dose functional imaging started approximately 45 min later. Key parameters of BOLD imaging were: nineteen 5-mm axial slices, matrix = 64x64, field-of-view = 20 cm, single-shot gradient-echo echo-planar readout, TR = 2 s, TE = 30 ms, measurement = 170 and 240 for task-based and resting-state BOLD imaging, respectively. Block-designed whole-field black-white flashing checkerboard was used for visual stimulation. The subjects were asked to keep their eyes open during all imaging. To monitor the change of local blood flow, ASL imaging was performed (TR = 4 s, TE = 18 ms, 30 pairs of tag and control images, pseudo-continuous labeling with tagging duration = 1 s and post-labeling delay = 1.2 s). Signals of respiration and pulse were recorded along with the scanner transistor-transistor logic pulse. As a control arm, the experiment was repeated in ten of the subjects based on the same procedure except that placebo was provided this time.

After motion correction, RETROICOR (6) was applied to BOLD images to remove physiological noise. Three subjects were excluded from further analysis because of excessive motion. The areas activated by the flashing checkerboard in both sessions (family-wise corrected $p \le 0.05$ and cluster size $\ge 3$ voxels) were used as the seed for functional connectivity calculation. For group analysis, results were normalized to the Montreal Neurological Institute templates. The threshold of cluster size was set to 20 to account for the change in voxel dimension after spatial normalization (3.1x3.1x5 $mm^3$ vs. 2x2x2 $mm^3$).

## Results and Discussion

**Figure 1** shows group functional connectivity of the visual cortex (N = 17). After caffeine ingestion, the connection between visual cortex and the lateral geniculate nucleus (LGN) is slightly decreased, whereas the integration of extrastriate visual areas is increased (uncorrected $p < 10^{-5}$). Overall, two hundred milligrams of caffeine reduced the local blood flow in gray matter by 24±7 %. In contrast, no statistical inter-session difference was observed in local blood flow or functional connectivity in the placebo experiment. The primary visual cortex (V1) receives most visual inputs relayed by LGN, whereas extrastriate areas such as V2, V4, and MT have been shown to be modulated by attention. Since the subjects were instructed to keep their eyes open during resting-state BOLD imaging, such change in functional connectivity suggests increased association of visual attention and adjusted configuration for faster and higher-order processing of visual signals. Meanwhile, LGN is less connected presumably to avoid competition for computation resources as the signal transmission from LGN to V1 can largely rely on the optical radiation (anatomical connectivity supported by fiber tracts).

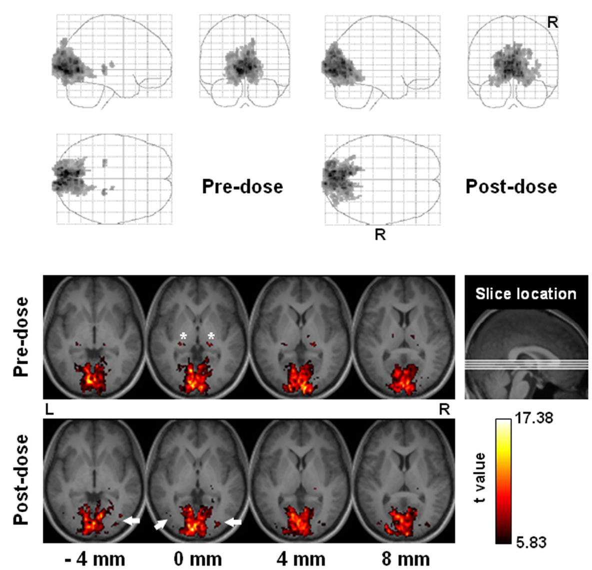


**Figure 1.** Group functional connectivity of the visual cortex (N = 17). Top panel is the projection viewed from right, behind (right side on the right), and above (right side at bottom). Bottom panel is the sectional axial view in neurologic convention. The lateral geniculate nucleus and extrastriate areas are marked with asterisks and arrows, respectively.

## References

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