Caffeine Reduces the Initial Dip in the Visual BOLD Response

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Introduction

The initial dip in the BOLD signal is thought to reflect an early transient increase in deoxyhemoglobin due to a focal increase in the cerebral metabolic rate of oxygen ($CMRO_2$) [1]. It precedes the positive BOLD signal that occurs when an increase in cerebral blood flow (CBF) leads to a subsequent decrease in deoxyhemoglobin. Because it is tightly linked to $CMRO_2$, the initial dip may be a more specific marker of neural activity than the positive BOLD signal. In addition, a better understanding of the initial dip may provide insight into the relation between functional changes in $CMRO_2$ and CBF. However, the initial dip has not been consistently observed across studies. While some studies have reported the initial dip [2,3,4], other studies have found little or no evidence for an initial dip [5,6]. These contradictory results may be due to many factors, notably the use of anesthesia and other drugs [7]. One possible factor is caffeine, which has been shown to significantly alter the temporal dynamics of the BOLD signal [8]. Because it is widely consumed, variations in caffeine usage may play a large role in the variability of initial dip findings in human fMRI studies. In this study, we show that caffeine can reduce the initial dip.

Methods

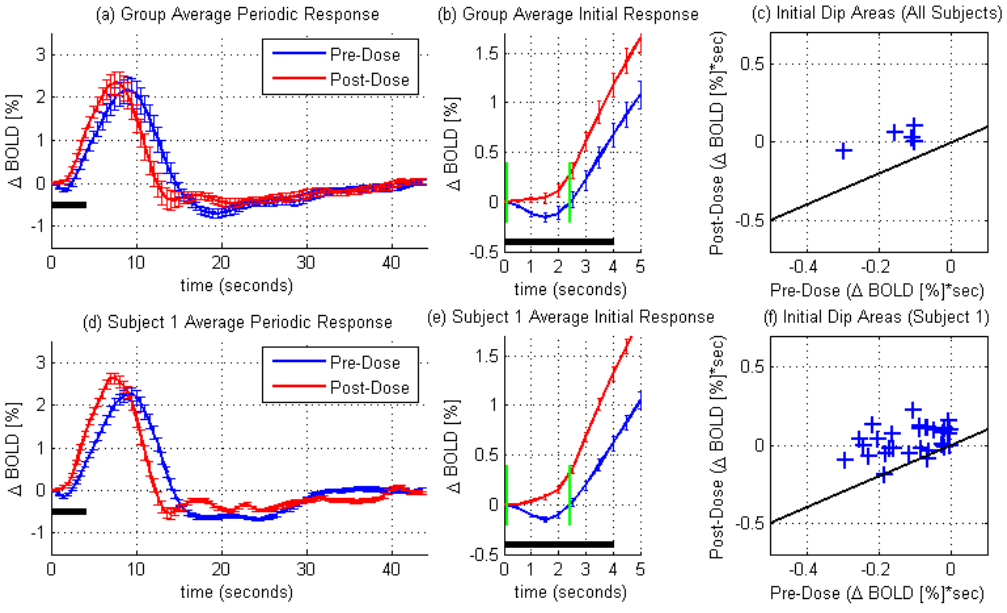
Five subjects participated in the study after giving informed consent. Each experiment was 2 hours long, with 45 minute pre-dose and 45 minute post-dose imaging sessions. Between sessions, each subject ingested a 200 mg oral dose of caffeine and waited outside of the magnet for 30 minutes. The subjects viewed a full-field, full contrast radial 8 Hz flickering checkerboard. A periodic single trial design was used (4 seconds on, 40 seconds off, 5 cycles, 2 runs). Images were acquired on a 3T GE whole body system with a head transmit coil and an 8 channel receive head coil. The imaging sequence was a single shot spiral with TR=0.5s, TE=25ms, flip angle 45 degrees, FOV 24 cm, 64x64 matrix, three 8 mm oblique slices aligned with the calcarine sulcus. Two periodic single trial runs with six 4 mm oblique slices were also acquired for 3 of the subjects. An additional functional run was acquired with a block design paradigm (20 seconds on, 40 seconds off, 4 cycles) using a PICORE QUIPPSII arterial spin labeling (ASL) sequence with dual echo spiral readout (TE1/TE2=9.1/30ms; TI1/TI2 = 600/1500ms). High resolution 3D anatomical scans were used to align the pre-dose and post-dose data. Correlation analysis of the block design runs was used to define a functional region of interest (ROI). For each voxel within the functional ROI, an average response was calculated by averaging across cycles and runs of the periodic single trial data. For each response, the ***initial dip area*** was defined as the integral of the signal (pre-dose or post-dose) from 0 seconds to the first zero-crossing of the pre-dose signal (approximately 2.5 seconds). By this method, a response with an initial dip yielded a negative initial dip area. Voxels showing a negative initial dip area in the pre-dose session were used to calculate average pre-dose and post-dose responses for each subject and for voxel-wise comparisons of pre-dose and post-dose initial dip areas.

Results

Figure (a) shows the group average (N = 5) pre-dose (blue) and post-dose (red) periodic responses, with a magnified view in (b). The error bars indicate standard error, and the horizontal black bars show time of stimulus. The initial dip is clearly present in the pre-dose response and is attenuated in the post-dose response. The time period used to calculate the initial dip area is indicated by the green bars. Figure (c) shows the average post-dose versus pre-dose initial dip areas for each subject, with the solid black line denoting equal areas. A two-sided paired t-test showed significant (p=1.8e-3) differences between the pre-dose and post-dose initial dip areas, corresponding to a reduction in the initial dip (i.e. post-dose area was more positive than the pre-dose area). Representative data from one of the subjects is shown in Figures (d)-(f). A two-sided paired t-test across voxels showed significant differences (p=2.30e-8) between the pre-dose and post-dose initial dip areas for this subject (see Fig (f)), reflecting a significant reduction in the initial dip. Significant differences in areas were also found for the other four subjects, with a maximum p-value across subjects of p=8.91e-4. All the results shown are from the 8mm slice data. Analysis of the 4mm slice data yielded comparable results.

Discussion

Caffeine appears to reduce the initial dip in the BOLD signal. Recent experimental and theoretical modeling work suggests that the vasoconstrictive properties of caffeine can lead to a quickening of the cerebral blood flow (CBF) response to neural stimulus [8,9]. With the faster CBF response, the initial increase in CMRO2 is offset by a faster increase in oxygen delivery. This can reduce the initial increase in deoxyhemoglobin, thus reducing or eliminating the initial dip.



References

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