Caffeine reduces resting-state functional connectivity in the motor cortex

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Introduction

Functional connectivity maps based on the spatial correlation of resting-state fluctuations in the blood oxygenation level-dependent (BOLD) signal are finding increasing use in applications such as the localization of functional regions, disease diagnosis, and enhanced understanding of information processing strategies employed by the brain [1,2]. However, the basic mechanisms underlying the correlation in low-frequency BOLD fluctuations are not entirely understood. In particular, the relative contributions of neural and vascular sources are not well characterized. Biswal et al. (1997) found that increases in baseline cerebral blood flow (CBF) induced by mild hypercapnia diminished low-frequency oscillations in the resting BOLD signal and caused a substantial decrease in functional connectivity within the sensorimotor cortex [3]. In contrast, reductions in baseline CBF induced by the application of a nitric oxide synthase blockade have been shown to increase low-frequency vascular fluctuations [4]. More recently, reductions in baseline CBF due to caffeine have been shown to significantly alter the temporal dynamics of the BOLD signal, including an increase in post-stimulus oscillations [5]. The goal of this study was to assess the effect of caffeine on resting-state functional connectivity maps.

Methods

Following a 12-hour period of caffeine abstinence, 5 healthy subjects (ages 24 to 41) were scanned on a GE Signa 3T whole body system with an 8-channel receive-only head coil. The imaging procedure consisted of a half hour pre-dose session and a half hour post-dose session. Subjects were removed from the scanner after the initial session, given an over the counter tablet containing 200 mg of caffeine, and placed back into the scanner approximately 30 minutes later. Both sessions included a high-resolution anatomical scan, a bilateral finger tapping block paradigm (20s rest followed by 5 cycles of 30s activity/30s rest), and three 5-minute resting scans. Functional data were collected over 6 oblique 6-mm thick slices through the primary motor cortex with an in-plane resolution of 3.75×3.75mm. Data from the motor task scan and one resting baseline scan were acquired with a PICORE QUIPSS II arterial spin labeling sequence with dual echo spiral readout (TR = 2s, TI1/TI2 = 600/1500 ms, TE1/TE2 = 9.2/30 ms and flip angle = 90°). Images for the two additional resting scans were acquired using a BOLD-weighted sequence with spiral readout (TE = 30 ms, TR = 500 ms, and flip angle = 45°).

The anatomical volume from the post-dose session was aligned to that of the pre-dose session and the rotation and shift parameters were then used to coregister all images within and across sessions. Further preprocessing included physiological noise correction using cardiac and respiratory data collected during image acquisition, and removal of constant and linear trends. Pre-dose and post-dose activation maps (P<0.05 after Bonferonni correction) were generated from the data acquired during the motor task runs using a general linear model analysis. The intersection of the pre-dose and post-dose maps was used to define regions of interest (ROIs) within the left and right motor cortices. Time series data from the BOLD sensitive resting runs were low pass filtered with a cutoff frequency of 0.08 Hz. The average signal from the right ROI was used to define a reference time course. This reference time series was then correlated with all of the voxel time series within the brain to generate a functional connectivity map (r > 0.35) for each subject and condition. These maps provided a qualitative assessment of the change in functional connnectivity with the caffeine dose. For a more quantitative analysis, functional connectivity was measured within and across motor cortices using the method described in [3]. In summary, every voxel time course within the two ROIs was used as a reference to generate functional connectivity maps. The quantity $\bar{n}_{LR}/n_L$ was used as a measure of the connectivity between the left and right motor cortices, where $\bar{n}_{LR}$ is the average number of voxels passing the threshold (r > 0.35) in the left ROI when using the voxels in the right motor cortex as seed voxels, and n_L is the total number of voxels in the left ROI. The quantities $\bar{n}_{LL}/n_L$ and $\bar{n}_{RR}/n_R$ were calculated in a similar fashion and served as measures of connectivity within the left and right motor corticies, respectively. Note that as stated in [3], the additional metric $\bar{n}_{RL}/n_R$ is necessarily equal to $\bar{n}_{LR}/n_L$.

Results

Figure 1 shows representative pre-dose and post-dose functional connectivity maps (using the average right ROI reference function) for Subject 1. The color bar shows the range of correlation coefficients. A visible reduction in both the number of significant voxels and the value of the correlation coefficients can be seen in the post-dose map as compared to the pre-dose map. Figure 2 shows the average pre-dose and post-dose values of the functional connectivity measures $\bar{n}_{LR}/n_L$, $\bar{n}_{LL}/n_L$, and $\bar{n}_{RR}/n_R$. The caffeine dose led to significant reductions in the connectivity between the left and right motor cortices $\bar{n}_{LR}/n_L$ (p = 0.008) and the connectivity within the right motor cortex $\bar{n}_{RR}/n_R$ (p = 0.01) and a nearly significant reduction of the connectivity within the left motor cortex $\bar{n}_{LR}/n_L$ (p = 0.08).

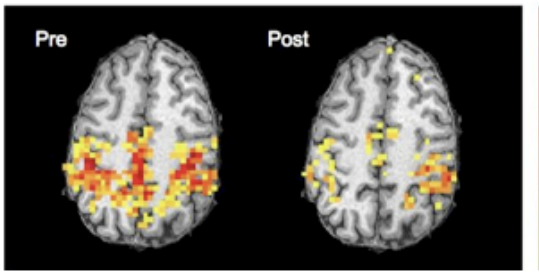

Figure 1. Functional connectivity map with reference time course from the right ROI

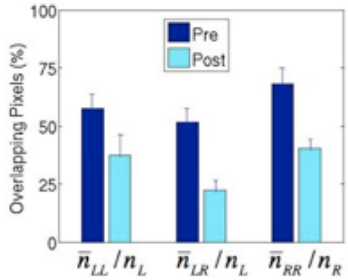

Figure 2. Mean pre-dose and post-dose functional connectivity measures (standard error shown)

Discussion

The caffeine-induced reduction in functional connectivity was similar to the previously reported decrease in connectivity due to hypercapnia. However, the underlying mechanisms are likely to be very different because caffeine reduces baseline CBF while hypercapnia increases CBF. It has been shown that hypercapnic-induced vasodilation decreases vascular responsivness, while caffeine-induced vasoconstriction increases vascular responsivness [6,7]. Thus, while the decrease in connectivity with hypercapnia might be attributed to the decrease in vascular responsiveness, an understanding of the mechanisms through which caffeine reduces connectivity will require further study. Given the widespread use of caffeine, the findings of this study also suggest that caffeine usage should be carefully considered in the interpretation of functional connectivity studies. Other factors that can alter baseline CBF, such as age and medication, should also be considered.

References

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