Global Reductions in Resting-state BOLD Connectivity reflect Widespread Decreases in MEG Connectivity

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Purpose: In resting-state functional MRI, the temporal correlation between the blood oxygenation level-dependent (BOLD) signals from different brain regions is used to assess functional connectivity[1,2]. However, the BOLD signal is an indirect measure of neural activity and its complex hemodynamic nature[3] can challenge the interpretation of differences in connectivity that are observed across conditions or subjects[4]. Previous work[5,6] has shown that caffeine causes widespread reductions in BOLD connectivity across the brain. Because caffeine acts as both a neurostimulant and a vasoconstrictor, it was unclear whether the connectivity changes were due primarily to changes in the neural or vascular systems. In this study, we used joint magnetoencephalography (MEG) and fMRI measures to further elucidate the origins of the caffeine-induced changes in BOLD connectivity.

Methods: The study consisted of ten healthy subjects (aged 21-33) who were low caffeine users (<50 mg/day). We employed a double-blind placebo-controlled repeated measures design in which each subject participated in two independent control and caffeine sessions per imaging modality (where each session consisted of a pre-dose section and a post-dose (placebo or caffeine) section). *MEG:* Magnetic fields were recorded using an Elekta/Neuromag™ whole-head MEG system with 204 gradiometers and 102 magnetometers in a magnetically shielded room (IMEDCO-AG, Switzerland). Each MEG section consisted of two resting-state scans (5 min/scan) during which subjects were instructed to stay awake with their eyes closed, keep their mind blank and their hands open and laying flat. An additional empty-room dataset was collected as a reference for background noise levels. *fMRI:* BOLD data were acquired using a GE MR750 3T system (EPI with 166 volumes, 30 slices, 3.438x3.438x5mm^3 voxel size, 64x64 matrix size, TR=1.8s, TE=30ms). A single 5-min resting-state functional scan (eyes closed) was acquired in each section. In addition, high resolution anatomical data were collected using a magnetization prepared 3D fast spoiled gradient (FSPGR) sequence (TI=600ms, TE=3.1ms, FOV = 25.6cm, 256x256x176 matrix).

Data Analysis: *MEG:* Data were pre-processed using MaxFilter (Neuromag™) to remove environmental noise and signal artifacts due to magnetic interference from sources outside the brain. Temporal independent component analysis (fastICA algorithm) was applied to remove artifact-related components such as eye blinks and cardiac activity. A 7mm fixed source grid was defined on the brain's gray and white matter boundary (based on the anatomical MRI) and then divided into cortical regions (ROIs) using FreeSurfer computed parcellations for each subject. Data were then frequency filtered (1-50Hz) and projected into source space using the array-gain constraint minimum-variance regularized vector beamformer. The absolute value of the Hilbert transform of the reconstructed source time-courses provided the envelope of oscillatory power fluctuations, which was then epoched into 500ms blocks[7]. *fMRI*: White matter (WM), grey matter, and cerebral spinal fluid (CSF) partial volumes fractions were computed from the anatomical MRI using FSL. The post-dose anatomical volume was registered to the pre-dose volume using AFNI, and the resulting rotation and shift parameters were applied to the post-dose functional data. Nuisance terms were removed by means of multiple linear regression using the following regressors: linear and quadratic trends, 6 motion parameters, RETROICOR and RVHRCOR regressors, and the mean BOLD signal calculated from WM and CSF voxels (partial volume threshold of 0.99 for each tissue type) and the data were then low-pass filtered (fc = 0.08 Hz). For each modality, an average time-course was computed for each of the Freesurfer cortical ROIs. The Pearson correlation coefficient was computed between the time series for each pair of ROIs and used to construct a connectivity matrix. A subject's mean global correlation was defined as the average correlation across all ROI pairs.

Results: In both modalities, correlation values in the post-dose caffeine data were visibly lower than in the pre-dose caffeine data, while no widespread difference was observed in the control session (see representative subject data in top 2 rows of Figure 1). To further assess differences, the correlation values were converted using Fisher's transformation to z-scores. The bottom row of Figure 1 shows the mean changes in z-score (pre-dose minus post-dose) averaged across the group (upper triangle) for all ROI pairs, as well as the t-statistics of the ROI pairs which exhibited a significant change (lower triangle; $p<0.05$). The broad decreases in connectivity seen in both modalities were confirmed quantitatively using a repeated-measures two-way ANOVA (analysis of variance) which examined the effect of (1) caffeine/control session and (2) ROI pair on the measured connectivity. For both fMRI and MEG, the ANOVA showed a significant caffeine/control effect ($p < 0.01$) with a non-significant interaction term ($p> 0.23$), suggesting that the effect of caffeine on the connectivity was largely independent of ROI pair. The top section of Figure 2 shows each subject's mean global correlation for the pre and post-dose caffeine data from each modality, and the bottom section displays the respective change in the mean global correlation for each modality. While all subjects showed a decrease in their overall connectivity regardless of modality, there was not a significant relation between the magnitude of the fMRI and MEG changes ($r = -0.18$, $p = 0.62$; Spearman's $r=-0.12$, $p = 0.73$).

Discussion: Our findings suggest that reductions in neural connectivity (as measured with MEG) underlie the observed caffeine-induced reductions in the BOLD connectivity. Although all subjects showed a connectivity decrease for both modalities, the magnitude of the changes did not show a significant relation between the two modalities. Two of the subjects exhibited a larger decrease in MEG connectivity than fMRI connectivity and also had the lowest mean global correlations (and hence the smallest changes) in the fMRI data. Recomputing the correlation between the magnitude of changes using the remaining 8 subjects showed a stronger relation ($r = 0.62$, $p = 0.09$; Spearman's $r =0.71$, $p =0.06$) between the two modalities. As the widespread reductions in connectivity with caffeine have been shown to be related to a reduction in the global signal, our results also provide further evidence for a neural basis to the fMRI global signal[6,8]. In summary, this study demonstrates the similarity in connectivity changes as assessed with MEG and fMRI and provides a firmer basis for the use of fMRI as a tool for the evaluation of neural functional connectivity.

References: [1] Biswal, B. et al, Magn. Reson. Med., 34:537-541, 1995. [2] Fox, M.D et al, J. Neurophysiol 101:3270-3283, 2009. [3] Buxton, R.B. et al., NeuroImage 23(Supp. 1) S220-S233, 2004. [4] He, H. et al. NeuroImage 59(3):2339-2348, 2012. [5] Rack-Gomer, A.L. et al, NeuroImage 46(1):56-63, 2009. [6] Wong, C.W. et al. NeuroImage 63(1):356-364, 2012. [7] Brookes, M.J. et al., NeuroImage 56(3):1082-1104, 2011. [8] Scholvinck et al., PNAS 107:10238-10243, 2010.

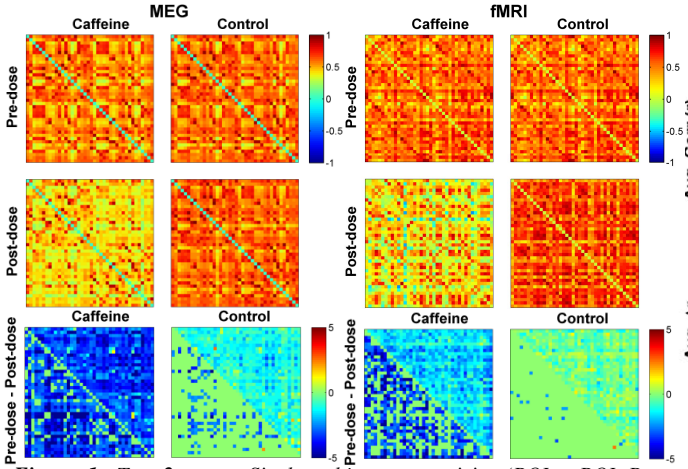

Figure 1. *Top 2 rows: Single subject connectivity (ROI-to-ROI Pearson correlations) matrices. Bottom row: Upper triangle shows mean z-score changes across group (blue color – decrease, red color – increase). Lower triangle shows t-statistics of ROI pairs exhibiting significant change ($p <0.05$).*

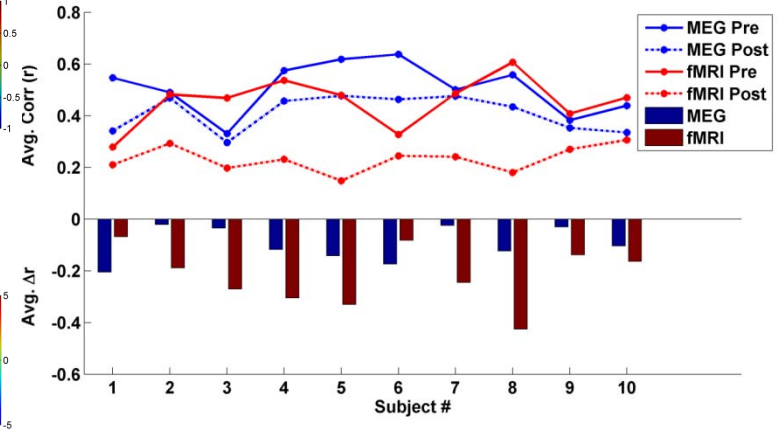

Figure 2. *Top panel: Mean global correlation for the MEG (blue) and fMRI (red) caffeine session data (solid line – pre-dose, dotted line – post-dose). Bottom panel: Corresponding change in mean global correlation for each subject (MEG – blue bars, fMRI – red bars).*