Caffeine-induced reductions in the resting-state fMRI global signal reflect increases in EEG vigilance measures

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PURPOSE

Pre-processing of resting-state fMRI data often involves a controversial step known as global signal regression (GSR), which may produce spurious anti-correlations between the Default Mode Network (DMN) and the Task Positive Network (TPN) [1, 2, 3]. Prior work has found that caffeine reduces the amplitude of the global signal and enhances the anti-correlation between the DMN and TPN [4]. In this study, we examined the neural-electrical basis behind this caffeine-related reduction in the global signal using simultaneous EEG-fMRI. We showed that across subjects, the caffeine-induced change in the global signal amplitude is negatively correlated with the change in vigilance as assessed with EEG.

METHOD

Simultaneous EEG-fMRI data were acquired on ten healthy subjects with low caffeine intake (4 males and 6 females; < 50 mg daily) using a 3 Tesla GE MR750 system and a 64 channel EEG system (Brain Products). Each imaging session consisted of a pre-dose and a post-dose session, in between which subjects were removed from the scanner and given a tablet containing 200 mg of caffeine. The functional scan in the post-dose session began 40 minutes after the caffeine intake. For this analysis, data from a 5 minute resting-state scan (eyes closed) were considered. EEG signals were recorded at 5kHz sampling rate and Vision Analyzer 2.0 software (Brain Products) was used for MR gradient artifact removal. A low pass filter with cut off frequency 30Hz was applied to all channels and the processed signals were down-sampled to 250Hz. OBS-ICA (as implemented in EEGLAB) was applied to remove cardio-ballistic and residual artifacts [5, 6]. Short-time Fourier transform with 1311 point 4-term Blackman-Harris window and 65.7% overlap was used to create a spectrogram for each channel with 1.8s temporal resolution. Functional MRI data were acquired with the following parameters: echo planar imaging with 166 volumes, 30 slices, 3.438x3.438x5mm^3 voxel size, 64x64 matrix size, TR=1.8s, TE=30ms. Nuisance regressors (0^{th}+1^{st}+2^{nd} order Legendre, 6 motion time courses and their first derivatives, mean BOLD signals from the WM and CSF voxels and their first derivatives, RETROICOR [7] and RVHRCOR [8] physiological noise terms) were removed from the raw data through linear regression. To identify motion-contaminated time segments, outlier detection was applied to the mean of all EEG amplitude time courses, and the outlier time segments were removed from both the spectrogram and fMRI time series.

For each time point and channel, a relative amplitude EEG spectrum was computed by normalizing the spectrum by its overall power. The relative EEG spectra were then averaged across time points and channels to create a mean spectrum for each subject and condition. A measure of vigilance was derived from the mean spectrum as the root mean square (rms) amplitude in the alpha band (7-13Hz) divided by the rms amplitude in the delta and theta bands (1-7 Hz) [9]. For each voxel, a percent change BOLD time series was obtained by subtracting the mean value and then dividing the resulting difference by the mean value. The global signal amplitude was formed by first averaging the percent change time series across all brain voxels and then calculating the standard deviation of the average time series. Caffeine-induced changes in the vigilance measure and global signal amplitude were calculated by subtracting the pre-dose values from the post-dose ones. To create voxel-wise correlation maps with the posterior cingulate cortex (PCC), seed ROIs were created using a sphere with a diameter of 12mm centered about a seed coordinate, created by transforming the Talairach space coordinates [0, -51, 26] into the subject space [4]. The BOLD time courses within the PCC ROI were averaged and then correlated with every other voxel in the brain.

RESULTS AND DISCUSSION

The left panel of Fig. 1 demonstrates a significant negative relation (r = -0.83) between changes in the global signal amplitude and EEG vigilance. Correlation maps are displayed in the middle panel for two representative subjects. Caffeine increases the vigilance and enhances the anti-correlation between the default mode network (DMN) and task positive network (TPN) in subject 1 (bottom)), but not in subject 9 (top). The corresponding amplitude spectra of the global EEG amplitude time courses are shown in the right panel. The post-dose spectra for subject 1 (bottom row) exhibit a pronounced reduction in delta power and an increase in alpha power as compared to the pre-dose spectra, while the pre-dose and post-dose spectra for subject 9 show a high degree of similarity. In summary, we have shown that decreases in the global signal amplitude are associated with an increase in the vigilance state of the subjects. Our finding suggests that pre-processing methods that attempt to remove the effects of global signal differences may also be minimizing the effect of connectivity differences that are related to changes in vigilance.

[1] Fox et. al., PNAS 2005, 102: 9673-9678. **[2]** Fox et. al., J Neurophysiol 2009, 101:3270-3283. **[3]** Murphy et. al., Neuroimage 2009, 44:893-905. **[4]** Wong et al., Neuroimage 2012, 63:356-64. **[5]** Delorme et. al., J of Neuroscience Methods 2004, 134:9-21. **[6]** Debener et. al., Neuroimage 2007, 34:587-597. **[7]** Glover et. al., Magn Reson Med 2000, 44:162-167. **[8]** Chang et. al., Neuroimage 2009. 47:1448-1459. **[9]** Olbrich et. al., Neuroimage 2009, 45:319-332.

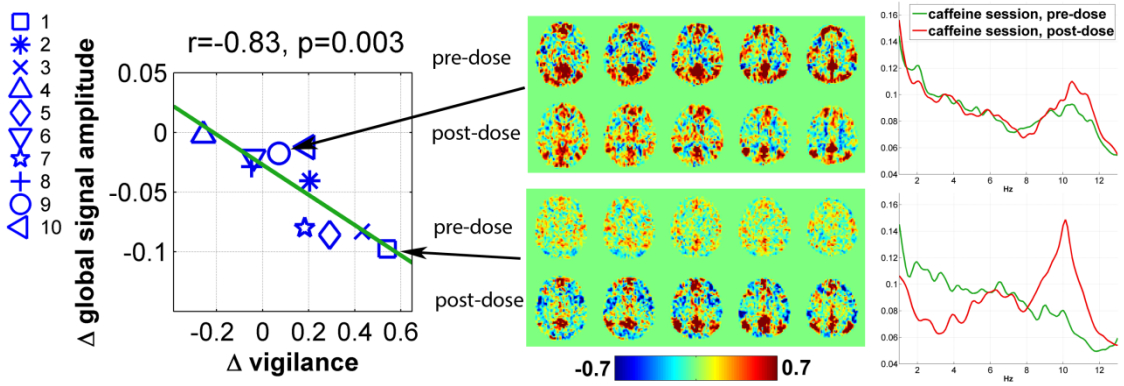

Fig. 1 Caffeine-related changes in the global signal amplitude and vigilance measure (left panel); Caffeine session correlation maps using PCC as the seed ROI for two representative subjects (middle panel) and the corresponding EEG amplitude spectra (right panel)