Neuroelectrical basis of the resting-state BOLD global signal as determined with simultaneous EEG-fMRI

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INTRODUCTION

In resting-state functional MRI (fMRI) studies, the removal of a global signal component (i.e. the mean BOLD signal from the entire brain) is a common pre-processing step. However, the validity of this step has been questioned because global signal regression (GSR) can produce spurious anti-correlations between functional brain networks, such as the default mode network (DMN) and the task positive network (TPN) [1-2]. In addition, recent work by Scholvinck et. al. using combined measurements of local field potentials and BOLD fluctuations in monkeys has shown that the BOLD global signal is tightly coupled to underlying neural activity [3]. This finding suggests that global signal regression may remove important information about brain function from resting-state studies. For this experiment, we used simultaneous electroencephalography (EEG) and fMRI measures to (1) assess the neuroelectrical basis of the resting-state BOLD global signal in humans and (2) determine how regression using different components of the global signal (i.e. EEG-related and non EEG-related) affects the anti-correlation between the DMN and TPN.

METHODS

Simultaneous EEG-fMRI data were collected for 8 healthy subjects (4 males and 4 females) during a 5-minute resting-state run with eyes-open. EEG data were recorded using a 64 channel EEG system (Brain Products) at 5kHz sampling rate. Vision Analyzer 2.0 software (Brain Products) was used for MR gradient and cardio-ballistic artifact removal [4-5]. A low pass filter with a cutoff frequency of 30Hz was applied to all channels and the processed signals were down-sampled to 250Hz. Independent component analysis (ICA) as implemented in EEGLAB [6] was applied to remove residual EEG artifacts. A spectrogram was created containing the EEG power time courses at different frequencies. Five frequency bands of interest were defined, including the delta (1-4Hz), theta (5-7Hz), alpha (8-12Hz), beta (13-30Hz), and all (1-30Hz) frequency bands. For each band, a mean EEG power time course was calculated by averaging all power time courses within that band. The data were then low-pass filtered with a cutoff frequency of 0.08Hz. Functional MRI data were acquired using a 3T GE MR750 system with the following scan parameters: echo planar imaging with 166 volumes, 30 slices, 3.438x3.438x5mm^3 voxel size, 64x64 matrix size, TR=1.8s, and TE=30ms. Nuisance terms (0^{th}+1^{st}+2^{nd} order Legendre polynomials, 6 motion parameters) were removed from the raw data through linear regression. The data were then low-pass filtered with a cutoff frequency of 0.08Hz. The BOLD global signal was calculated as the average of all BOLD time-courses in the brain.

We applied singular value decomposition (SVD) to the matrix of EEG power time courses and determined the number of principal components (PCs) required to explain 98% of the total EEG variance in each frequency band. We then projected the BOLD global signal onto the space spanned by the selected EEG components from each frequency band. The ratio of the variance of projected signal to the variance of the global signal was calculated for each EEG frequency band. These values represent the percentage of the BOLD global signal variance that is explained by 98% of the EEG variance. We denote the projection of the global signal onto the EEG signal space for the full band (1-30Hz) as GS⇒EEG. The component that is orthogonal to the full band EEG space is denoted as GS⊥EEG. Resting-state BOLD connectivity maps were created using the posterior cingulate cortex (PCC) as a seed region and correlating the average signal from the PCC with all BOLD time courses in the brain. Functional connectivity maps were obtained for each subject with either no global signal regression or regression using one of the following signals: the global signal, the GS⇒EEG signal, or the GS⊥EEG signal.

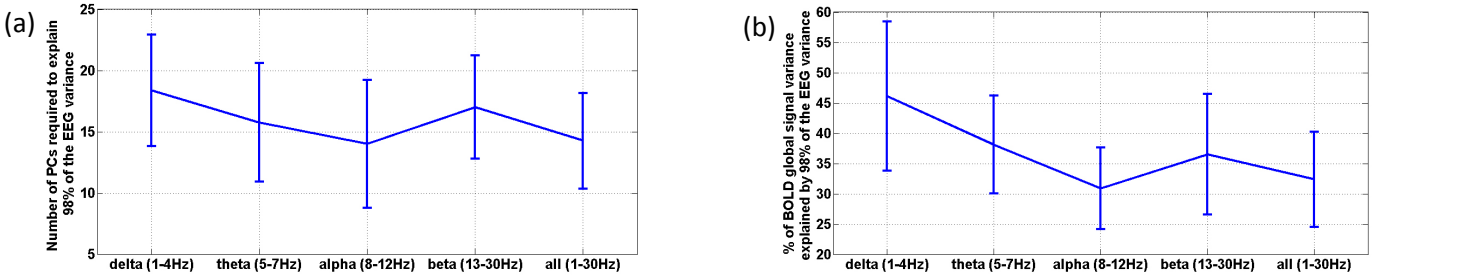

Fig. 1 Number of EEG PCs required to explain 98% of total EEG variance is shown in (a) and percentage of BOLD global signal variance explained by 98% of EEG variance is shown in (b) for the 5 frequency bands. Data points are the average across subjects and error bars represent standard deviation.

RESULTS AND DISCUSSION

The average number of EEG components required to explain 98% of the EEG variance for each frequency band is shown in Fig. 1a. In most cases, less than 20 PCs are required to explain 98% of the EEG variance. Fig. 1b shows the percentage of the BOLD global signal variance that can be explained by 98% of the EEG variance. The EEG power time courses explained between 18% and 64% of the BOLD global signal variance, implying that a substantial component of the BOLD global signal has a neuroelectrical basis. Fig. 2 shows functional connectivity maps for a representative subject (thresholded at overall p of 0.01). In the first row, without global signal regression, the anti-correlation between the DMN (in red) and TPN (in blue) is not very apparent. Global signal regression causes the anti-correlation between the DMN and TPN to be stronger and more widespread (bottom row of Fig. 2), consistent with prior findings [1]. Functional connectivity maps obtained with regression of the GS⊥EEG and GS⇒EEG components are shown in the second and third rows of Fig. 2, respectively. Interestingly, the anti-correlation pattern is more pronounced in the map obtained after removal of the global signal component that lies within the EEG signal subspace, as compared to the map obtained when regressing out the global signal component that is orthogonal to the EEG power fluctuations. This result suggests that the detection of the anti-correlated relation between the DMN and TPN depends on the removal of a global signal component of neuroelectrical origin. Maps for the other subjects show a similar pattern. In conclusion, we find that the BOLD global signal is coupled to EEG power time courses, suggesting that it has a neuroelectrical basis in humans. Therefore, caution should be used in the interpretation of functional connectivity results when global signal regression is performed.

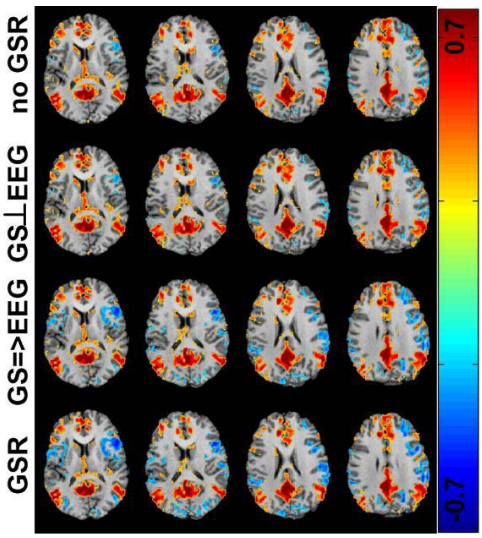

Fig. 2 Correlation maps for a representative subject

[1] Fox et. al., J Neurophysiol 2009, 101:3270-3283. **[2]** Murphy et. al., NeuroImage 2009, 44:893-905. **[3]** Scholvinck et. al., PNAS 2010, 107:10238-10243. **[4]** Allen et. al., NeuroImage 1998, 8:229-239. **[5]** Allen et. al., NeuroImage 2000, 12:230-239. **[6]** Delorme et. al., J of Neuroscience Methods 2004, 134:9-21.