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Differences in the resting-state fMRI global signal amplitude between the eyes open and eyes closed states are related to changes in EEG vigilance

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ABSTRACT

In resting-state functional connectivity magnetic resonance imaging (fcMRI) studies, measures of functional connectivity are often calculated after the removal of a global mean signal component. While the application of the global signal regression approach has been shown to reduce the influence of physiological artifacts and enhance the detection of functional networks, there is considerable controversy regarding its use as the method can lead to significant bias in the resultant connectivity measures. In addition, evidence from recent studies suggests that the global signal is linked to neural activity and may carry clinically relevant information. For instance, in a prior study we found that the amplitude of the global signal was negatively correlated with EEG measures of vigilance across subjects and experimental runs. Furthermore, caffeine-related decreases in global signal amplitude were associated with increases in EEG vigilance. In this study, we extend the prior work by examining measures of global signal amplitude and EEG vigilance under eyes-closed (EC) and eyes-open (EO) resting-state conditions. We show that changes (EO minus EC) in the global signal amplitude are negatively correlated with the associated changes in EEG vigilance. The slope of this EO–EC relation is comparable with the slope of the previously reported relation between caffeine-related changes in the global signal amplitude and EEG vigilance. Our findings provide further support for a basic relationship between global signal amplitude and EEG vigilance.

Introduction

In recent years, resting-state functional magnetic resonance imaging (fMRI) has been increasingly used as a tool to study functional brain connectivity in both health and disease (Fox and Raichle, 2007). The functional connectivity measures used in resting-state fMRI reflect the temporal synchrony of blood oxygenation level dependent (BOLD) signals across brain regions (Biswal et al., 1995; Fox et al., 2005; Fransson, 2005; Raichle et al., 2001). These connectivity measures are often dominated by the presence of a global signal component that appears to varying extents across the brain. To deal with this effect, many studies have adopted a pre-processing approach referred to as global signal regression (GSR), in which the global signal component is regressed out of the measured BOLD signals prior to the computation of connectivity measures. This approach has been shown to increase the spatial specificity of the correlation maps and to better reveal the anti-correlation between resting-state networks (e.g., the default mode network and the task positive network) (Birn, 2012; Fox et al., 2005; Greicius et al., 2003). However, there is some concern about the use of GSR, as it has been shown to introduce systematic biases into correlation-based measures of functional connectivity (Fox et al., 2009; Hahamy et al., 2014; Murphy et al., 2009; Saad et al., 2012). At present, there is not a universally agreed upon standard regarding the use of GSR, with some studies employing GSR, other studies using alternate noise reduction methods, and yet another set of studies that perform analyses with and without the use of GSR (Yeo et al., 2015).

In conjunction with the ongoing discussion regarding the use of GSR, there has also been interest in developing a better understanding of the global signal. In a study of resting monkeys, Scholvinck et al. (2010) reported that the local field potential power measured at a single cortical site exhibited widespread correlation with BOLD fMRI signals, providing evidence of a neural basis for the global signal. A recent study in sleep-deprived monkeys has demonstrated that specific neurophysiological events observed during sleep are associated with large scale fluctuations in cerebral blood volume and may therefore represent a significant contribution to the global signal (Liu et al., 2015a, 2015b). Using simultaneous EEG-fMRI measures in human subjects, we have shown that the amplitude of the global signal was inversely correlated with electroencephalographic (EEG) measures of vigilance across subjects and experimental runs (Wong et al., 2013), with higher vigilance states

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characterized by lower global signal amplitudes (defined as the standard deviation of the global signal). In addition, we found that increases in EEG vigilance measures associated with the ingestion of caffeine were significantly correlated with decreases in the global signal amplitude. There is also some evidence that the global signal may carry diagnostic information. For example Yang et al. (2014) recently reported that the variance of the global signal was significantly higher in patients with schizophrenia as compared to normal controls. However, the authors of that study acknowledged that the potential confound of vigilance differences between groups would need to be carefully considered in follow-up work.

In this study, we extend our prior work to determine whether the previously described relation between the global signal and vigilance would also be observed when contrasting measures obtained in the eyes-open versus eyes-closed states. Prior studies have shown that resting-state fMRI activity is significantly different between the eyes-closed and eyes-open conditions (Bianciardi et al., 2009; Jao et al., 2013; McAvoy et al., 2008; Patriat et al., 2013; Xu et al., 2014; Yan et al., 2009; Yang et al., 2007; Yuan et al., 2014; Zou et al., 2009). In general, these studies have found that the amplitude of the resting-state BOLD signal is decreased in the eyes-open condition as compared to the eyes-closed condition. For example, Jao et al. (2013) found that the average variance of the BOLD signal (i.e., signal variances computed on a per-voxel basis and then averaged across the brain) was significantly lower in the eyes-open condition. Furthermore, in our earlier studies, we reported that global signal effects were generally lower in the eyes-open condition as compared to the eyes-closed condition (Wong et al., 2012, 2013). Taking into account the prior findings, we hypothesized that decreases in global signal amplitude associated with opening of the eyes would be correlated with increases in EEG vigilance measures. We also examined whether the relationship between changes in the global signal amplitude and vigilance observed with the opening of the eyes would be similar to the relationship previously observed with the administration of caffeine (Wong et al., 2013).

Methods

Experimental protocol

Twelve healthy volunteers were initially enrolled in this study after providing informed consent. Two subjects were not able to complete the entire study, resulting in a final sample size of 10 subjects (4 males and 6 females, aged 24 to 33 years with an average age of 25.6 years). As prior work has shown that differences in dietary caffeine consumption may cause variability in the BOLD response (Laurienti et al., 2002), we recruited caffeine-naive subjects who consumed less than 50 mg caffeine daily (as assessed over a two month period prior to the study).

In this study we used data from the protocol described in our prior work (Wong et al., 2012, 2013). A repeated measures design was used, with each subject participating in two imaging sessions: a caffeine session and a control session. For the test of the primary hypotheses in this study, we analyzed the eyes-open and eyes-closed data from the control session. For the additional analysis, we compared the current findings with our prior analysis of the eyes-closed data from the caffeine session (Wong et al., 2013).

The order of the two sessions was randomized in a double-blinded manner. For each session, the operator obtained a capsule that contained 200 mg of either caffeine or cornstarch. The two imaging sessions were separated by at least two weeks. Each session consisted of a pre-dose and a post-dose imaging section, with each section lasting for about one hour. Upon completion of the pre-dose section, participants were taken out of the magnet and given the capsule. The subject was then placed back in the scanner, with the first functional scan of the post-dose section obtained approximately 40 min after capsule ingestion. This interval was chosen based on studies showing that the absorption of caffeine from the gastrointestinal tract reaches 99% about 45 min after ingestion, with a half-life ranging from 2.5 to 4.5 h (Fredholm et al., 1999).

Each scan section consisted of (1) a high-resolution anatomical scan, (2) arterial spin labeling scans (these results are reported in our prior study (Wong et al., 2012) but not considered here), and (3) two 5 minute resting-state scans with simultaneous EEG recording (one eyes-closed and one eyes-open). Subjects were instructed to lie still in the scanner and not fall asleep during resting-state scans. The order of the eyes-open and eyes-closed scans was randomized. During the eyes-open (EO) resting-state scans, subjects were asked to maintain attention on a black square located at the center of a gray background. During the eyes-closed (EC) resting-state scans, subjects were asked to imagine the black square. An impedance check was performed prior to each EEG data acquisition while the subject was in the desired state (EC or EO) for at least 1.5 min. EEG data acquisition began 30 s before each fMRI scan and ended 30 s after. Thus, the subject was in the desired state (EC or EO) for at least 2 min prior to the acquisition of the combined EEG and fMRI data. Field maps were acquired to correct for magnetic field inhomogeneities.

MR data acquisition

Imaging data were acquired on a 3 Tesla GE Discovery MR750 whole body system using an eight-channel receiver coil. High resolution anatomical data were collected using a magnetization prepared 3D fast spoiled gradient (FSPGR) sequence (TI = 600 ms, TE = 3.1 ms, flip angle = 8°, slice thickness = 1 mm, FOV = 25.6 cm, matrix size = $256 \times 256 \times 176$).

Whole brain BOLD resting-state data were acquired over thirty axial slices using an echo planar imaging (EPI) sequence (flip angle = 70°, slice thickness = 4 mm, slice gap = 1 mm, FOV = 24 cm, TE = 30 ms, TR = 1.8 s, matrix size = $64 \times 64 \times 30$).

Field maps were acquired using a gradient recalled acquisition in steady state (GRASS) sequence (TE1 = 6.5 ms, TE2 = 8.5 ms), with the same in-plane parameters and slice coverage as the BOLD resting-state scans. The phase difference between the two echoes was then used for magnetic field inhomogeneity correction of the BOLD data.

Cardiac pulse and respiratory effect data were monitored using a pulse oximeter (InVivo) and a respiratory effort transducer (BIOPAC), respectively. The pulse oximeter was placed on each subject's right index finger while the respiratory effort belt was placed around each subject's abdomen. Physiological data were sampled at 40 Hz using a multi-channel data acquisition board (National Instruments).

EEG data acquisition

EEG data were recorded using a 64 channel MR-compatible EEG system (Brain Products, Munich, Germany). The system consisted of two 32 channel BrainAmp MR Plus amplifiers powered by a rechargeable battery unit. The system was placed behind the scanner bore, which was connected using a 125 cm long data cable to a BrainCap MR with 64 recording electrodes (Brain Products, Munich, Germany). All electrodes in the cap had sintered Ag/AgCl sensors incorporating 5 kΩ safety resistors. The separate ECG electrode had a built-in 15 kΩ resistor. The arrangement of the electrodes in the cap conformed to the international 10/20 standard. FCz and AFz were the reference and ground electrodes, respectively. The EEG data were recorded at a 5 kHz sampling rate with a passband of 0.1–250 Hz. A phase locking device (Syncbox, Brain Products, Munich, Germany) was used to synchronize the clock of the EEG system with the master clock of the MRI system. Before each scan section, the electrode impedances were set below 20 kΩ, while the impedances of the reference and ground electrodes were set below 10 kΩ. Prior to recording EEG data in each resting-state scan, a snapshot of the electrode impedance values was taken from