A Method to Determine the Necessity for Global Signal Regression in Resting-State fMRI Studies

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Introduction: In resting-state functional MRI studies, the efficacy of global signal regression method remains questionable (1-2). We demonstrate that the accuracy of the estimated global signal is determined by the level of global noise. A method to quantify global noise levels is then introduced. We show that a criteria to determine the necessity for global signal regression can be found based on the method.

Methods: Sixteen amnestic mild cognitive impaired (aMCI) and 20 cognitively normal (CN) subjects were included in the study. The study was conducted with Medical College of Wisconsin Institutional Review Board approval. Written informed consent was obtained from each participant. The resting-state functional connectivity fMRI datasets were obtained at a 3T Signa GE scanner.

In determining whether or not to apply global signal regression in R- fMRI studies, we conducted experiments, using simulated data and human R-fMRI data.

To determine how the signal-to-global noise ratio (SGNR, defined as the standard deviation of the signal time course/standard deviation of the global noise time course) levels affect the errors of the measured voxelwise Pearson product-moment correlation coefficient (*r*), we define the *r* error ***without*** using the global regression E1 in Eq [1] and the *r* error using global regression as E2 in Eq [2].

$$E1 = \frac{\sum_i^n \sum_{j\neq i}^n (|r'_{ij} - r_{ij}|)}{\sum_i^n \sum_{j\neq i}^n (|r_{ij}|)} \quad [1] \qquad E2 = \frac{\sum_i^n \sum_{j\neq i}^n (|r''_{ij} - r_{ij}|)}{\sum_i^n \sum_{j\neq i}^n (|r_{ij}|)} \quad [2]$$

where n is the total number of voxels, r_{ij} is the *r* value between the sinusoidal signals (for simulated data) or the preprocessed time series (for human R-fMRI data) of voxel *i* and *j*. r'_{ij} is the measured *r* value between the mixed time courses (with added global noise) of voxel *i* and *j* without using the global signal regression. r''_{ij} is the measured *r* value between the time courses calculated after the global signal regression procedure. To characterize how different levels of SGNR produce different numbers of voxels that negatively correlate with global signal, we define a global negative index as: # of voxels negatively correlated with global signal / total # of voxels. The global negative index was measured with discrete SGNR values ranging from 1 to 100.

Results:

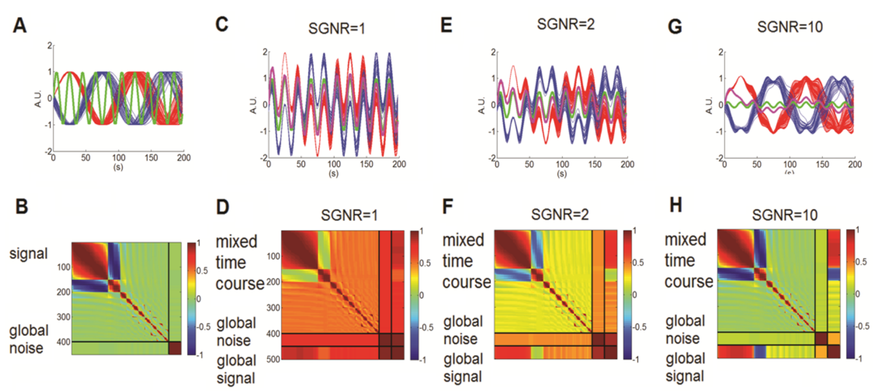

Fig 1. Characteristic relationship between global signal and the simulated R-fMRI signal. (**A**) The signals in the first cluster (150 voxels) are red, the signals in the second cluster (50 voxels) are blue. The signals of the rest 200 voxels are not shown. The global noise is green. (**B**) The *r* value among the 400 signals and the global noise (replicated 50 times for better illustration). (**C**, **E** and **G**) The mixed time courses in the first cluster are red, the mixed time courses in the second cluster are blue, the global noise is green and the global signal is purple with a SGNR of 1, 2 and 10, respectively. (**D**, **F** and **H**) The *r* value among the 400 mixed time courses, the global noise, and global signal with SGNR of 1, 2 and 10, respectively.

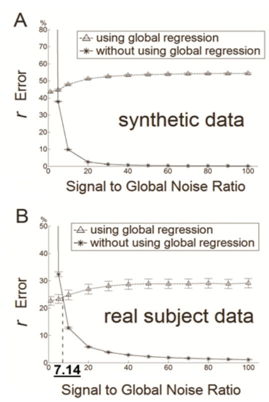

Fig2. Relationship between SGNR and *r* error simulated using synthetic data (**A**) and real subject data (**B**). In **Fig2B**, the dot-dashed line and solid line cross each other at SGNR value of 7.14. Performing the global signal regression above this SGNR, induces more errors.

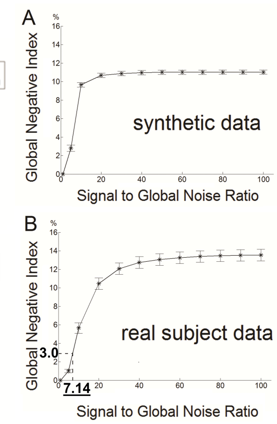

Fig3. Relationship between SGNR and mean global negative index simulated using synthetic data (**A**) and real subject data (**B**). The global negative index measurement of the criteria in doing and not doing global signal regression is 3.0 at the SGNR level of 7.14 determined in **Fig2B**.

Discussion:

In the present study, we demonstrated that the accuracy of the global signal regression is determined by the level of global noise. When the global noise level is high, the global signal resembles global noise. When the global noise level is low, the global signal resembles the R-fMRI time courses of the largest cluster, but not global noise. To answer the question as to whether or not the global signal should be considered a nuisance effect to be removed, we introduced a global negative index to quantify global noise levels. We demonstrated the monotonic relationship between the signal-to-global noise ratio and the global negative index. Finally, we discovered that there is a criterial global negative index associated with a criterial SGNR. Performing the global signal regression below this criterial global negative index induced less errors. Therefore, it is highly suggested that the global regression be performed. Performing the global signal regression above this criterial global negative index, induced more errors. Therefore, we suggest that the global signal regression not be performed. One can decide whether or not to apply this technique for each individual data set by comparing the global negative index of the data set to the criterial global negative index.

References: 1. Murphy K, et al., 2009. Neuroimage 44, 893-905. 2. Weissenbacher A, et al., 2009. Neuroimage,47, 1408-1416.

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