A Randomized Global Signal Regression Method for Resting State Functional Connectivity Studies

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INTRODUCTION: The presence of negative correlations between the default mode network (DMN) and the dorsal attention network (also known as the task positive network (TPN) [1] has been a subject of recent controversy in the resting-state functional MRI (fMRI) literature. It has been suggested that the negative correlations could be an artifact caused by global signal regression performed during data preprocessing, which causes the distribution of correlations with a seed signal to have a zero mean and thus forces negative correlations to exist between networks [3,4]. Although negative correlations between the DMN and TPN have been shown to exist without global signal regression [2,5], the results are not as pronounced as those obtained with global signal regression. In this study, we consider the use of an alternative estimate of the global signal that utilizes a random sample of voxels chosen to be outside the regions of interest (e.g. DMN and TPN) that are used to compute the correlation. Because this estimate does not include voxels within the regions of interest, its use does not force negative correlations to exist. In addition, by randomly selecting a small sample of voxels, we aim to minimize the effects of voxels that are functionally correlated with those in the regions of interest.

METHODS: We used a resting-state dataset (BS002; 4 fixation runs from 17 normal right-handed young-adults) originally analyzed by Fox et al. [3] and downloaded from www.brainscape.org. Image preprocessing steps included slice timing correction, head-motion correction, spatial normalization to Talairach space, and spatial smoothing (FWHM = 6mm). The resultant data were low-pass (<0.1Hz) filtered and nuisance terms were regressed out, including constant and linear trends, head-motion parameters and an optional global signal term. Spherical seed regions of interest (ROIs) with a radius of 9mm were defined based on Talairach coordinates for the Posterior Cingulate Cortex, (PCC, [-4,-50,38]) in the DMN and the left medial temporal region (MT+: [-46,-64,0]) in the TPN. Correlations between these regions were then computed under three different conditions: (1) no global signal regression ('no-gs'); (2) regression with a whole brain global mean signal ('whole-gs'); and (3) regression with a randomized global signal ('rand-gs'). The 'rand-gs' signal was calculated as the mean signal from a sample of voxels randomly selected from all brain voxels outside of the ROIs, which were first dilated by 3 voxels in each direction to exclude neighboring voxels. Prior to averaging (for both 'whole-gs' and 'rand-gs'), the voxel signals were demeaned and normalized by their standard deviation. The sample size normalized by the number of available voxels was denoted as the fraction *f*. We also computed whole brain correlation maps with the PCC seed region for each of the three conditions. The brain was first partitioned into cubic grids (10×10×10 voxels), and the 'rand-gs' signal for each grid was then calculated from a sample fraction *f* of those voxels outside of the dilated PCC ROI and respective dilated grid region.

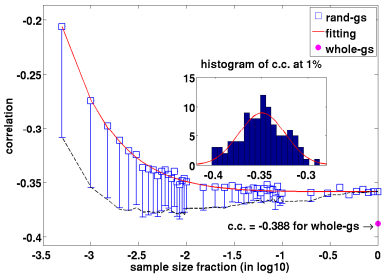

Fig. 1. Correlation values vs. sample size fraction. Error bars represent the standard deviation of all iterations at each *f*.

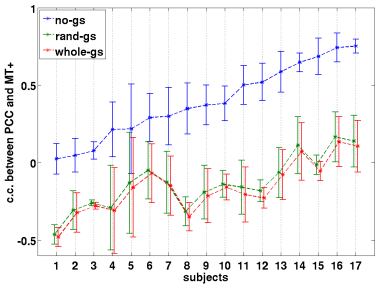

Fig. 2. Correlation between ROIs across the 3 global signal conditions. Error bars show the standard deviation of 4 runs for each subject.

RESULTS: Fig. 1 shows the correlation between the PCC and MT+ in one subject using the 'rand-gs' method, where the fraction of voxels used in global signal estimation was varied from 0.0005 to 1.0 (i.e. -3.3 to 0.0 in log10), and iterations of the random sampling at each fraction value were performed to estimate the mean and standard deviation. As compared to the positive correlation values obtained without global regression (cc = 0.309 for the 'no-gs' case), the 'rand-gs' correlation values are negative even for small fraction values on the order of 0.001 (i.e. about 0.1%). As the fraction increases, the correlation values follow a exponentially truncated power law (red curve), and tend to converge to a stable correlation value around $f = 0.01$ (i.e. $\log_{10} f = -2$). The correlation value of cc = -0.388 obtained with the 'whole-gs' method was lower than the mean correlation values obtained with the 'rand-gs' approach. A histogram of correlation values obtained with 100 iterations of the 'rand-gs' method at $f = 0.01$ roughly follows a Gaussian distribution (Fig. 1).

The correlation between the PCC and left MT+ is shown for each subject in Fig. 2. Negative correlations are found in most subjects using the 'rand-gs' (with $f = 0.01$) and 'whole-gs' methods, whereas they are only present in a few cases with the 'no-gs' method. The mean difference in correlation between the 'whole-gs' and 'rand-gs' methods is 0.03±0.01. This difference can be shown to be proportional to m/N (~ 10^{-2} in this case), where m is the number of voxels in the seed ROIs and N is the number of voxels in the whole brain.

The whole brain correlation maps are shown in Fig. 3 for the same subject in Fig.1. The anti-correlated networks (DMN red/yellow; TPN blue/green) are not obvious for the 'no-gs' case (top panel), but are apparent in the 'rand-gs' ($f = 0.01$, bottom panel) and 'whole-gs' (middle panel) cases. The later two look similar because their difference is proportional to m/N (~ 10^{-2} in this case).

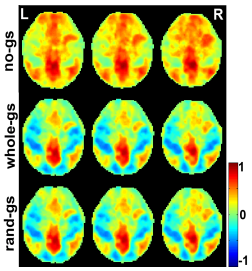

Fig. 3. Correlation Maps with seed ROI at PCC.

DISCUSSION: One of the motivations behind our randomized sampling approach was to "average" out the contributions to the global signal from voxels (outside of the seed ROIs) that were correlated with voxels in the seed region. The fact that negative correlations are found even when using only 0.1% of these voxels suggests that the anti-correlations between the DMN and TPN do not simply reflect the mathematical constraints described by [4]. Instead our findings are consistent with those of [3], which found that anti-correlations persisted even when removing voxels that were highly correlated or anti-correlated with MT+ from computation of the global signal. We were surprised to find that using just 1% (f=0.01) of the available voxels provided estimates similar to those obtained with all of the available voxels ($f = 1.0$). This finding indicates a widespread and fairly uniform distribution of a global signal component. We also found that the difference between the 'rand-gs' and 'whole-gs' correlation estimates was small (on the order of m/N), which supports the general validity of prior studies that used the 'whole-gs' method with small seed regions. The proposed 'rand-gs' method does not impose mathematical constraints on the computed correlation values, and should therefore be generally applicable for computing correlation maps for resting-state fMRI studies, while avoiding the concerns raised in [4].

REFERENCES: [1] Fox et al., PNAS, 102:9673-9678, 2005. [2] Chang et al., Neuroimage 47:1448-1459, 2009. [3] Fox et al., J Neurophysiol 101:3270-3283, 2009. [4] Murphy et al., Neuroimage 44: 893-905, 2009. [5] Uddin et al., Hum Brain Mapp 30:625-637, 2009.