

A geometric view of global signal confounds in resting-state fMRI

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Introduction One of the primary measures of resting-state functional connectivity is the correlation between the blood oxygenation level dependent (BOLD) time series observed in different brain regions. The computation of the correlation is often dominated by the presence of a strong global component that can introduce significant variability across functional connectivity maps acquired from different scans or subjects. A variety of global signal correction methods have been proposed, but there is currently a lack of a clear consensus on the best approach to use, and some approaches, such as global signal regression (GSR), may produce significant negative bias in the correlation values [1,2]. Here we introduce a framework for visualizing the signal structure of resting-state fMRI data and demonstrate that a portion of the global signal can be viewed as an additive confound. An approach for minimizing the contribution of this additive confound is presented and compared with existing global signal correction methods.

Theory

It is useful to approximate the resting-state fMRI data as vectors in a 3d space by performing a principal component analysis (PCA) of the data and using the top three components to define the coordinate system [3]. The top row of Figure 1 shows the distribution of the resting-state vectors from three separate 7 minute scans, where the color denotes the number of vectors in each sector. The bottom row shows the correlation maps (with a seed voxel in the posterior cingulate cortex) corresponding to each of the scans. As the vectors become more tightly clustered around the vertical axis, their angular spread decreases and the correlation maps become more homogeneous.

A useful metric for characterizing the spread of the resting-state vectors is the median angle between the vectors and the first principal component (which is essentially the global mean). The median angles are 62, 49, and 30 degrees for Figs. 1a-1c, respectively. As a simple geometric model to explain the difference in median angle between scans, we consider a collection of resting-state vectors that are of the same magnitude and equally distributed around a global mean vector (red arrow) at an angle of 60 degrees (Fig 2 top row). An overall increase in the correlation of the time series vectors can be modeled as a decrease in the angles between the vectors and the global mean vector (from 60 degrees to 30 degrees), causing the global signal vector to grow even though the lengths of the individual vectors do not change. On the other hand, the angular spread of the vectors can also be modified through the addition of a global signal confound, shown as the green arrow in the bottom row of Fig. 2. This additive global signal confound will have three effects: (1) an increase in the global signal vector (sum of the red and green arrows); (2) an increase in the lengths of the individual vectors; and (3) a reduction in the angle between the individual vectors and the global signal (from 60 degrees to 42 degrees), with a corresponding increase in the correlation between the vectors.

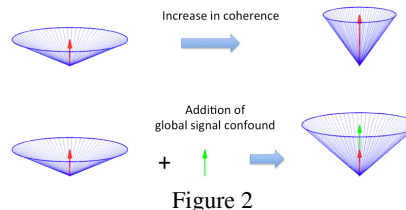


Figure 2

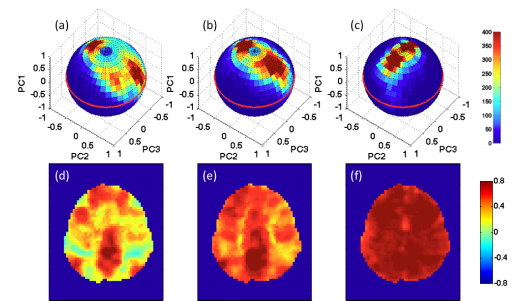


Figure 1

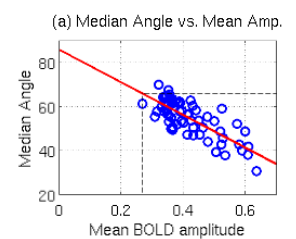


Figure 3

Results and Discussion

We can differentiate between the two scenarios in Fig. 2 by examining the relation (see Fig. 3) between the median angle and the mean BOLD amplitude (i.e. average length of the vectors) for the 68 resting-state scans from [4]. The mean BOLD amplitude increases as the median angle decreases, supporting the presence of an additive confound. Note that in the absence of an additive confound, the mean BOLD amplitude would ideally be independent of the median angle. As the scans with larger median angles and smaller mean BOLD amplitudes will have smaller additive confounds, we can use these scans to define a target median angle (indicated by the dotted line in Fig 3). To reduce the effects of additive confounds in the other scans, we increase their median angles to match that of the target. Functional connectivity maps (seed region in posterior cingulate cortex) obtained with this “median angle shift” method are shown in the bottom row of Fig. 4. For comparison, maps prior to correction (top row) and with various correction methods (white matter and CSF regression, post-hoc centering, and GSR [4,5]) are also shown. The proposed method reduces the variability due to the global signal confound while producing less negative bias than the GSR approach and outperforming the WM+CSF and post-hoc centering methods. **References:** [1] Fox et al, J. Nphys, 101:3270, 2009 [2] Murphy et al, NIMG 44:893, 2009. [3] He & Liu, ISMRM 2011, p.1607. [4] Fox et al, Neuron 103:10046 2006. [5] Van Dijk et al, J. Nphys. 103:297, 2010. [6] Lowe et al., NIMG 7:119, 1998.

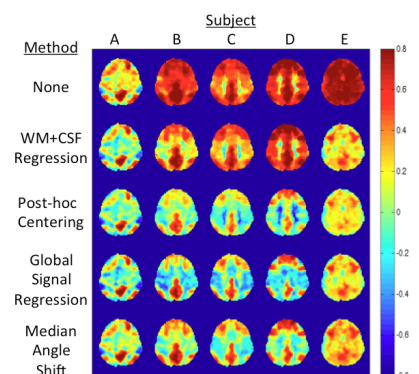


Figure 4