A new model-based intrinsic connectivity measure: global functional connectivity

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Target Audience/Purpose: functional connectivity researchers. To introduce an improved intrinsic connectivity measure.

Introduction:

BOLD resting-state functional connectivity (RS-fMRI) is a popular technique[1-4] but suffers from methodological difficulties, such as requiring functional localization of various regions of interest (ROIs). The seeded RS-fMRI method involves fMRI-localization to define a seed region, the creation of whole-brain map of Pearson linear correlation coefficients, conversion of correlation to t-score, followed by normalization of the null portion of the connectivity t-score distribution[1-2]. Intrinsic connectivity[3] measures attempt to avoid the localization requirement by taking some variant of total brain connectivity at each voxel. Initial work focused on the average thresholded correlation of each voxel to all others, but this is not robust. Recent work by Scheinost et al introduced a model-based measure, intrinsic connectivity distribution (ICD)[4], or the integrated correlation distribution at each voxel over some threshold. This has advantage over past methods as it is less coupled to subtle bias in the distribution.

We have developed a novel method similar to ICD, which is also based on the distribution at each voxel but which is simpler, more intuitive and more robust than ICD, and is based on a method we first proposed many years ago to correct for global signal effects[2] . At each voxel, the correlations are first converted to t-scores, then this distribution is fitted to a Gaussian within the FWHM range, and the resulting percent difference between data and fitted distribution > 2.5 sigma plus mean is taken as the positive global functional connectivity, which we call gfc.. The same is done for negative gfc < mean minus 2.5 sigma threshold. Assuming the data distribution is a true null (not true, but reasonable and widely used) in the FWHM region, the difference between the area under the observed distribution and the fitted normal is the net area under the tail of the distribution and can be taken as a measure of connectedness of that voxel to other brian regions.. Intrinsic connectivity is not meaningful unless the underlying method is robust and meaningful. Thus, this development is highly significant for intrinsic connectivity.

Fig 1: The data (blue) is fitted within the FWHM to a Gaussian (red), pos/neg excess is the difference b/w data and fitted (orange).

Methods:

RS-fMRI scans were acquired in 6 low-motion subjects using a bite-bar at 3 Tesla, corrected for volumetric motion, physiologic noise and spatially filtered to 4mm FWHM. The BOLD scan was modified to acquire physiologic signals and the unsaturated volumes. The first four unsaturated volumes were used to obtain a map of CSF matched to the EPI scan. A T1 MPRAGE was also acquired, segmented to gray matter (GM) and aligned to EPI. The EPI-CSF mask and the aligned gray mask were combined to produce a highly accurate GM EPI mask. For each GM voxel, the timeseries was low-pass temporal filtered to 0.1Hz and a GM map of Student's t to this voxel was generated. The t distribution was fitted to a Gaussian within the FWHM region in MATLAB to obtain the null mean and sigma of the data distribution[2]. A fitted histogram for the same bins was generated and subtracted from the data histogram, then divided by the sum total of the fitted bins (fitted histogram was normalized within FWHM region). The sum of the resulting bins greater than 2.5 sigma plus mean was stored as the positive gfc, and the same done for the negative gfc. The mean square error (MSE) was inspected, and no voxel contained more than 2x the MSE averaged over the volume, indicating good fit to the data at all voxels (found to be a critical step in past work, as some data do not behave as well due to noise).
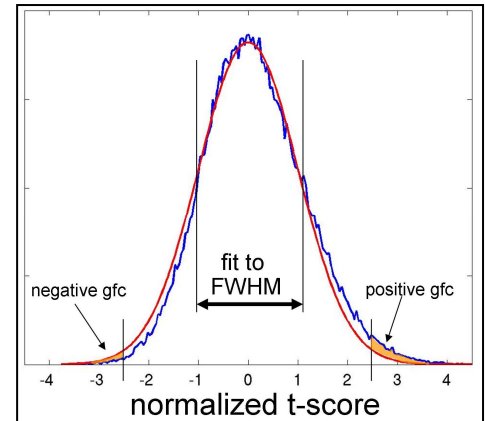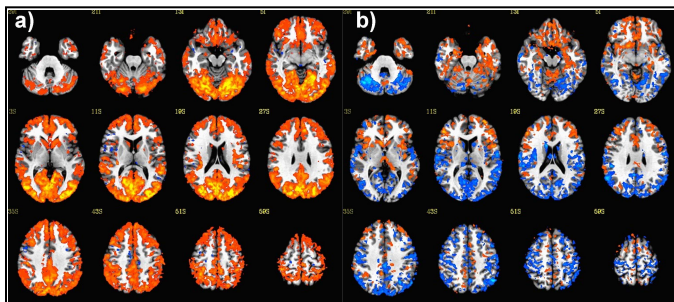

Fig 2 averaged a) positive, b) negative gfc maps in Talairach space. Threshold adjusted for visual display.

Results:

Fig 1 shows the fitting process, indicating the FWHM region the fit is restricted to and the excess connectivity at each tail. Fig 2 shows the positive and negative gfc averaged over the 6 subjects. The polarity of the excess shown is as defined, thus a negative-valued (blue) excess means there are less voxels connected than would be theoretically predicted by an extension of a distribution fitted to the assumed null of the data.

Conclusions:

The gfc images imply a large portion of the gray matter is well-connected at rest to other brain regions, but a few regions stood out, including premotor and insula. Future work will focus on comparison with other intrinsic connectivity measures, improvements to the GM map (partial thalamus was lost in some subjects), modulation of gfc with continuous tasks and dynamic gfc.

References: 1) Biswal, B et al MRM 34 (1995), 537-541. 2) Lowe, MJ et al, NeuroImage 7 (1998) 119-132. 3) Cole M et al, NeuroImage 49 (2010) 3132-3148. 4) Scheinost, D et al, NeuroImage 62 (2012) 1510-1519.