Functional Connectivity Measured With Mutual Information at 7 Tesla

A. T. Newton[1], J. C. Gore[1,2], B. P. Rogers[2], C. J. Gatenby[2], and V. L. Morgan[2]

[1]Biomedical Engineering, Vanderbilt University, Nashville, TN, United States, [2]Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States

Introduction: Measures of functional connectivity describe the degree to which brain regions are coupled for the performance of a functional task, and have been shown to correlate with other measures such as the ability to perform a task. [1] A variety of mathematical approaches have been used to measure functional connectivity in fMRI data, and a common method is linear cross correlation of the time series imaging data between brain regions, which reduces to calculation of a simple correlation coefficient. This measure has been shown to provide valuable information, though it has a variety of limitations that have been previously reported. [2] One specific disadvantage is its assumption of the linear relationship between signals, while evidence suggests that connectivity measures may vary nonlinearly [3]. Here, we performed a within subject reproducibility study (N=5), hypothesizing that mutual information ('I') between fMRI time courses is a better marker of functional connectivity due to its sensitivity to nonlinear relationships between signals, and its insensitivity to phase lags compared to 0th order cross correlations ('r'). Furthermore, we aimed to show preliminary evidence that performing these functional connectivity measurements at ultra high field (7T) would take advantage of the predicted benefits of BOLD based imaging at such fields, including the potential of higher spatial resolution and increased $T2^*$ contrast.

Methods: (*Image acquisition*) All data were acquired on a Philips Achieva 7T human scanner with a T/R volume head coil. High resolution (0.75x0.75x2mm voxels), T1-weighted images were acquired for reference. All functional data were acquired using a two shot, gradient echo EPI sequence, with TE=25ms. Just prior to resting state data acquisition, images were acquired while the subject performed a block designed finger tapping task, (FOV=192mm,1.5x1.5x2mm voxels, 14 slices, acquisition time=2000ms/vol.) consisting of left handed finger tapping (20s), right handed finger tapping(20s), and a resting condition (20s), repeated three times. The analysis of those images was used to select slices to be acquired in the resting state as well as to identify regions of interest (ROIs) for analysis of the resting state data. Finally, five resting state data sets were acquired (1024 volumes, two slices/volume,1.5x1.5x2mm voxels, FOV=192mm, total acquisition time=350ms/vol.) whose slices corresponded to two of the slices from the block design experiment including the primary motor cortex. (*Analysis*) Three ROIs were identified using activation maps generated with SPM5 [5]: (region #1) a seed ROI, shown as cyan in Figure 1, (#2) all active voxels (active during right and/or left handed tapping) not included in the seed ROI, shown as blue in Figure 1, and (#3) all other voxels in the brain, shown as gray in Figure 1. The seed ROI was drawn over primary motor cortex on the left side of the brain, and all voxels within that region that were not significantly activated during right hand finger tapping were discarded (p=0.01, minimum cluster size=5 voxels). The average time course from the seed region, as well as each voxel's individual time course, was low pass filtered at 0.1Hz, and linearly detrended. Correlation coefficient maps and mutual information maps were calculated in the resting state data, comparing each voxel's time course and the average time course in the seed region. Correlations were calculated via the standard Pearson's correlation coefficient estimate, and mutual information was calculated via histogram approximation as described by [4]. Because mutual information by definition cannot be negative, the absolute value of all correlation measures was taken. Contrast to noise between region #2 and region #3 was calculated for both the correlation coefficient maps and the mutual information maps, defined as shown in equation 1 (right).

$$\text{CNR} = {[\text{mean(roi\#2)} - \text{mean(roi\#3)}]}\big/{\text{var(roi\#3)}} \qquad (1)$$

Results: For all resting state data sets, contrast to noise between region #2 and region #3 was higher when using mutual information than when using linear correlation coefficients (top right, Figure 1). A paired t-test showed that the mean CNR between region #2 and region #3 was significantly different for the two measures (alpha=0.05).

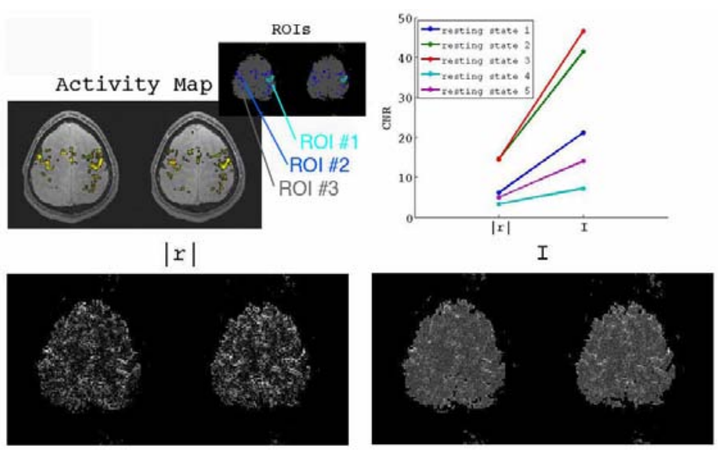

Figure 1 – (top left quarter) Combined activation map for left and right handed finger tapping , and ROIs drawn based on that activity. *cyan:* ROI#1, the seed roi; *blue:* ROI #2, voxels activated during right and/or left handed finger tapping not including voxels in ROI #1; *gray:* ROI #3, voxels within the brain not significantly active during finger tapping. (top right quarter) CNRs comparing ROI #2 to ROI#3 for each resting state data set. (bottom half) An example map of |r| and I values. Resting state data set #1 was chosen as the example.

Conclusions: These data suggest that mutual information may be a more specific and sensitive measure of functional connectivity in the motor system than traditional correlation coefficients. Furthermore, because there are no negative measures of mutual information, interpretation of the results may be simplified as well. The success of mutual information analysis is contingent on acquiring an adequate number of images for accurate estimation of mutual information via histogram approximation, and measurements made with fewer images may require a different estimation scheme. Finally, these results also show that future studies of functional connectivity, regardless of its measure, are possible at ultra high fields, and may benefit from improvements in spatial resolution.

References

1. Hampson, M., et al., Neuroimage, 2006. **31**(2): p. 513-9.
2. Sun, F.T., L.M. Miller, and M. D'Esposito, Neuroimage, 2004. **21**(2): p. 647-58.
3. Friston, K.J., et al., Neuroimage, 1997. **6**(3): p. 218-29.
4. Pereda, E., R.Q. Quiroga, and J. Bhattacharya, Prog Neurobiol, 2005. **77**(1-2): p. 1-37.
5. http://www.fil.ion.ucl.ac.uk/spm/software/spm5/

Acknowledgements: funding by: R01 EB00461