Global ROI-based Functional Connectivity MRI (fcMRI) Analysis for Classification of Alzheimer's Disease

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Introduction. In contrast to the traditional approach of examining functional connectivity for a few, prespecified, ROIs, we performed a global functional connectivity analysis; we considered all ROI pairs from a large ensemble of anatomically predefined ROIs to determine classification of Alzheimer's disease using resting-state data.

Methods. <u>Sample Size:</u> Twenty normal healthy (Control) and 20 Alzheimer's disease (AD) study subjects.
<u>Preprocessing:</u> The high-resolution anatomical image for each study subject was transformed and aligned with a reference template containing 116 anatomically defined ROIs. Each ROI was then mapped back to the lower-resolution functional imaging data. The average time course within each ROI ($y_i(t)$, i = 1,…,116) was extracted from the functional imaging data. In addition, the average time courses within white matter voxels (wm(t)) and within CSF voxels (csf(t)) were calculated for use as "nuisance" regressors. The 6 dof estimated motion parameters, white matter and CSF time courses (mp(t), wm(t), csf(t)), along with their temporal derivatives, were used as nuisance regressors in a multiple linear regression model for removing unwanted signal disturbances. A 0.015-to-0.1 Hz Fourier bandpass filter was then applied to the detrended data.
<u>Cross-correlation Analysis:</u> Functional connectivity between ROI pairs was assessed by calculating the Pearson product-moment correlation coefficient. That is, for each pair of ROI's i and j, the corresponding detrended and filtered time series $z_i(t)$ and $z_j(t)$ were used to calculate the correlation coefficient r_{ij}:
(1) $\quad r_{ij} = \Sigma_t[(z_i(t)-m_i)(z_j(t)-m_j)] / [\Sigma_t(z_i(t)-m_i)^2 \Sigma_t(z_j(t)-m_j)^2]^{1/2}$, where $m_i = \text{mean}(z_i(t))$, $m_j = \text{mean}(z_j(t))$.
<u>Group Analysis:</u> For each element of the CC matrix; i.e., for each pair of ROIs (i,j), a statistical test was performed to compare the two groups of corresponding correlation coefficients; i.e., AD vs. Control study subjects. The nonparametric two-sample Wilcoxon rank-sum test was used for statistical comparison of the correlation coefficients of the two groups of study subjects. The statistical output of the Wilcoxon rank-sum test, for each ROI pair, was converted to z-values to facilitate comparison across experiments. This matrix of z-values from the Wilcoxon rank-sum test will be referred to as the "W-matrix".
<u>Functional Connectivity Networks:</u> The W-matrix was then used to discriminate between AD and Control study subjects. For the set of 116 ROIs, there are 6670 distinct elements of the W-matrix. The histogram of these W-matrix z-values was used to select two subsets of ROI pairs: one subset containing ROI pairs for which the AD study subjects show significantly higher CCs than the Control study subjects as indicated by the Wilcoxon rank-sum test (subsequently referred to as the "Red Network"), and a second subset containing ROI pairs for which the AD study subjects show significantly lower CCs than the Control study subjects (hereafter, "Blue Network"). That is,
(2) $\quad$ Red Network $\equiv$ { (i,j) │ W-matrix (i,j) > UL }, and Blue Network $\equiv$ { (i,j)│ W-matrix (i,j) < LL } where the threshold limits are labeled UL (upper limit) and LL (lower limit).
<u>Network-based Functional Connectivity Indices:</u> Once the Red and Blue Networks were defined, the Red and Blue Network Functional Connectivity Indices, RNFCI and BNFCI, respectively, for study subject s, were calculated as follows:
(3) $\quad$ RNFCI(s) $\equiv \Sigma \Sigma$ CC(s)(i,j) / #(Red Network), and BNFCI(s) $\equiv \Sigma \Sigma$ CC(s)(i,j) / #(Blue Network) where the double summation is over all pairs (i,j), i < j, with (i,j) $\in$ Red (or Blue) Network, and CC(s)(i,j) is the ROI-based correlation coefficient for study subject s, for ROI pair (i,j). Also, "#(…)" refers to the total number of links between nodes (ROIs) of the network.
<u>Classification Method:</u> By calculating the RNFCI and BNFCI indices for each study subject, we were able to reduce the 6670 CC values per study subject to a more manageable 2 values per study subject. The Fisher Linear Discriminant Function was then calculated from the (RNFCI, BNFCI) pairs for the 2 groups; this provided optimal classification of unknown study subjects into the Control and AD groups. This classification method was evaluated by estimating the classification error rate using the unbiased "leave-one-out" (LOO) method.

Results and Discussion. The graph of the thresholded CC matrix for a single study subject is illustrated in Fig. 1. Large positive (or negative) values for the CC indicate functional connectivity between the corresponding pairs of ROIs. The CC matrix was calculated for each study subject. The AD and Control groups were compared using W-matrix calculations. The Red and Blue functional connectivity networks, for group comparison of AD and Control study subjects, are illustrated in Fig. 2. The thresholded W-matrix appears in the lower-right corner of Fig. 2, where we have set LL = -1.28 and UL = 2.42, corresponding to the fifth and 95th percentiles of W-matrix z-values, respectively. Red elements indicate AD CC > Control CC, whereas blue elements indicate AD CC < Control CC. Each red or blue dot corresponds to an ROI pair; the spatial links between these ROI pairs are illustrated in the Sagittal, Coronal, and Axial Views by red and blue line segments, respectively. Plotted in Fig. 3 are values for 20 Control study subjects (blue squares) and 20 AD study subjects (red squares). For automatic discrimination and classification of study subjects, the Fisher Linear Discriminant function was calculated. The linear discriminant is also plotted in Fig. 3, along with the estimated 50% and 90% probability containment ellipses for the Control and AD populations. Note that all of the Control study subjects are located above the linear boundary, and all but one of the AD study subjects are located below the linear boundary. The accuracy of the classification algorithm was evaluated using the LOO method. The results are summarized by the ROC curve, illustrated in Fig. 4. The ROC curve shows the tradeoff between sensitivity and specificity. One commonly used metric for evaluating the accuracy of a classifier is the area under the ROC curve (AUC). For the data presented in Fig. 4, the AUC is 0.88, with a standard error of 0.056 (based on 20 AD and 20 Control study subjects).

Conclusions. The global ROI-based resting-state fcMRI analysis allows discrimination between AD and Control populations with high sensitivity and specificity.
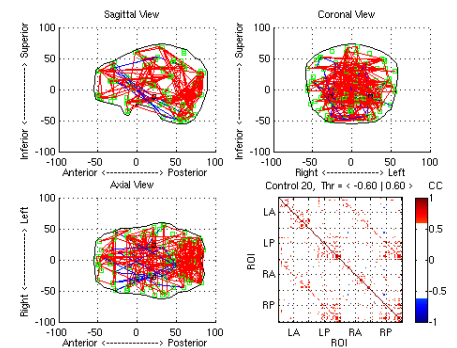
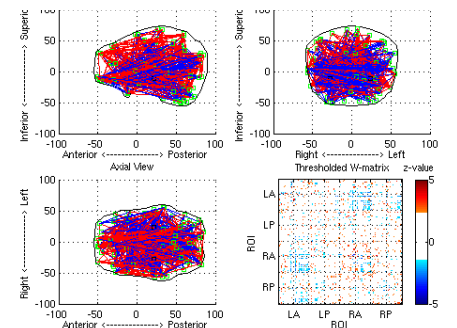**Figure 1**. Graph of CC matrix (single subject)

Figure 2. "Red" and "Blue" functional connectivity networks. (5th and 95th percentiles)
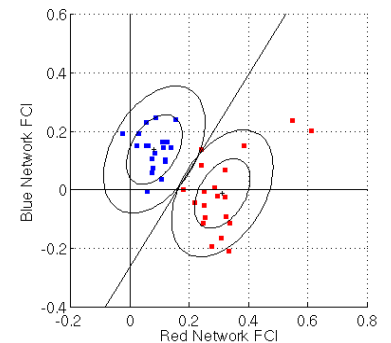

Figure 3. Plot of (RNFCI, BNFCI) pairs for AD (red) and Control (blue) subjects.
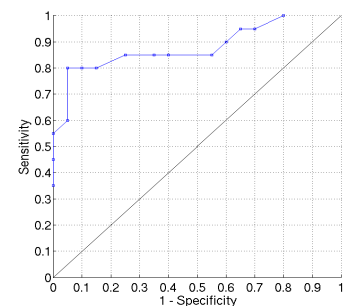

Figure 4. ROC curve for AD vs. Control discrimination algorithm performance.