Detection of Changes in Functional Connectivity MRI (fcMRI) following Aricept® Treatment in Subjects with Mild Alzheimer's Disease

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Introduction: A method for global ROI-based functional connectivity MRI (fcMRI) discrimination of Alzheimer's (AD) vs. normal healthy (control) study subjects was applied to observe changes in functional connectivity for mild AD study subjects following 3 months of Aricept® administration.

Methods: Sample size: Fourteen mild AD study subjects (MMSE 23-27) (study subject no. 12 was excluded because of excessive head motion)

Preprocessing: The high-resolution anatomical image for each study subject was transformed and aligned with a reference template; it contained 116 anatomically defined ROIs. Each ROI was 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 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.

Cross-correlation Analysis: Functional connectivity between pairs of ROIs 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) $r_{ij} = \Sigma_t[(z_i(t)-m_i)(z_j(t)-m_j)] / [\Sigma_t(z_i(t)-m_i)^2 \Sigma_t(z_j(t)-m_j)^2]^{1/2}$, where m_i = mean($z_i(t)$), m_j = mean($z_j(t)$).

Functional Connectivity Networks: In a separate study, ROI pair networks were identified to discriminate between AD and Control study subjects using the fcMRI data. The "Red Network" contains ROI pairs wherein the AD study subjects show significantly higher CCs than the Control study subjects; the "Blue Network" contains ROI pairs for which the AD study subjects show significantly lower CCs than the Control study subjects

Network-based Functional Connectivity Indices: Using the previously defined Red and Blue Networks, the Red and Blue Network Functional Connectivity Indices, RNFCI and BNFCI, respectively, for study subject *s*, were calculated:

(2) 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.

Comparison Method: From a separate study, the Fisher Linear Discriminant function was calculated from the (RNFCI, BNFCI) pairs for each study subject, to provide optimal classification of unknown study subjects into Control and AD groups. The *same* linear discriminant was used to evaluate changes in functional connectivity for the current study, to compare AD study subjects pre-Aricept® vs. post-Aricept® . A paired *t*-test was used to test changes in distance relative to the linear discriminate boundary.

Results and Discussion: The ROI-based correlation coefficient (CC) matrix for a single study subject is illustrated in Fig.1 (pre-Aricept®) and Fig.2 (post-Aricept®). These two CC matrices were calculated for each study subject. The Red and Blue functional connectivity networks, for discrimination of AD and Control study subjects, are illustrated in Fig. 3. 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. 4 are (RNFCI, BNFCI) pairs for 13 AD study subjects pre-Aricept® (red squares) and post-Aricept® (blue squares). The Fisher Linear Discriminant Function, as previously calculated for automatic discrimination of AD and Control study subjects, is also plotted in Fig. 4, along with the estimated 50% and 90% probability containment ellipses for the Control and AD populations. The (signed) distances of each study subject relative to the linear discriminant, pre- and post-Aricept®, are listed in Table 1. A paired *t*-test of the change in distance (df=12, *t*-stat=2.90, *p*-value=0.013) indicates a statistically significant change in functional connectivity (post- vs. pre-Aricept®).

Conclusions: Using the previously developed method for global ROI-based functional connectivity MRI (fcMRI) discrimination of AD vs. Control study subjects, there was a statistically significant change in functional connectivity for AD study subjects following 3 months of Aricept® administration.

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Table 1. Distance from Fisher Linear Discriminant

subject	Pre-Aricept®	Post-Aricept®	Delta
1	-0.074	0.069	0.143
2	-0.130	-0.014	0.116
3	-0.115	-0.133	-0.018
4	-0.209	-0.143	0.066
5	-0.106	-0.103	0.003
6	-0.200	-0.156	0.043
7	-0.210	-0.148	0.061
8	-0.028	0.040	0.068
9	-0.227	-0.237	-0.009
10	-0.050	0.043	0.093
11	-0.008	-0.041	-0.033
12	-	-	-
13	0.007	0.073	0.066
14	0.063	0.045	-0.018
Mean	-0.099	-0.054	0.045

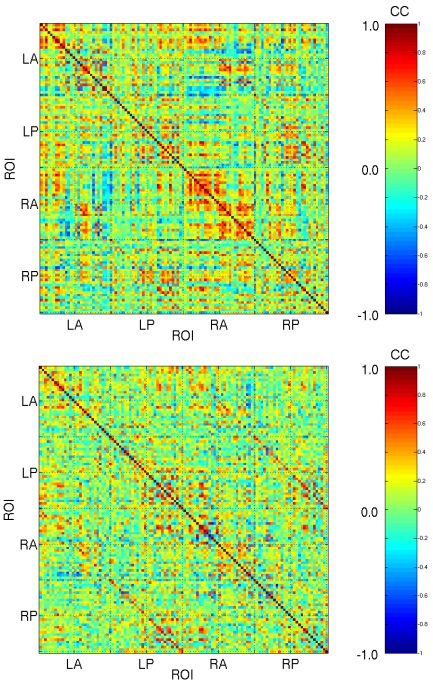

Figure 2. CC matrix, post-Aricept

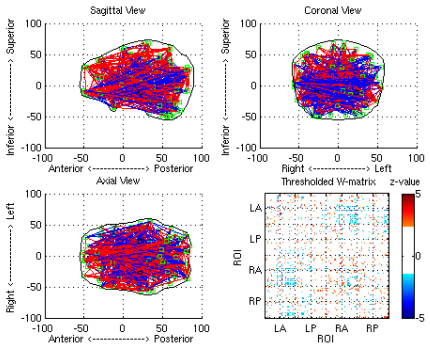

Figure 3. "Red" and "Blue" functional connectivity networks. (5th and 95th percentiles)

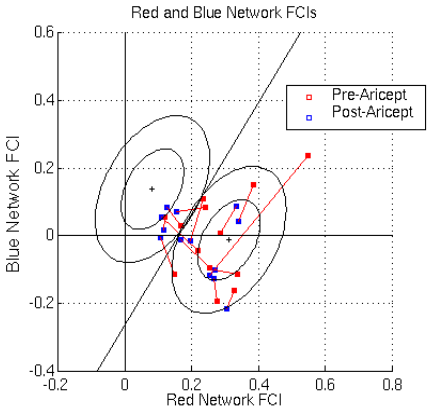

Fig. 4. FCI values for pre-Aricept (red) and post-Aricept (blue) study subjects.