Different Stages in Alzheimer's Disease Target Different Large-Scale Networks, Assessed by Resting-State Functional Connectivity

G. Chen[1], B. D. Ward[1], C. Xie[1], W. Li[1], G. Chen[1], J. L. Jones[2], M. Franczak[2], P. Antuono[2], and S-J. Li[1,3]
[1]Department of Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, United States, [3]Department of Psychiatry and Behavioral Medicine, Medical College of Wisconsin, Milwaukee, WI, United States

Introduction: It has been demonstrated that Alzheimer's disease (AD) targets the brain's specific large-scale networks (LSN). However, it is not known if AD, in different disease phases, targets different brain networks during disease progression. To address this question, the LSN analysis method (1) was employed to identify the LSNs in the whole brain targeted by either the dementia phase or prodromal phase of the disease.

Materials and Methods: Subjects and imaging acquisition. Twenty mild AD, 15 amnestic mild cognitive impaired (aMCI) and 20 cognitively normal (CN) subjects were included in the study. The study was conducted with Medical College of Wisconsin Institutional Review Board approval. Written informed consent was obtained from each participant. The detailed inclusion and exclusion criteria for the three subject groups have been described previously (2). Imaging was performed using a whole-body 3T Signa GE scanner. Sagittal resting-state functional MRI (fMRI) datasets of the whole brain were obtained in six minutes with a single-shot gradient echo-planar imaging pulse sequence. The fMRI imaging parameters were: TE of 25 ms, TR of 2 s, flip angle of 90º, 36 slices were obtained without gap, slice thickness was 4 mm with a matrix size of 64×64 and field of view of 24×24 cm. High-resolution SPGR 3D axial images were acquired for anatomical reference. The parameters were: TE/TR/TI of 4/10/450 ms, 12º flip angle, 144 slices, 1-mm slice thickness and a matrix size of 256×192.

Functional connectivity measurement. A series of preprocessing steps common to most fMRI analyses was conducted, using the Analysis of Functional NeuroImages (AFNI) software. The preprocessing includes allowing for T1-equilibration effects; slice-acquisition-dependent time shifts correction; despiking; motion correction; detrending; removal of cardiac, respiratory, white matter, CSF and global signal effects; and low-frequency band-pass filtering, as previously described in detail (1). Each subject's functional image was automatically parcellated into 116 regions (1,3). The functional connectivity between any of the 26 cerebellum regions and the 116 whole-brain regions was assessed by the Pearson product-moment correlation coefficient (r). The r values were age corrected (1).

Identify LSNs targeted by different disease phases. The LSN analysis method (1) was employed to identify LSNs targeted by different disease phases. In the LSN analysis, the nonparametric, two-sample Wilcoxon rank-sum test was employed in the between-group analysis. The Wilcoxon rank-sum test produced one z-value for each pair of ROIs. The absolute z-value indicates the statistical significance of the r value group difference, while the sign of the z-value indicates which group has the higher mean r value. A number of connections with the largest negative z-values were defined as the decreased connection set. The averaged r value in this set for each subject was obtained as the Decreased Connectivity Index (DCI). Similarly, a number of connections with the largest positive z-values were defined as the increased connection set, and the averaged r value in the increased connection set was obtained as the Increased Connectivity Index (ICI). Fisher's linear discriminant analysis was performed with the DCI and ICI to differentiate a subject as a group member, using the MatLab (Mathworks, Natick, MA) function, "classify." The Leave-One-Out (LOO) error estimate method, the receiver operation characteristics (ROC) curves and the area under the curve (AUC) were used to evaluate the accuracy of the classifier. The LOO error estimate uses one subject at a time to evaluate the classifier; the remaining subjects are used to train the classifier. This entire process is repeated for each subject. Optimized differentiation criteria were empirically determined, because the decreased and increased connections that could differentiate two groups were not known a priori, and their corresponding DCI and ICI values could affect the differentiation. The combination of decreased and increased connections that yielded the highest AUC was chosen, and the decreased and increased connections that repeated in every LOO step were selected to determine each subject's DCI and ICI. Finally, regression analysis was performed between the connectivity index values and behavioral scores. The cerebellum (CB) is suggested to be affected last by AD pathology. Therefore, the functional connectivity between the CB and the whole-brain regions was examined, testing whether it was targeted by the dementia phase of AD. In contrast, the cerebrum is suggested to be affected early by AD pathology. Therefore, the functional connectivity within the cerebrum regions was examined, testing whether it was targeted by the prodromal phase of AD.

Results and Discussion: Figures 1-3 show the different patterns of altered LSN connectivity in different disease phases. The changes in the network index significantly differentiate subjects in different disease phases and significantly correlate with behavioral scores. These results indicate that during the disease progression different disease phases could target different neural networks and the changes in LSN connectivity patterns are dependent on different phases of AD progression. The identification of the transitional property of LSN indices in different dysfunctional networks can play a significant role in dynamically characterizing AD stages in a temporally ordered manner in the continuum of AD progression.

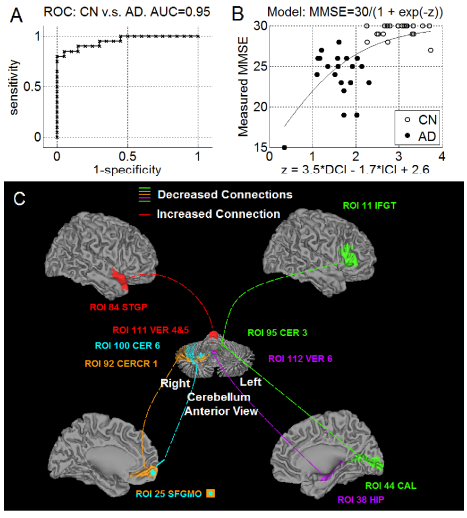

Figure 1. Patterns of altered LSN connectivity between CN and AD subjects. (A) The ROC curve. (B) The relationship between the LSN index and behavioral score. (F=20.09; df=2, 37; P<1.24e-6). (C) Five decreased connections and one increased connection between the cerebellum and cerebrum.

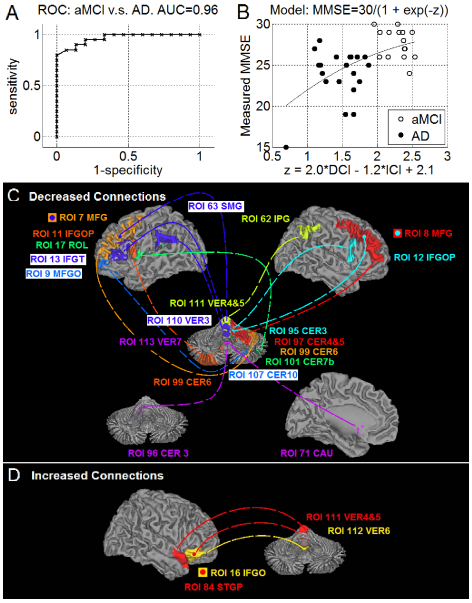

Figure 2 (middle). Patterns of altered LSN connectivity between aMCI and AD subjects. (A) The ROC curve. (B) The relationship between the LSN index and behavioral score. (F=7.97; df=2, 32; P<0.0016). (C) There are 13 decreased connections and three increased connection between the cerebellum and cerebrum.

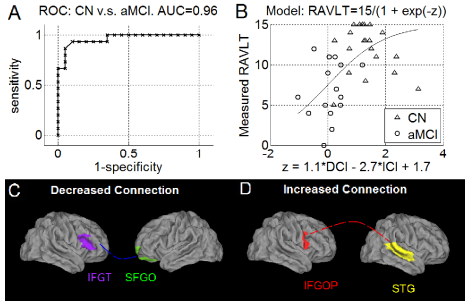

Figure 3. Patterns of altered LSN connectivity between CN and aMCI subjects. (A) The ROC curve. (B) The relationship between the LSN index and behavioral score. (F=5.83; df=2, 32; P<0.0069). (C) One decreased connection and one increased connection within the cerebrum.

References: 1. Chen et al., Radiology in press (2010). 2. Li et al., Radiology 225:253-259 (2002). 3. Tzourio-Mazoyer et al., NeuroImage 15, 273-289 (2002).

Acknowledgements: This work was supported by NIH-NIA R01 grant AD 20279 (SJL) and NIH-NCRR CTSI grant 1-UL1-RR031973. The authors thank Ms. Carrie O'Connor for editorial assistance.