Classification of AD, MCI and Controls Using Large-Scale Network Analysis

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

INTRODUCTION

There has been great interest in developing objective biologically based markers that can be used to predict risk, diagnose, stage, or track the course and treatment of dementia and other neurodegenerative diseases. Alzheimer disease (AD) is the most common form of dementia. Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia, and is often considered a risk factor for AD. In this study, we employed resting-state MRI connectivity methods and the large-scale network analyses to discriminate between AD, MCI and healthy control subjects.

MATERIALS AND METHODS

Resting-state functional connectivity maps (1) were collected from 56 subjects (21 AD, 15 MCI and 20 age-matched controls). These subjects were recruited through the Memory Disorders Clinic at the Medical College of Wisconsin (Milwaukee, Wis.). Informed consent was obtained from all subjects for this Institutional Review Board-approved study. The detailed inclusion and exclusion criteria for the three groups of subjects (AD, MCI and control) have been described previously (2). One of the AD subjects was excluded from the analysis because of incomplete brain coverage.

Imaging was performed using a whole-body 3T Signa GE scanner with a standard transmit receive head coil. An automated shimming protocol was used to improve the field homogeneity and reduce image distortion. During the resting-state acquisitions, no specific cognitive tasks were performed, and the study participants were instructed to close their eyes and relax. Sagittal resting-state functional MRI (fMRI) datasets of the whole brain were obtained in 6 minutes with a single-shot gradient echo-planar imaging (EPI) pulse sequence. The fMRI imaging parameters were: TE of 25 ms, TR of 2 s, flip angle of 90º; 36 slices were obtained; 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, flip angle of 12º, number of slices of 144, slice thickness of 1 mm, matrix size of 256×192.

The high-resolution anatomical image for each subject was transformed and aligned with a reference template containing 116 anatomically defined ROIs (3). Each ROI was then mapped back to the lower resolution resting-state fMRI data. The time course data within each ROI was extracted and voxelwise averaged. Each of the 116 averaged time course data were then detrended and corrected for motion and respiration effects. Possible white matter, cerebrospinal fluid (CSF) and global signal contaminations were removed using linear regression. Finally, a band-pass filter was applied to keep low-frequency fluctuations within the 0.015 Hz and 0.1 Hz frequency range.

Large-scale networks were established as a biomarker to discriminate between AD, MCI and healthy subjects. At first, the functional connectivity of any given paired ROIs was assessed by the Pearson product-moment correlation coefficient (CC) of the time courses of the paired ROIs. As a result, 6670 (116x115/2) pairwised CC values were acquired for each subject. Second, the statistical significance of each pairwised CC value between any two of the three groups was determined. To avoid making any assumption about the distribution of the CC values, the nonparametric two-sample Wilcoxon rank-sum test was employed instead of the parametric tests (such as the *t*-test). The *z*-values from the Wilcoxon rank-sum test were then thresholded to find the ROI pairs, in which one group had significantly stronger or weaker connections than the other group. The union of the stronger ROI pairs was defined as the red network. The average CC values of the stronger ROI pairs in the red network were defined as the red network functional connectivity index (RNFCI). Similarly, the union of the weaker ROI pairs was defined as the blue network and their averaged CC values as the blue network functional connectivity index (BNFCI). The RNFCI and BNFCI then were used as the classifier to discriminate between AD, MCI and control subjects. For cross-validation of the classifier, we further employed the "leave-one-out error estimate" (LOO) method (4). This entire process was repeated for each subject, one at a time, and the error rate was recorded, providing an unbiased error estimate of the classification.

RESULTS AND DISCUSSION

Tables 1-3 show the results of the LOO estimate in a two-by-two analysis. The first row shows the number of subjects within each group classified by clinical assessment as the "golden standard." The second and the third rows show the percentage and the absolute number of the subjects (in parenthesis) that were classified with the RNFCI and BNFCI network method. The last row shows the overall accuracy of the classifier. We used a green font for the true positive and true negative numbers, and a red font for the false positive and false negatives. We employed the large-scale network analysis to discriminate between control, AD and MCI subjects. The latter can be discriminated from controls and ADs with an accuracy of 86% and 80%, respectively. The estimated false positive and negative cases largely may be related to the error of clinical assessment, and the possible discrepancy between clinical assessment and network tests conducted in this study may provide physicians with a reference for better diagnosis. Clearly, further longitudinal study will be needed to validate this method. In summary, this non-invasive network approach not only can distinguish between control, MCI and AD subjects, but also can provide different neural network patterns between different groups, i.e. the red network and the blue network, which will lead us to deeper understanding the mechanisms of dementia.

CON vs. AD	CON (20)	AD (20)
Classified as CON	**90%(18)**	15% (3)
Classified as AD	10% (2)	**85%(17)**
Accuracy	87.5% (35 out of 40)	

Table1. Classify between control and AD subjects.

CON vs. MCI	CON (20)	MCI (15)
Classified as CON	**85%(17)**	13% (2)
Classified as MCI	15% (3)	**87%(13)**
Accuracy	86% (30 out of 35)	

Table2. Classify between control and MCI subjects.

MCI vs. AD	MCI (15)	AD (20)
Classified as MCI	**80%(12)**	20% (4)
Classified as AD	20% (3)	**80%(16)**
Accuracy	80% (28 out of 35)	

Table3. Classify between MCI and AD subjects.

REFERENCES: 1. Fox et al., Nat Rev Neurosci 8: 700-711 (2007). 2. Li et al., Radiology 2251, 253–259 (2002). 3. Tzourio-Mazoyer et al., NeuroImage 15, 273– 289 (2002). 4. Theodoridis S and Koutroumbas, K. Pattern Recognition, 3rd ed. Academic Press (2006).

ACKNOWLEDGEMENTS: This work was supported by NIH Grant 20279