

Large-scale functional network reconfiguration associates with its underlying gray matter atrophy in AD

W. Li¹, G. Chen¹, X. Liu¹, C. Xie^{1,2}, G. Chen¹, B. D. Ward¹, J. Goveas³, J. Jones⁴, M. Franczak⁴, P. Antuono⁴, and S-J. Li^{1,3}

¹Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, ²School of Clinical Medicine, Southeast University, Nanjing, Jiangsu, China, People's Republic of, ³Psychiatry and Behavior Medicine, Medical College of Wisconsin, Milwaukee, WI, United States, ⁴Neurology, Medical College of Wisconsin, Milwaukee, WI, United States

INTRODUCTION

Although atrophy is one of the hallmarks of Alzheimer's disease (AD) [1], the relationship between brain atrophy and system-level dysfunction in functional connectivity networks is not well understood. While severe neurodegeneration in the late stage of AD is likely to result in functional alterations, the extent to whether the morphological changes lead the functional changes or vice-versa in mild stage of the disease is still unclear [2]. Our current study investigates how functional networks evolve among brain regions involving atrophy in patients with mild cognitive impairment (MCI) and AD.

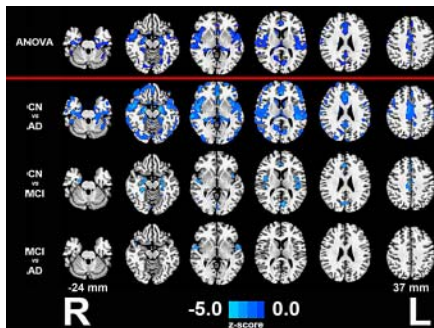


Figure 1 Atrophic brain regions in AD and MCI. First row, ANOVA showing the differences among AD, MCI, and CN group with statistical threshold adjusted to $p < 0.01$. Bottom three rows show the post hoc between group difference comparisons for CN vs. AD, CN vs. MCI, and MCI vs. AD. The threshold was $p < 0.005$, corrected for multiple comparisons.

METHODS

Subjects and MRI parameters: Twelve mild AD, 15 amnesic MCI, and 20 cognitively normal (CN) subjects were recruited in this study. Medical College of Wisconsin Institutional Review Board approved the study and a written informed consent was obtained from each participant. The inclusion and exclusion criteria for the three groups of subjects followed previous guideline [3]. MR images were scanned using a whole-body 3T Signa GE scanner. High-resolution anatomical images were acquired using 3D spoiled gradient-echo (SPGR) sequence (TE/TR/TI of 4/10/450 ms, FA = 12°, number of slices of 144, slice thickness of 1 mm, matrix size = 256×192) for anatomical analysis. Resting-state functional MR images were obtained using a single-shot EPI sequence (TR/TE/FA/thickness/matrix size = 2s/25ms/90°/4mm/64x64) with 36 sagittal slices for large-scale functional network analysis. **Imaging Analysis:** Anatomical images were segmented to gray matter (GM) for each subject. The GM images were then normalized, spatially transformed into common space, and divided into AD, MCI, and CN groups, so that their global GM concentration could be compared [4]. Brain regions showed significant atrophy in the AD group, when compared with the CN group. They were selected as regions of interest (ROIs) for network analysis. Then, the ROIs were mapped onto a whole-brain template with 116 parcellated regions [5]. Each subject's functional image was then automatically parcellated onto the template. The functional connectivity between any of the atrophic ROIs and the remaining nonatrophic ROIs was calculated as the Pearson correlation coefficient [6]. Finally, statistical analyses were performed among the three groups to compare the differences in the number of positive and negative connections.

RESULTS AND DISCUSSION

Figure 1 shows significant GM atrophy in the brain regions of diseased patients compared to those of normal subjects, particularly in the bilateral hippocampus, posterior cingulate cortex, anterior cingulate cortex, insula, middle temporal gyrus, inferior parietal cortex, precuneus, dorsal lateral prefrontal cortex and subcortical regions after ANOVA and posthoc analyses among the three groups. **Figure 2** shows that the functional networks involving atrophic regions had a significantly increased number of negative connections in patients; these are proportional to disease severity. **Figure 3** shows that no significant group differences in number of negative or positive connections were found in nonatrophic brain regions. The current results suggest that network-level functional connectivity alterations in patients with dementia are largely involved in underlying atrophic brain regions, but not in nonatrophic brain regions. We also argue that functional network reconfiguration may already be present prior to severe morphological changes in late stages of the disease.

REFERENCES: 1. Palop et al., Nature (2006) 2. Seely et al., Neuron (2009) 3. Li et al., Radiology (2002) 4. Chételat et al., Neuroimage (2005) 5. Tzourio-Mazoyer et al., Neuroimage (2002) 6. Chen et al., Radiology (in press)
ACKNOWLEDGEMENTS: This work was supported by NIH-NIA R01 grant AD 20279 (S.J.L).

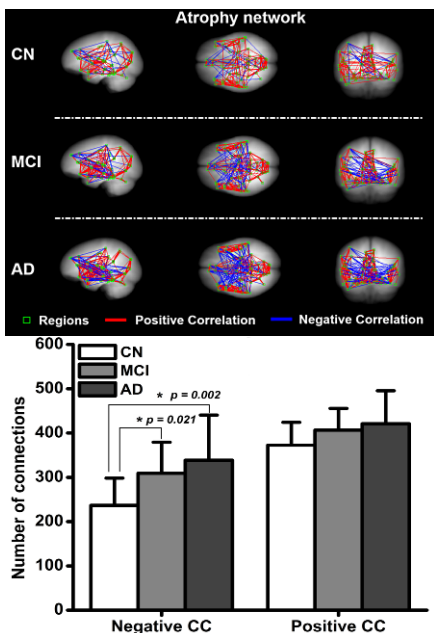


Figure 2 Functional connectivity pattern involving atrophy brain regions. The number of negative connections ($cc < -0.3$) is significantly increased in MCI and AD compared with CN, but no significant changes in positive connections ($cc > 0.3$) (negative, $F = 7.78$, $p = 0.001$; positive, $F = 3.039$, $p = 0.06$).

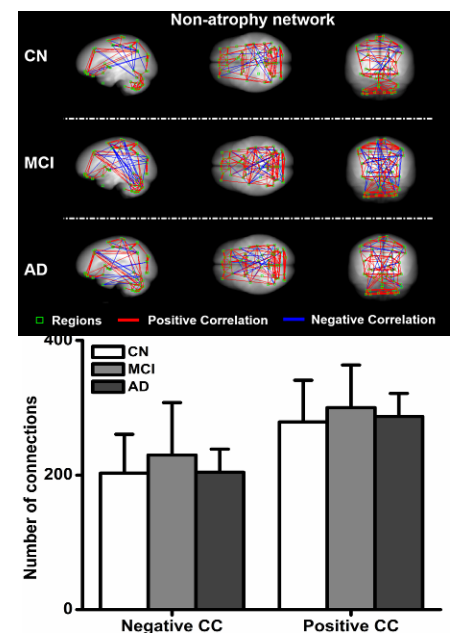


Figure 3 Functional connectivity pattern involving nonatrophy brain regions. No significant changes in number of negative or positive correlations among three groups (negative $F = 0.61$, $p = 0.55$; positive, $F = 0.98$, $p = 0.38$).