Decreased Granger Causality Strength between the Right and Left Hippocampal Network in Patients with Alzheimer Disease

G. Chen[1], W. Li[1], C. Xie[1], P. Antuono[2], and S-J. Li[1]

[1]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [2]Neurology, Medical College of Wisconsin, Milwaukee, WI, United States

Introduction: Functional connectivity MRI (fcMRI) using a resting-state approach is widely used in neurological research. However, this method has been limited to the calculation of a synchronous relationship quantified with cross-correlation values without knowing the causality influence. Granger Causality (GC) test has been used extensively to find the causalities between different time series. Although several papers using GCT on task event have been published [1-2], there is a dearth of literature relevant to resting-state studies using GCT. The purpose of this study is to investigate the change in the granger causality strength of the hippocampal networks in cognitively healthy (CN) study participants and Alzheimer's disease (AD) patients.

Methods: A total of 33 participants were recruited for this study. One CN was excluded due to the large motion during MRI scan. Eighteen CN study subjects (8 females and 10 males with age 74.6 ± 6.6 yrs) and 14 Alzheimer's disease (AD) study subjects (age 77.57 ± 6.57 yrs) entered the data analysis. **MRI protocol**: Imaging was carried out on a 3T GE Signa whole-body scanner with a standard transmit-receive head coil. Thirty-six slices (sagittal-resting functional MRI datasets of the whole brain) were obtained in 6 minutes with a single-shot gradient echo-echo planar imaging (EPI) pulse sequence with TE/TR/flip angle/slice thickness, 25ms/2,000ms/90°/4mm, matrix size=64x64 and field of view=24x24 cm. High-resolution SPGR 3D images were acquired in axial direction for anatomical reference (TE=4ms, TR=10ms, TI=450ms, flip angle=12°,144 slices, slice thickness=1mm and matrix size=256x192). **Data analysis**: The data was processed with AFNI software. The preprocessing includes motion corrections, removing Legendre polynomials of order up to 3. Ten ROIs (Posterior Cingulated Cortex, Paracentral Gyrus, left and right Hippocampus, Medical Frontal Cortex, left and right Dorsolateral Prefrontal Cortex, left and right Inferior Parietal Cortex, and right Inferior Temporal Gyrus) significantly connected as a hippocampal network [3]; we selected these from each study participant. The average values of the time courses of the 27 voxels around the largest z-score voxel for each ROI region were extracted for each individual. A band-pass filter was applied to the normalized time signals to keep only low-frequently fluctuations within the 0.01Hz and 0.1Hz range. Then, Granger Causality analysis was applied. There are 10 summary time series (Eq.1)**.** One MVAR (multivariate auto regression) model (Eq.2) is used to calculate the full regression; it measured the directed influence strength values of all possible causalities from all other regions to region ***j***. In order to find the effective causality connection between time series ***j*** and ***k*** in both directions, partial regression (Eq. 3) for each time series was calculated. If the F-test of residuals of full and partial regressions was greater than tabular significance values, then, the null hypothesis (***k*** does not cause ***j***) was rejected, meaning that ***k*** causes ***j***. Finally, a two-sample *t*-test was applied to the two groups' sum of the strength values of all effective causality edges from right to left and all effective causality edges from left to right to distinguish the significant changes between CN and AD groups.

Results and Discussion: Figure 1 indicates both decreased right-to-left and left-to-right effective granger causality strength between the left and right hippocampal networks in AD (Blue) group. Compared to the CN (Red) group (Total strength: right-to-left=0.433±0.1655. left-to-right=0.3491±0.1014), the AD group (Total strength: right-to-left=0.2302±0.1063. left-to-right=0.2170±0.1597) has the significantly lower (p<0.0004 for the right-to-left, p<0.008 for the left-to–right) effective granger causality strength for the right-to-left or left-to-right hippocampal-directed networks. The fMRI and GC test confirmed decreased strength of granger causality between left and right hippocampal networks in AD. Our study develops a way to measure the strength of granger causality among brain regions and provides new evidence that AD patients have significantly decreased granger causality strength between left and right brains.

(Eq.1). $X(t) = (x_1(t), x_2(t), x_3(t), \ldots, x_{10}(t))^T$

(Eq.2). $x_j(t) = c_j 1 + \sum_{i=1}^{p} A_j(i) X(t-i) + E_j(t)$

(Eq.3).

$$x_j(t) = c_j 2 + \sum_{i=1}^{p} A_{jk}(i)(x_1(t), \ldots, x_{k-1}(t), x_{k+1}(t), \ldots, x_{10}(t))^T + U_{jk}(t)$$

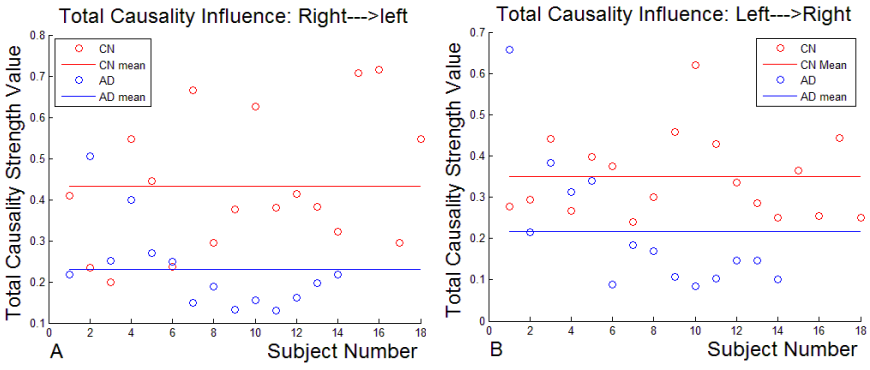

Figure 1: The distribution of each individual's total strength of right-to-left (A) or left-to-right (B) effective granger causality in hippocampal network for CN (Red) and AD (Blue) groups.

Reference:

1. Roebroeck A et al., Neuroimage. 2005; 25(1):230-42.
2. Deshpande G et al., Hum Brain Mapp. Epub 2008 Jun 6.
3. Wu Z et al., ISMRM 16(2008):261.

Acknowledgement: This work is supported by NIH Grant AG20279, General Clinical Research Center RR00058, the DANA Foundation, and Extendicare Foundation.