Dynamic Changes in Causal Strength in Memory Encoding Networks in Alzheimer's Disease Detected by Granger Causality Analysis

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Introduction: As a disconnection syndrome, Alzheimer's disease (AD) shows significant disconnection between brain regions not only in structure but also in function level [1-2]. The functional connectivity approach has discovered that the hippocampus [3] and default mode networks [4] are disrupted in AD patients. But the efferent and afferent changes within hippocampus network of AD are not known. In the present study, the Granger causality analysis [5], which can find the causal relationship among different time series, was employed to identify the directional hippocampus network in cognitively normal (CN) subjects, and detect the changes in the directional network in AD patients.

Methods: Forty participants, including 20 CN subjects (age 74.6 ± 6.6 yrs, MMSE scores: 29 ± 1.3) and 20 mild AD patients (age 77.57 ± 6.57 yrs, MMSE scores: 24.75 ± 2.6) were recruited for this study. Among the 40 subjects, one AD and three CN subjects were excluded for this analysis because of the failure of the imaging volume to include all of the relevant brain regions. 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 of 64x64 and field of view of 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 were processed with AFNI software. The preprocessing includes motion corrections, removing Legendre polynomials of order up to 3. Twenty ROIs in the hippocampus and default mode network were selected from each study participant; these included the left and right of the Cerebellum Tonsil (CBT), Hippocampus (HP), Parahippocampal Gyrus (PHP), Medical Frontal Cortex (MFC), Posterior Cingulated Cortex (PCC), Dorsolateral Prefrontal Cortex (DLPFC), Inferior Parietal Cortex (IPC), Lateral Parietal Cortex (LPC), Superior Frontal Cortex (SFC), Paracentral Gyrus (PAR). The average values of the time courses of these ROI regions in Talairach space 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, the Granger Causality analysis was applied to calculate the causality strength of each edge (between two regions) to build a weighted directed graph among the 20 brain regions. A two-sampled *t*-test was applied to find those edges, which have a significantly different edge strength between AD and CN subjects.

Results and Discussion: As shown in Figures 1 and 2, many edges have significantly different causal strengths between CN and AD subjects. Those edges in the AD group that have higher causality strength than those in the CN group were defined as the increased causal network (IN) (Fig. 1), and those that have decreased causal strength as the decreased causal network (DN) (Fig. 2). The average of all edge strengths within each network was defined as the network's index (DNI and INI, respectively). Each subject has DNI and INI values. It was found that the right parahippocampal gyrus (PHP) has significant changes in causal strength in AD patients. Most afferents from the neocortex to the right PHP are significantly decreased (left), but efferent paths from PHP to neocortex are increased (right). These results are consistent with previous findings. In normal subjects, memory-encoding functions are related to the higher level of acetylcholine (Ach), which enhances projection from associate cortex to PHP, and suppresses the feedback projection from PHP to the associate cortex [6]. Because the Ach level in AD is significantly lower than that in CN subjects, these processes are reversed, resulting in decreased projections from the associate cortex to the PHP, and increased projection from the PHP to the associate cortex. These results suggest that the dynamic changes in network strength may underlie the loss of memory-encoding function in AD patients. Interestingly, both network strengths (DNI and INI) significantly correlated with behavioral scores (mini-mental status examination (MMSE)), as shown in Figure 3, indicating that the network phenotype is significantly correlated with behavioral phenotype. These results support a notion that disorders in human behaviors are dependent on how their neural networks are wired and interacted. Abnormal behaviors have abnormal network activity and they are correlated.

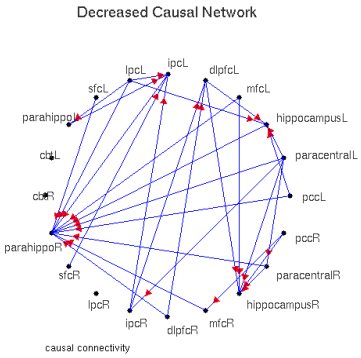

Figure 1: Decreased Causal Network (DN)

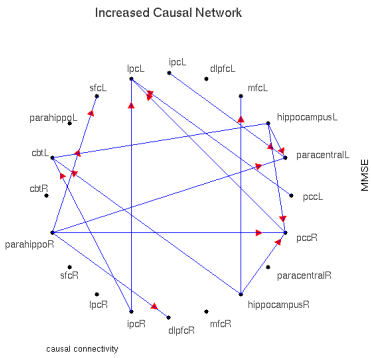

Figure 2: Increased Causal Network (IN)

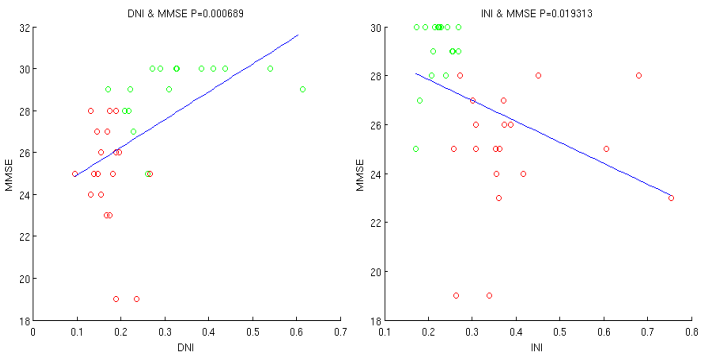

Figure 3: Left scatter plot shows the DNI value and MMSE score were positive correlated (p<0.0001). Right scatter plot shows the INI value and MMSE score were negative correlated (p<0.02).

Reference:
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