The Effective Connectivity between the MTL and PCC is Significantly Reduced in aMCI Subjects when Using Structural Equation Modeling

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Introduction: Alzheimer's Disease (AD) is a neurodegenerative disease characterized by severe memory impairment. It has been a puzzle that neuroimaging studies using PET and SPECT have consistently showed hypometabolism in the posterior cingulated cortex (PCC) in AD patients, while MRI studies discovered that the atrophic change of AD initially occurred in the medial temporal lobe (MTL) (1). The leading hypothesis for this apparent discrepancy is that the regional neural projections from the MTL to the PCC have been disrupted, resulting in hypoperfusion and hypometabolism in the PCC. In the present study, we test this hypothesis by using Structural Equation Modeling (SEM) (2) to analyze the effective connectivity changes between the PCC and MTL with amnestic mild-cognitive impairment (aMCI) subjects.

Materials and Methods: Scans were acquired on a GE 3T Signa scanner using a birdcage RF head coil. A set of SPGR anatomical images were acquired for co-registration with functional images. The latter were obtained by using a single-shot EPI sequence (TE=27ms, TR=2500ms, slice thickness=5mm, FOV=24cm, matrix size=128×128, 28 coronal slices) to cover the whole brain. A total of 120 volumes were collected during a 5 min scan for each subject. Eight aMCI subjects and 14 healthy elderly controls were in the study. Written informed consent was obtained from all subjects prior to study participation. The memory-encoding task was performed with a block-designed paradigm consisting of two cycles of three blocks, corresponding to three cognitive tasks: baseline, repeated present familiar pictures, and present with novel pictures. Familiar and novel pictures lasted 40 sec, respectively. Each picture was visible for 2.5 sec. For the baseline task, a stationary fixation cross picture was displayed for 30 sec in a block, The functional data was pre-processed using AFNI. This included motion correction, linear detrending, spatially smoothing with a 4-mm FWHM Gaussian kernel and employing a low-pass temporally smoothing technique with a 4-sec Gaussian kernel. The General Linear Model (GLM) was then used to find regions with significant functional activation by testing the contrast: novel versus repeated condition. The significance level of $P<0.001$ was applied to detect activated voxels. The SEM analysis was based on the activation map. The anatomical model for SEM consisted of three ROIs (for left hemispheres only): the PCC/Precuneus, the Hippocampus/Parahippocampus, the Lingual gyrus. The lingual gyrus works as a visual stimulus input for the network. For each individual subject, the time series from activation, local maxima, and the first neighboring voxels within each ROI were extracted. The first principle component time course was obtain by applying the PCA, which will be used in representing the time course for this ROI. Then, the segments of signal corresponding to the novel condition in each representative time series were extracted and concatenated for all subjects in the same group, resulting in two time series sets for each ROI: one set for the aMCI group and the other for the control group. Finally, the time series were normalized and entered into the SEM analysis as inputs. SEM was performed using the program Mx (http://www.vcu.edu/mx/) applying a maximum-likelihood algorithm for estimating path coefficients. Statistical inferences about group differences were based on a stacked-model approach.

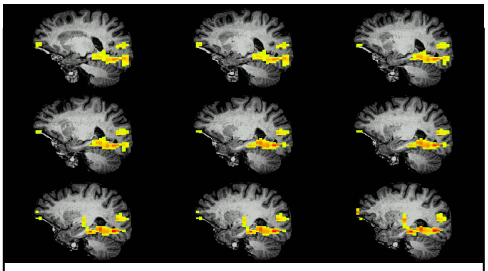

Figure 1: A representative activation map from a control subject.

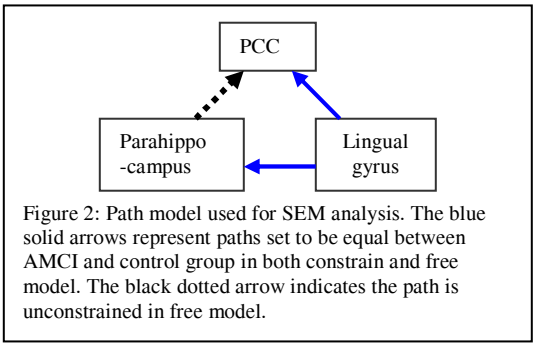

Figure 2: Path model used for SEM analysis. The blue solid arrows represent paths set to be equal between AMCI and control group in both constrain and free model. The black dotted arrow indicates the path is unconstrained in free model.

Results and Discussion: Figure 1 shows the contrast test result using GLM with a control subject. The activation map exhibited significant activities in predefined ROIs. In the constrained model, all correspondent path coefficients for the aMCI and normal groups were set to be equal, while the free model released the constrain on the link from the parahippocampus to the PCC. The hypothesis test using a constrained model versus a free model was rejected with $P<0.01$. The free model came up with a connection strength of 0.20 from the parahippocampus to the PCC for the normal group and 0.10 for the aMCI group. This result indicated that the connection strength from the parahippocampus to the PCC is significantly reduced in aMCI group than in the control group. Since the fMRI BOLD signal represents the afferent activity at the target regions (3), it is conceivable that the atrophic MTL projection to the PCC was significantly reduced in the aMCI subjects. It is suggested that the mechanisms responsible for the apparent discrepancy between the PET and MRI findings are due to the reduced effective connectivity between the MTL and PCC.

Reference: 1. Greicius M.D. et al,. PNAS:2004:101(13):4637-42 **2.** McIntosh A and Gonzalez-Lima F. Human Brain Mapping, 1994; 2(1-2):2-22. **3.** Logothetis N.K., Wandell, B.A. Annu. Rev. Physiol. 2004; 66:735-69.

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