Abnromal changes in Default Mode Network in Alzheimer¡¯s Disease and Mild Cognitive Impairment Subjects Investigated by DTI and Resting-state fMRI

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Introduction: Alzheimer's Disease (AD) is the main cause of dementia in the elderly, while Mild Cognitive Impairment (MCI) is regarded as a transitional state between normal aging and dementia. The Default Mode Network (DMN) is particularly relevant for AD and MCI since DMN structures are vulnerable to atrophy, deposition of the amyloid protein, and generally show a reduced glucose metabolism. In this study, we evaluated the abnormal changes of both microstructure and functional connectivity in DMN in AD and MCI subjects using Diffusion Tensor Imaging (DTI) and resting-state function MRI (rs-fMRI)

Materials and Methods: A total of 75 subjects were studied, including 26 AD (F/M 17/9, age 67.58±7.34 years), 19 MCI (F/M 9/10, age 63.21±8.33 years) and 30 elder healthy controls (HC, F/M 16/14, age 68.20±2.59 years). All MRI image datasets were acquired on a Siemens whole-body clinical MRI 3T scanner equipped with 32-channel head coil. Two types of rs-fMRI experiments were performed: 1) a total of 45 rs-fMRI datasets, including all AD and MCI subjects, were acquired using the following acquisition protocol: TE/TR=35/1600 ms, and 400 time frames of gradient recalled echo EPI corresponding to 10min and 30s scan per data set; 2) 19 data sets of 6 min long rs-fMRI scans were acquired from 30 HC subjects with TE/TR=35/2500ms and 145 timeframes. The other acquisition parameters included: 42 oblique slices of 4 mm thick and 3×3 mm^2 in-plane resolution. The slices were all parallel to the plane of the anterior and posterior commissure line. During the resting-state acquisition the subjects were instructed to close their eyes and relax. DTI were obtained using a spin-echo EPI sequence (TR/TE=5200/91ms, 42 axial slices, voxel size 2×2×3.6mm^3) with 30 orientations for the diffusion-sensitizing gradients b-value of 1000mm*s^{-2}. All rs-fMRI data were processed using AFNI with correction for slice-dependent time shifts and head motion, and transformed to MNI152 template to yield a volumetric time series resampled at 4mm cubic voxels. A temporal band-pass filter was performed within the frequency range of 0.01-0.1 Hz. The effect of global signal was removed using linear least squares fitting. In addition, the time series of AD and MCI subjects was reduced to the same duration with the time series of HC by removing a few time points at the end to keep the same sampling rate and SNR. Correlation coefficient (CC) maps were obtained by selecting a seed region in bilateral posterior cingulated (PCC) and the Fisher z transformation was performed to obtain Z-score maps. The post-processing of the DTI data was performed using shell scripts calling C-programs from the AFNI and FSL package. The main steps included: 1) correction for motion and eddy current distortion by the FDT tool in FSL; 2) calculation of mean diffusivity (MD) and fractional anisotropy (FA) maps using 3dDWItoDT program in AFNI; 3) transformation of all MD and FA maps to MNI152 template by the TBSS package in FSL; 4) average FA and MD were calculated of the regions separately within DMN using 3dROIstats program in AFNI, including bilateral anterior cingulated (ACC), middle frontal gyrus (MFG), superior frontal gyrus (SFG), hippocampus , parahippocampal gyrus (PHG), middle temporal gyrus (MTG), PCC, precuneus (PCu) respectively. All ROI regions were from the Talairach-Tournoux Atlas database in AFNI then transformed to MNI152 template. Two sample t-tests with covariates of age, gender and TR (3dtest++, AFNI) was used to compare the different functional connectivity within DMN between AD and MCI, AD and HC, MCI and HC respectively ($p<0.05$, cluster size > 20 voxels). Differences in FA and MD values among the AD, MCI and HC groups were evaluated using MANOVA with covariates of age and gender followed by the LSD test as a post hoc test. Statistical analysis was performed by SPSS 17.0 ($p<0.05$).

Results: Table.1 shows the regions of reduced functional connectivity between AD and MCI, AD and HC, MCI and HC. Table.2 shows the regions of increased functional connectivity between AD and MCI, AD and HC, MCI and HC. Functional connectivity of MTG, PCC and SFG are all reduced and PCu is increased in both AD and MCI, compared with HC. Comparing AD with MCI, functional connectivity of MFG is reduced, and MTG is increased. In addition, we investigated the DTI measurements in all DMN regions, and found a decreasing trend in FA value and increasing trend in MD value while evolving from HC to MCI and then AD. For AD compared with HC, FA of all DMN regions is significantly decreased and MD is increased. For MCI compared with HC, FA of all DMN regions is significantly decreased and MD of left hippocampus and bilateral PHG are significantly decreased. ComparingAD with MCI, there is no statistical significant difference in FA values in all DMN regions, but MD of all DMN regions is significantly increased.

Conclusion: In summary, the results of the study support the view that MCI shares features with AD. The structural and functional connectivity of DMN in both AD and MCI patients are abnormal. The increased functional connectivity of MTG and PCu might be due to compensatory mechanisms. The elevated MD value of the left hippocampus and bilateral PHG in MCI are consistent with the pathological process that neuronal degeneration starts from hippocampal area and spreads to temporal and parietal association cortices. Our investigation is beneficial to further understanding of the structural and functional changes of AD in different stages. Moreover, it may contribute to an improved differential diagnosis in AD and MCI which are often clinically difficult to distinguish.

Table.1 Regions of reduced functional connectivity with the PCC

Region	Side	Cluster	Coordinates (MNI)			T-score
			x/-x	y/-y	z/-z	
AD vs MCI						
MFG	R	38	-19	-56	+26	3.75
AD vs HC						
PCC	B	224	0	+47	+26	6.43
SFG	R	60	-43	-12	+46	5.13
MFG	R	35	-19	-56	+26	4.28
MTG	R	29	-51	+63	+26	3.85
MCI vs HC						
PCC	B	299	0	+43	+26	6.82
SFG	L/R	28/28	+48/-43	-12/-20	+42/+34	3.52/4.22
MTG	L/R	22/26	+56/-55	+63	+14/+26	3.08/4.11

B=bilateral; L=left; R=right

Table.2 Regions of increased functional connectivity with the PCC

Region	Side	Cluster	Coordinates (MNI)			T-score
			x/-x	y/-y	z/-z	
MCI vs AD						
MTG	L	41	+52	+59	+10	2.79
PCu	R	26	-11	+59	+38	3.12
AD vs HC						
PCu	L/R	97/56	+8/-11	+43/+47	+70/+74	3.49/3.98
MCI vs HC						
PCu	L/R	27/23	+12/-11	+39/+47	+78/+74	3.9/4.21

L=left; R=right