Aberrant resting-state activity in default mode network of subjects with amnestic mild cognitive impairment

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Introduction The default mode network (DMN) is a brain sub-system that is presumptively active when a person is left undisturbed to engage in introspective modes of cognition including free thinking, remembering the past, envisioning the future, and meditating the perspectives of others [1]. Given the structural and functional relationship of the DMN to regions important to memory, the study of disrupted DMN activity in mild cognitive impairment patients with an amnestic component (aMCI), a prodromal phase of Alzheimer's disease (AD), is especially compelling. A few fMRI studies [2-5] have investigated altered DMN functions in aMCI patients with both consistencies and discrepancies in selective DMN changes. Additional evidence is necessary to understand the changes of activity in different regions in the DMN that are consistent and potentially reliable indicators of aMCI and future development of AD. In this study, we examined eight subjects with aMCI and eight normal controls with resting-state fMRI, and focused data analysis on the functional connectivity of the DMN. We adopted a model-free group approach using independent component analysis (ICA) [6] with an imaging protocol that allows acquisition of oblique-coronal slices perpendicular to the long axis of the hippocampus to obtain more specific information for the medial temporal lobe (MTL) with fewer susceptibility artifacts.

Methods Comprehensive neuropsychological tests (MMSE, Boston Naming Test, Logical Memory I and II, COWAT, Animal Naming, Trail Making A & B, Symbol Digit Test, Block Design, and Benton Visual Retention), clinical tests (CDR and Modified Hachinski Ischemic Scale), ADLs, and the CES-Depression Scale were administered by trained professionals and neurologists to screen subjects. Eighteen right-handed subjects (ten with aMCI and eight normal controls (NC)) were consented and recruited from the community for participation in this study, which was approved by the Colorado Multiple Institution Review Board. Two subjects with aMCI did not qualify for the fMRI study due to incidental imaging abnormalities. Both groups were matched in gender, age and education.

Echo planar imaging (EPI) was performed in a 3.0T GE HDx MRI scanner (General Electric, Milwaukee, WI) equipped with an 8-channel head coil using the following parameters: ASSET=2, ramp sampling, TR/TE=2sec/30ms, FA= 70deg, FOV=22cmx22cm, thickness/gap=4mm/1mm, 25 oblique-coronal slices perpendicular to the long axis of the hippocampus, in-plane resolution 96x96 interpolated to 128x128, and 288 time points. Subjects were instructed to rest with eyes closed during EPI. A standard high resolution T2-weighted structural image aligned with the same orientation and coverage of the EPI scans was also collected. Furthermore, standard 3D SPGR T1-weighted high resolution axial structural images were collected.

Pre-procession including slice timing and motion correction was done using SPM5. The EPI functional images were first co-registered to the high resolution structural images, then normalized to the Montreal Neurological Institute (MNI) space. The normalized EPIs were spatially smoothed with a 6 mm FWHM Gaussian kernel. Spatial ICA was performed using the GIFT software v1.3g (http://icatb.sourceforge.net). For each group, the dimensionality of the data from each subject was estimated by the minimum description length (MDL) criterion [6]. We used the median of the estimated dimensions of each group, which equaled 40 for both groups, as the number of independent components to be estimated in group ICA. The DMN component was identified by selecting the component with the highest spatial correlation to the default network template supplied by the GIFT software. A visual inspection was also conducted to assure that the spatial component most resemble to DMN was selected. The selected DMN components were further analyzed in a second level random effect analysis by using two-sample t-test for group differences. The statistical maps were shown at corrected statistical significance less than p=0.05. All images were displayed in neurological convention, i.e. left is left.

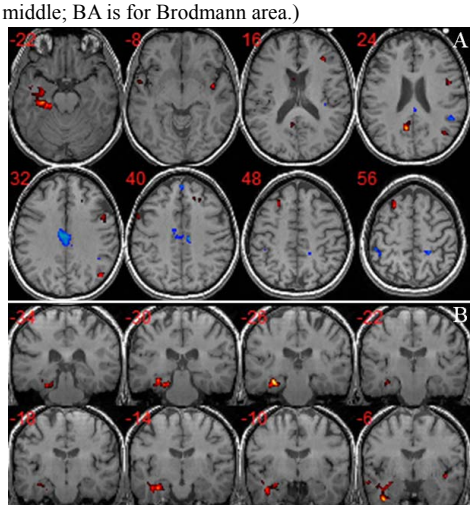
Results The differences between the two groups using the second level two-sample t-test is shown in the following figures with corrected p<0.05. In Figure A, the group difference is displayed in axial slice view, where hot red color represents decreased activities in aMCI (aMCI<NC) and cold blue color represents increased activities in aMCI (aMCI>NC). The most prominent decreased activities for aMCI compared to normal controls are in the left hippocampus (HC), left parahippocampal gyrus (PHG) and left fusiform gyrus (FG) along with those in lateral prefrontal cortex (LPFC), posterior cingulated cortex/retrosplenial cortex/precuneus (PCC/RSC/PC), left medial temporal gyrus (MTG), and right angular gyrus (AG). The decreased activities in left MTL for aMCI are observed consecutively from anterior to posterior slices as shown in coronal view in Figure B. On the other hand, the aMCI group shows increased activities mainly in middle cingulated cortex (MCC), medial prefrontal cortex (MPFC), and left inferior parietal lobe (IPL). In Table 1 and 2, we summarize the peak locations ("PLoc") in MNI coordinates and the size of clusters ("CS") of aberrant activities for the aMCI group. (Note: L is for Left; R is for Right; B is for Bilaterally connected in the middle; BA is for Brodmann area.)

Table 1 DMN activity difference: aMCI<NC (corrected p<0.05)

Region	L/R	BA	PLoc MNI (mm)	t-score	CS(voxels)
LPFC	L	8,9	-26,18,60	6.48	115
LPFC	R	8,9	26,30,36	3.19	79
HC	L		-30,-12,-22	4.20	36
PHG	L	36	-30,-26,-20	6.34	58
FG	L	37	-32,-26,-18	7.18	223
PCC/RSC/PC	B	23,30	-6,-60,22	5.92	191
MTG	L	21	-54, 4,-12	5.27	64
AG	R	39	48,-72,30	5.52	105

Table 2 DMN activity difference: aMCI>NC (corrected p<0.05)

Region	L/R	BA	PLoc MNI (mm)	t	CS(voxle)
MPFC	B	9	8,46,36	3.03	35
IPL	R	40	-46,-42,54	2.99	54
MCC	L	23	-2,-30,36	2.98	117
	R	23	4,-28,36	2.98	155



The MTL volume was segmented manually on subject's high resolution T2 image. The group difference of the MTL volume was calculated using a two-sample t-test and turned out to be non-significant. We also used each individual's DMN time course to calculate "fractional amplitude of low frequency fluctuations" (fALFF) [7], which was defined as the ratio of the amplitude sum across the 0.01-0.08 Hz range over the whole frequency range (0-0.25 Hz) in our study. The difference of fALFF between the aMCI and control group was not statistically significant.

Conclusion Aberrant DMN activities during the resting-state could be indicative of alterations in intrinsic brain architecture leading to functional deficiencies and compensatory changes seen in aMCI. Using an fMRI imaging protocol such that the slice orientation is parallel to the long axis of the hippocampus, decreased activity in left MTL was observed for aMCI even without statistically significant MTL volume differences between two groups.

References [1]. Bucker RL et al., 2008. *Ann. N.Y. Acad Sci.* 1124, pp 1-38. [2] Rombouts SA et al., 2005. *Hum Brain Mapp* 26, pp 231-. [3] Sorg C et al., 2007. *PNAS* 104, pp 18760-. [4] Bai F et al., 2008. *Neurosci. Lett.* 438, pp 111-. [5] Qi Z et al., 2010. *NeuroImage* 50, 48-. [6] Calhoun VD et al., 2001. *Hum Brain Mapp* 14, pp 140-. [7] Zou QH et al., 2008, *J. Neurosci. Meth.* 172, pp 137-.