The heterogeneity of aging brain: Altered functional connectivity in default mode network in older adults during verbal…

Article *in* Chinese medical journal · February 2012

DOI: 10.3760/cma.j.issn.0366-6999.2012.04.009 · Source: PubMed

Original article

The heterogeneity of aging brain: altered functional connectivity in default mode network in older adults during verbal fluency tests

DONG Li, SHEN Yuan, LEI Xu, LUO Cheng, LI Qing-wei, WU Wen-yuan, YAO De-zhong and LI Chun-bo

Keywords: *mild cognitive impairment; default mode network; verbal fluency tests; heterogeneity of aging; functional connectivity*

Background Successful aging (SA) and mild cognitive impairment (MCI) are heterogeneous groups of aging. To explore the heterogeneity, the functional connectivity was studied in these populations.

Methods The present study utilized functional connectivity magnetic resonance imaging (fcMRI) to investigate default mode network (DMN) in 8 healthy subjects of SA, 8 subjects of usual aging (UA), and 8 MCI patients during verbal fluency tests (VFTs). Functional connectivity (based seeds) of different groups was analyzed by using statistical test.

Results Compared with SA and UA groups, MCI subjects exhibited decreased functional connectivity in the DMN regions, including the inferior parietal lobule and left angular gyrus (t=3.53, P <0.001). Compared with UA and MCI groups, the SA elderly exhibited increased functional connectivity in the precuneus (t=3.53, P <0.001).

Conclusions These findings suggested that abnormalities of functional connectivity in DMN might be related with semantic memory impairment in aging. Left angular gyrus and precuneus might be the potential imaging-based biomarker for distinguishing heterogeneous process of elderly.

Chin Med J 2012;125(4):604-610

The default mode network (DMN) has been identified as a rest state of brain function,[1] which includes the bilateral posterior cingulate cortex (PCC)/precuneus, medial prefrontal cortex (MPFC), inferior temporal lobe, and inferior parietal lobule (IPL). These brain areas were active not only when subjects were at resting state, but also when individuals were engaged in internal tasks, such as autobiographical memory retrieval, envisioning the future.[2] Default mode abnormalities have been reported in Alzheimer's disease (AD)[3,4] and working memory tasks.[5] As a memory task, verbal fluency tests (VFTs) were widely used as neuropsychological tests whose fundamental component was the retrieval of semantically or lexically associated words from long-term memory storage.[6] Related with semantical memory retrieval, it also has been applied in studies of mild cognitive impairment (MCI) and AD.[7,8]

MCI refers to a transitional state between normal aging and AD; it does not notably interfere with activities of daily life.[9,10] Successful aging (SA) is a heterogeneous category of normal aging. Features of SA include well reserved cognitive function, independent activities of daily living, satisfied mood status (absence of any depressive or anxious symptoms) and no disability.[11,12] Apart from SA, another category is usual aging (UA) in which aging changes do not lead to pathology.[13,14] Previous studies have suggested that normal aging is associated with alterations in the connectivity of brain within the DMN.[15] Our study differs from previous studies in the discrepancies between diseased and healthy;[16] we focus on the heterogeneous groups of aging — SA and MCI elderly.

During VFTs, it was expected that an intrinsic, functional connectivity also existed. It was mediated through spontaneous low-frequency blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal fluctuations for the network of brain regions that support the default mode.[17-20] In this study, functional connectivity MRI (fcMRI) was utilized

DOI: 10.3760/cma.j.issn.0366-6999.2012.04.009

Key Laboratory for Neuroinformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, North Jianshe Road, Chengdu, Sichuan 610054, China (Dong L, Lei X, Luo C and Yao DZ)
Department of Psychiatry, Tongji Hospital of Tongji University, Shanghai 200065, China (Shen Y, Li QW and Wu WY)
Department of Biological Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China (Li CB)
Correspondence to: YAO De-zhong, Key Laboratory for NeuroInformation of Ministry of Education, School of Life Science and Technology, University of Electronic Science and Technology of China, North Jianshe Road, Chengdu, Sichuan 610054, China (Tel: 86-28-83201018. Fax: 86-28-83208238. Email: dyao@uestc.edu.cn); LI Chun-bo, Department of Biological Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai 200030, China (Tel: 86-21-64387250 ext. 3243. Fax: 86-21-64387986. Email: chunbo_li@yahoo.com)
DONG Li and SHEN Yuan contributed equally to this work.
The work was supported by grants from the National Natural Science Foundation of China (No. 30770769), the "973" Project (No. 2011CB707803), and the PCSIRT Project (No. IRT0910).

to research the heterogeneity of aging during VFTs, under the hypothesis of differences existed in aging. On the basis of above hypotheses, with seed at PCC and MPFC, DMN spatial patterns of all subjects were observed by cross-correlation functional connectivity analysis, which could be another useful perspective to study the aging and MCI.

METHODS

Subjects

All subjects were randomly selected (pseudorandom, uniformed distribution) from samples of cluster sampling (235 SA samples, 151 UA samples, 59 MCI samples, and a total of 445 samples) in Shiquan and Ganquan Community, Putuo District, Shanghai, China, in 2003. A survey, *Health Survey of Elder in Community in Shanghai, 2000*, consisted of mini mental state examination (MMSE), activity of daily living scale (ADL) and index of physical disease (IPD) etc were carried out with the criteria for each group.[11]

Totally 24 older adults were enrolled, 8 subjects met the standards of SA, 8 subjects met the criteria of UA, and 8 subjects were in the group of MCI. The study was approved by the Ethics Committee of the Tongji Hospital of Tongji University, and was performed according to the standards set by the *Declaration of Helsinki*. Written informed consent was obtained from each participant. All subjects were right-handed, normal hearing, and were normal level through the physical examination and routine laboratory tests, and without significant physical disease or disability. Detailed demographics findings are shown in Table 1. And there was no significant difference of age among three groups.

Data acquisition

Stimulation pattern

VFTs were chosen as stimulation paradigm, and led to block-design (eyes closed). The block-design consisted of six blocks, and each of them lasted 60 seconds. After inputted in the computer, the sound of command was auto-played to the headphone of subjects through E-prime software. When the subject heard the instruction, the volunteer was tasked to covertly retrieve as many words as possible that belonged to the given category (consisted of animals, vegetables and fruits).

Scanning process and parameters

Before scanning, subjects were required to fulfill simulated training for the compliance, check the handedness, and read the experimental instruction. Next, the behavioral data was obtained after scanning under the same environment. MRI scanning was performed on a 1.5 T scanner (Marconi USA). Anatomical T1-weighted images were acquired using a three-dimensional (3D)-spoiled gradient recalled (SPGR) sequence. Generating 25 axial slices, the imaging parameters were as follows: TR/TE=500 ms/12 ms, thickness/interval: 5.0 mm/ 1.0 mm, FOV=22 cm, matrix=256×256, flip angle=90^o. Functional images were collected by using a gradient-echo echo-planar imaging (EPI) sequence, and the imaging parameters were as follows: TR/TE=3000 ms/40 ms, thickness/interval: 5.0 mm/1.0 mm, FOV=24 cm, matrix=64×64, flip angle=90^o; 25 axial slices were acquired using a 3D-spoiled gradient recalled (SPGR) sequence, and 130 volumes were obtained during 390 seconds of a subject run.

Data preprocessing

Preprocessing of fMRI data was conducted through the SPM2 software package (statistical parametric mapping, *http://www.fil.ion.ucl.ac.uk/spm*, UK) including slice time correction, 3D motion detection and correction, and spatial normalization. To prepare the data for the main analyses, images were sampled to 3 mm×3 mm×3 mm and smoothed with a 6-mm full-width at half maximum of an isotropic Gaussian filter.

DMN identification

A pair of spherical regions (radius 10 mm) were selected as seeds, and they were positioned in the PCC/precuneus area (0, –52, 30) (Talairach coordinate)[17,18] and MPFC (–1, 47, –4) (Talairach coordinate).[19] Mean BOLD signal intensity time course were extracted from the seeds. Before computing the time series extracted from each brain voxel, two procedures were needed to remove possible variances. First, temporal band-pass filtering (0.01–0.08 Hz) was conducted through a phase-insensitive filter.[18,19] Second, through linear regression, six head motion parameters obtained from the realigning step were utilized to correct the time series.[18,19] Then, the cross-correlation functional connectivity analysis was performed by computing temporal correlation, between the seeds and all brain voxels.

The correlation coefficient of each voxel was the average of the correlations (or anticorrelations) with the two seed regions,[19] and it was later normalized to Z-scores with Fisher's r-to-z transformation. Therefore, an entire brain Z-score map was acquired for each subject. To achieve statistical significance of functional correlations at the group level, SPM8 (*http://www.fil.ion.ucl.ac.uk/spm*, UK) was utilized for the statistical test.

Linear trend cross groups

To investigate the underlying linear trend of altered

Table 1. Information of demography, MMSE scores and performances (number of words)

Groups	Age (years)	Female/male	MMSE scores	Animals	Vegetables	Fruits
SA	76.0±3.5	5/3	27.75±1.98	17.2±2.1	16.4±2.6	17.6±2.4
UA	76.0±2.7	4/4	22.63±3.16	13.8±2.0	12.5±1.4	15.9±2.2
MCI	77.0±5.6	4/4	17.87±4.64	10.1±2.3	9.0±1.2	9.4±1.5

functional connectivity across MCI, UA and SA groups, the Pearson's correlation and linear regression between correlation coefficients and MMSE scores were calculated, with threshold P <0.05 (uncorrected).

RESULTS

Behavioral performance

In line with expectations, the performance of SA group was better than UA group, while UA group was better than MCI group. Checking by one-way analysis of variance (ANOVA), there was significant difference between SA group and UA group in the performance of the first block (animals, P <0.01). Notable discrepancies also existed between SA group and MCI group and between UA group and MCI group (P <0.01). Details are also shown in Table 1.

Functional connectivity of each group

Through one-sample t-test (P <0.05, false discovery rate correction, k=10 voxels), results of each group were achieved to illustrate DMN in normal aging. The connectivity patterns of positive correlations appeared to be similar during visual inspection of SA and UA group. Apart from the regions around with the two seeds, significant functional connectivity for seeds in SA group was primarily found in middle temporal gyrus (Broadmann areas BA19/39), angular gyrus (BA39/40), inferior parietal lobule (BA40), occipital lobe (BA19/17/18/37), anterior cingulate cortex (BA32), superior temporal gyrus (BA39/38), inferior temporal gyrus (BA20), thalamus, and cerebellum. In the group of UA, the positive correlation maps were observed in anterior cingulated cortex (BA24/32), inferior parietal lobule (BA40/39), angular gyrus (BA39), superior temporal gyrus (BA22/39), middle temporal gyrus (BA21/37), occipital lobe (BA17/18/19), and cerebellum. Except for the two seed regions, less notable regions of connection for seeds were shown in MCI group. Occipital lobe (BA18/19), middle temporal gyrus (BA21/37), and anterior cingulate cortex (BA10/32) were barely received.

Alterations of DMN between groups

To receive more significant and credible regions of alteration between groups, results were first checked by one-way ANOVA. Table 2 shows the main regions with significant differences between groups which contain IPL (BA39/40), lingual gyrus (BA19), posterior cingulated (BA29), precuneus (BA7) and postcentral gyrus (BA43). Meanwhile, the reliable effects of different levels (groups) are shown in Figures 1A and 2A.

Compared with MCI group, Figure 1B–2B shows the statistical map produced by *post hoc* t-test comparison of functional connectivity of the SA group. Increased

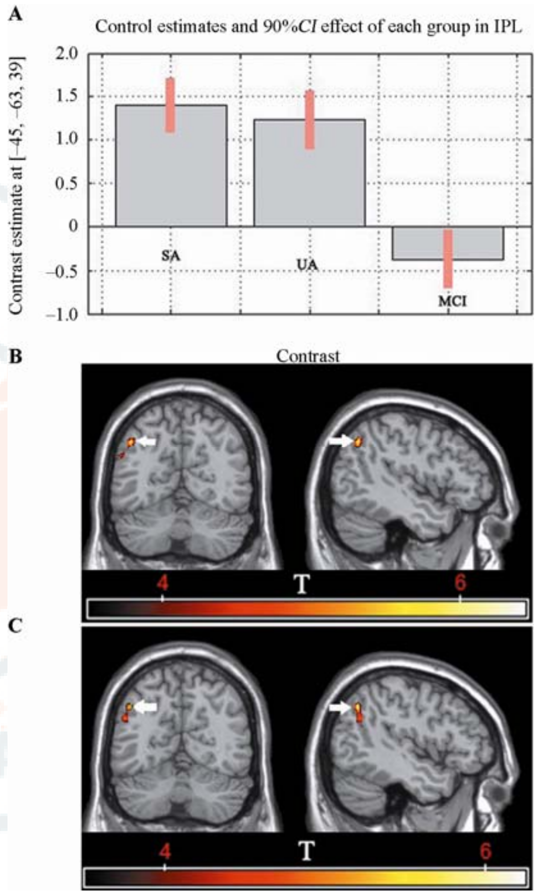

Figure 1. Comparison between groups in IPL (left angular gyrus, BA39/40, t=3.53, P <0.001, uncorrected, k=10 voxels). **A:** Through one-way ANOVA, it was shown that the peak significant effect existed at IPL (F=9.77, P <0.001, uncorrected, k=10 voxels). And this picture demonstrates that SA group and UA group carry the main functional connectivity, and MCI group contributes negative and additional effects. **B:** Compared with MCI group, increased functional connectivity for seeds was observed in IPL in SA group by means of *post hoc* test. **C:** Increased connection for seeds in IPL in UA group, compared with MCI group.

Table 2. Main effects of different groups in detail

Lobe	R/L	Brodmann	MNI coordinates x	y	z	F values	Voxels
Inferior parietal lobule	L	BA40/39	–45	–63	39	24.3	40
Superior temporal gyrus	L	BA39	–51	–60	27	21.74	
Lingual gyrus	R	BA19	12	–51	–6	23.5	15
Posterior cingulate cortex	R	BA29	12	–48	3	12.63	
Precuneus	L	BA7	–9	–57	45	18.6	16
Precuneus	L	BA7	–18	–60	51	12.84	
Posterior cingulate cortex	R	BA29	15	–39	12	15.79	10
Postcentral gyrus	R	BA43	54	–15	21	14.41	15
Posterior cingulate cortex	L	BA29	–3	–54	9	13.41	12

F=9.77, P <0.001, uncorrected, k=10 voxels. The coordinates were obtained in the Montreal Neurological Institute (MNI) space. R: right, L: left.

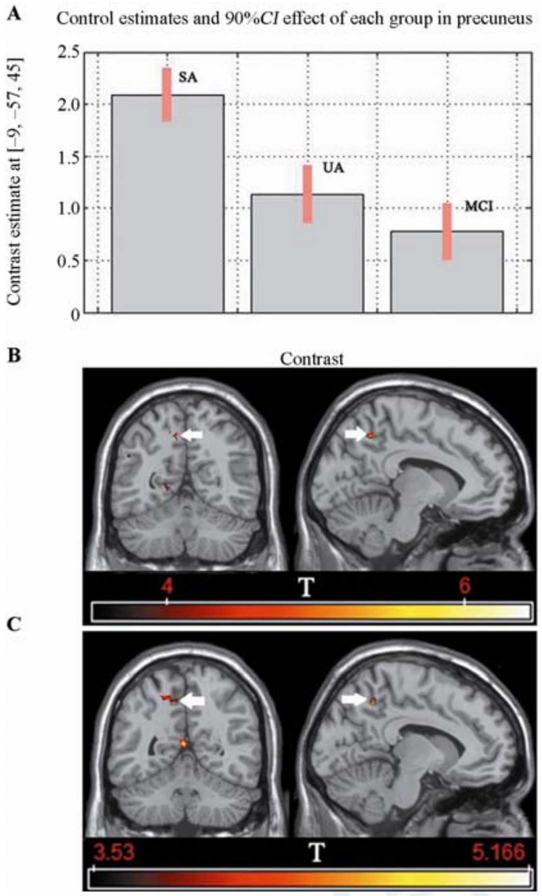

Figure 2. Comparison between groups in precuneus (BA7, t=3.53, P <0.001, uncorrected, k=10 voxels). **A:** Significant effect was shown in precuneus through one-way ANOVA (F=9.77, P <0.001, uncorrected, k=10 voxels). This picture exhibits that SA group carries the main functional connectivity, UA group contributes secondary effects, and MCI group contributes additional effects in this region. **B:** Compared with MCI group, SA group showed increased connection for seeds in precuneus. **C:** Compared to UA group, more significantly and importantly increased functional connectivity for seeds was found in SA group in precuneus. However, no significantly increased connection for seeds in precuneus was found in UA group, compared with MCI group.

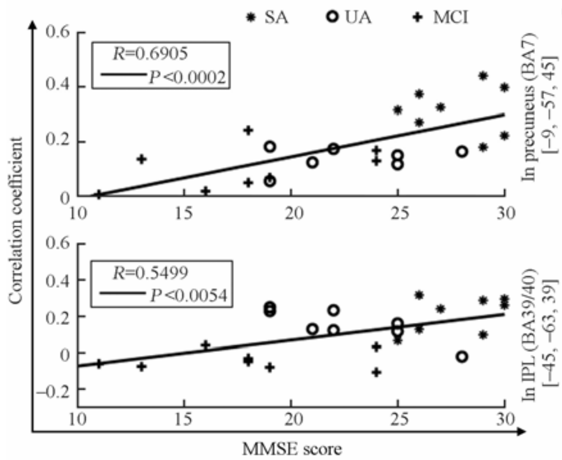

Figure 3. Linear trend of altered functional connectivity cross MCI, UA and SA groups. The horizontal axis is MMSE score, and vertical axis is correlation coefficient. The right edge is relative region and its MNI coordinate.

functional connectivity of SA group was observed in IPL (left angular gyrus, BA39/40) and precuneus (BA7). No significant decreased connectivity was found and the statistical threshold was P <0.001 (t=3.53, uncorrected, k=10 voxels). Compared with MCI group, increased connections of UA group were observed in IPL (angular gyrus, BA39) (Figure 1C). Compared to UA group, notable and increased functional connections of SA group were found in precuneus (BA7, Figure 2C).

Linear trend of functional connectivity across groups

Altered functional connectivity had significantly positive correlation with levels of cognitive status (MMSE scores) across MCI, UA and SA groups (Figure 3).

DISCUSSION

Function connectivity of aging in DMN during VFTs

Functional connectivity MRI analysis was considered to be an efficient method to identify spatial patterns of spontaneous coherent activity in the fMRI BOLD signals.[17-20] In the resting brain, functional connectivity, seeded at PCC and MPFC, has been adopted in the DMN.[17,19] Greicius and his colleagues considered that the network, constituted by the brain regions, such as PCC and ventral anterior cingulate cortex, would be modulated by task demands, and also suggested that the retrieval and manipulation of episodic memories and semantic knowledge were likely elucidated by the DMN.[21] Other researchers also mentioned that during the working memory task, functional connectivity in DMN also has been demonstrated in elders or adults in previous studies.[5,15] It was expected that the functional connectivity in DMN would repeat again in aging during VFTs. In this study, it was well demonstrated that the strong functional connectivity between nodes had been discovered in the group of SA during VFTs. In the group of SA and UA, the functional connectivity in DMN was well found in PCC/precuneus (BA7/31), medial frontal gyrus (BA10) and angular gyrus (BA39/40), which contained most of DMN spatial patterns.[2,17-19] Regions not in DMN, such as thalamus, cerebellum and some of occipital cortices, were also observed. These brain regions might also participate in the cognitive activity, and cerebellar contributions have been reported in Habas et al's study.[22] It meant that a complex functional connectivity existed in the brains of the aging.

It was thought that hippocampus contributed to the semantic memory.[23,24] However, each group subjects did not show significant correlation between seeds and hippocampal regions in current study. It was reported that there was an age-related decreased activation in hippocampus in memory recognition.[25] In hippocampus, atrophy of structure and decreased functional activity might be related with aging, and also affected by diseases, such as AD or MCI.[25-27] These factors (e.g. aging and relative disease) might be some important reasons why we could not find significant functional connectivity between hippocampus and seeds. Therefore, it does not mean that hippocampus does not contribute to semantic memory.

DMN alterations between groups

Previous studies have shown that altering functional connectivity or activity in DMN is related with AD or MCI.[28-30] It was expected that a cognitive task demanding a high level of neuronal cooperation might be a sensitive diagnostic tool for MCI in aging. So we hypothesized that the differences of connectivity between various groups of aging would appear in the VFTs. And the fcMRI analysis was applied to distinguish MCI group from healthy aging elderly, during VFTs. Our hypothesis was confirmed when significant changes of DMN connectivity were observed (Table 2).

Through one-way ANOVA, the significant alterations between groups were mainly found in parietal lobe and precuneus (Figures 1 and 2). Compared with the SA group and the UA group, significant decrease of functional connectivity in the MCI group was found in IPL (BA40) and especially in left angular gyrus (BA39, Figure 1). Using positron emission tomography (PET), Andreasen and his colleagues had reported that bi-parietal areas were activated in both short-term and long-term verbal memory, and suggested that these regions represented the distributed "storage" systems being referenced.[31] Semantic, visual, and temporal checks were probably involved in this referencing process.[31] In Woodard et al's study,[32] it was possible that PCC helped to establish and maintain memory traces to change them from short-term to long-term memory, and lesions in this region could produce retrograde memory impairment. Other studies have also demonstrated that PCC played a critical role in successful memory retrieval.[33-35] So, it was reasonable that the maintenance of functional connectivity in the parietal lobe, especially the PCC, as a key "hub" of convergence being strongly intercommunicated with other memory systems,[2] might contribute to the memory retrieval. In precuneus (BA7), a significant decrease of connectivity was found in the UA group and the MCI group compared with the SA group, and no significant discrepancies were observed between the UA group and the MCI group in this region (Figure 2). Precuneus, a region comprised of the posterior and dorsal portion of the medial parietal lobe, was adjacent to PCC. And the suggested pivotal role of the precuneus/posterior cingulate cortex in the default mode network was discussed in previous study.[36] It was speculated that precuneus might be as similar and important as PCC role in memory retrieval. Furthermore, when observing the close relationship between DMN and semantic memory,[37] one finds that the precuneus may play an important role in semantic memory. However, in AD, due to beta-amyloid deposition, DMN was related to episodic memory.[38] To some degree, it might partly account for the better performance of SA group than the other two groups (Table 1). In our study, it was demonstrated that the decrease of functional connectivity within the DMN in aging might partly result in deactivation of memory network and the further decline of semantic memory. Normal aging might be associated with alterations in the connectivity of brain regions within the DMN,[15] and memory networks should be less active in the MCI and AD groups.[39] In addition, subtle decline in other areas of cognition (such as executive functions) during VFTs might coexist with memory deficits, and might also partly account for the different performances of groups.[40-42] In some case, DMN alterations of functional connectivity, especially in left angular gyrus and precuneus, could be considered a biomarker for distinguishing heterogeneous elders,[13,43] such as the elderly of the SA and MCI groups, from aging elderly.

Moreover, a significant link between altered functional connectivity (correlation coefficients) and levels of cognitive status (MMSE scores) has been provided (Figure 3) and it seems to show that functional connectivity in precuneus (BA7) was sensitive to the levels of cognitive status. These further support the idea that decreased functional connection might reflect the state of functional brain organization in aging.

Limitation of this study

Although limited by the small samples size, there was no significant functional activity estimated by generalized linear model (GLM) during the verbal fluency tests. It may have been caused by the reason that the BOLD signals related to the task were too low to be estimated. So we calculated the functional connectivity of groups to study the aging. However, heterogeneity of aging in resting state will be planned to further research this topic. In addition, the survey and criteria (especially MMSE) were the main means of defining the SA, UA and MCI groups. It is an inevitable limitation that the true states of subjects could not be absolutely detected through the proposed standard. Finally, the heterogeneity of the MCI group may have an effect on the outcome of our study. Here, we focused on the function of memory based on the memory task. The other cognitive alteration in MCI and aging will also be investigated by using resting-state or the special task relative fMRI in future.

Conclusion

Results from the present fcMRI study provided evidence for DMN maintenance and abnormalities in heterogeneous older adults with SA and MCI groups during VFTs. It was also suggested that areas in DMN might be utilized to participate in semantic process, and decrease of functional connectivity in DMN might partly lead to impairment of semantic memory. The current results also suggested that altered functional connectivity in DMN might reflect chronic, abnormal alterations on the early stage of AD in the brain, which could probably serve as a biomarker to distinguish between heterogeneous elders and usual aging elderly. Further investigations based on simultaneous EEG-fMRI[44,45] might reveal more detailed information about the impairment of DMN. Furthermore, this research might be a useful insight into questions about heterogeneity of aging brain.

Acknowledgement: The authors would like to thank all staffs of Key Laboratory for NeuroInformation of Ministry of Education, and also staffs of Shanghai Mental Health Center and Tongji Hospital.

REFERENCES

1. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A 2001; 98: 676-682.
2. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008; 1124: 1-38.
3. Koch W, Teipel S, Mueller S, Buerger K, Bokde AL, Hampel H, et al. Effects of aging on default mode network activity in resting state fMRI: does the method of analysis matter? Neuroimage 2010; 51: 280-287.
4. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev 2009; 33: 279-296.
5. Hampson M, Driesen NR, Skudlarski P, Gore JC, Constable RT. Brain connectivity related to working memory performance. J Neurosci 2006; 26: 13338-13343.
6. Lezak MD. Neuropsychological assessment. New York: Oxford University Press; 1995: 429-560.
7. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Arch Neurol 2004; 61: 1290-1293.
8. Cooper DB, Lacritz LH, Weiner MF, Rosenberg RN, Cullum CM. Category fluency in mild cognitive impairment: reduced effect of practice in test-retest conditions. Alzheimer Dis Assoc Disord 2004; 18: 120-122.
9. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. Arch Neurol 2009; 66: 1447-1455.
10. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56: 1133-1142.
11. Li C, Wu W, Jin H, Zhang X, Xue H, He Y, et al. Successful aging in Shanghai, China: definition, distribution and related factors. Int Psychogeriatr 2006; 18: 551-563.
12. Jeste DV, Depp CA, Vahia IV. Successful cognitive and emotional aging. World Psychiatry 2010; 9: 78-84.
13. Rowe JW, Kahn RL. Human aging: usual and successful. Science 1987; 237: 143-149.
14. Rowe JW, Kahn RL. Successful aging and disease prevention. Adv Ren Replace Ther 2000; 7: 70-77.
15. Sambataro F, Murty VP, Callicott JH, Tan HY, Das S, Weinberger DR, et al. Age-related alterations in default mode network: impact on working memory performance. Neurobiol Aging 2010; 31: 839-852.
16. Zhang D, Raichle ME. Disease and the brain's dark energy. Nat Rev Neurol 2010; 6: 15-28.
17. Fransson P. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 2005; 26: 15-29.
18. Fransson P. How default is the default mode of brain function? Further evidence from intrinsic BOLD signal fluctuations. Neuropsychologia 2006; 44: 2836-2845.
19. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005; 102: 9673-9678.
20. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007; 8: 700-711.
21. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A 2003; 100: 253-258.
22. Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, et al. Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 2009; 29: 8586-8594.
23. Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, et al. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 2005; 207: 35-66.
24. Prince SE, Daselaar SM, Cabeza R. Neural correlates of relational memory: successful encoding and retrieval of semantic and perceptual associations. J Neurosci 2005; 25: 1203-1210.
25. Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 2004; 14: 364-375.
26. Jack CR Jr, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurology 2000; 55: 484-489.
27. Mega MS, Small GW, Xu ML, Felix J, Manese M, Tran NP, et al. Hippocampal atrophy in persons with age-associated memory impairment: volumetry within a common space. Psychosom Med 2002; 64: 487-492.
28. Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A 2004; 101: 4637-4642.
29. Wang K, Liang M, Wang L, Tian L, Zhang X, Li K, et al. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. Hum Brain Mapp 2007; 28: 967-978.
30. Qi Z, Wu X, Wang Z, Zhang N, Dong H, Yao L, et al. Impairment and compensation coexist in amnestic MCI default mode network. Neuroimage 2010; 50: 48-55.
31. Andreasen NC, O'Leary DS, Arndt S, Cizadlo T, Hurtig R, Rezai K, et al. Short-term and long-term verbal memory: a

positron emission tomography study. Proc Natl Acad Sci U S A 1995; 92: 5111-5115.
32. Woodard JL, Seidenberg M, Nielson KA, Miller SK, Franczak M, Antuono P, et al. Temporally graded activation of neocortical regions in response to memories of different ages. J Cogn Neurosci 2007; 19: 1113-1124.
33. Maddock RJ, Garrett AS, Buonocore MH. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience 2001; 104: 667-676.
34. Shannon BJ, Buckner RL. Functional-anatomic correlates of memory retrieval that suggest nontraditional processing roles for multiple distinct regions within posterior parietal cortex. J Neurosci 2004; 24: 10084-10092.
35. Berryhill ME, Phuong L, Picasso L, Cabeza R, Olson IR. Parietal lobe and episodic memory: bilateral damage causes impaired free recall of autobiographical memory. J Neurosci 2007; 27: 14415-14423.
36. Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. Neuroimage 2008; 42: 1178-1184.
37. Wirth M, Jann K, Dierks T, Federspiel A, Wiest R, Horn H. Semantic memory involvement in the default mode network: a functional neuroimaging study using independent component analysis. Neuroimage 2011; 54: 3057-3066.
38. Mormino EC, Smiljic A, Hayenga AO, Onami SH, Greicius MD, Rabinovici GD, et al. Relationships between beta-amyloid and functional connectivity in different components of the default mode network in aging. Cerebral Cortex 2011; 21: 2399-2407.
39. Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, et al. Alterations in memory networks in mild cognitive impairment and Alzheimer’s disease: an independent component analysis. J Neurosci 2006; 26: 10222-10231.
40. Nutter-Upham KE, Saykin AJ, Rabin LA, Roth RM, Wishart HA, Pare N, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. Arch Clin Neuropsychol 2008; 23: 229-241.
41. McDowd J, Hoffman L, Rozek E, Lyons KE, Pahwa R, Burns J, et al. Understanding verbal fluency in healthy aging, Alzheimer’s disease, and Parkinson's disease. Neuropsychology 2011; 25: 210-225.
42. Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 2004; 44: 195-208.
43. Phelan EA, Larson EB. “Successful aging” — where next? J Am Geriatr Soc 2002; 50: 1306-1308.
44. Lei X, Qiu C, Xu P, Yao D. A parallel framework for simultaneous EEG/fMRI analysis: methodology and simulation. Neuroimage 2010; 52: 1123-1134.
45. Lei X, Xu P, Luo C, Zhao J, Zhou D, Yao D. fMRI functional networks for EEG source imaging. Hum Brain Mapp 2011; 32: 1141-1160.

(Received July 19, 2011)
Edited by JI Yuan-yuan