Radiol med (2012) 117:865–871
DOI 10.1007/s11547-011-0780-8

NEURORADIOLOGY
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Spontaneous brain activity in mild cognitive impairment revealed by amplitude of low-frequency fluctuation analysis: a resting-state fMRI study

Attività cerebrale spontanea nel deterioramento cognitivo lieve, dimostrata dall'analisi dell'ampiezza delle fluttuazioni a bassa frequenza: studio fMRI resting-state

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Received: 7 May 2011 / Accepted: 28 June 2011 / Published online: 12 January 2012

Abstract
Spontaneous low-frequency fluctuations (LFF) in the blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal have been shown to reflect cerebral spontaneous neural activity. The objective of this study was to explore brain functional changes in patients with mild cognitive impairment (MCI) by measuring the amplitude of the BOLD signals. Eighteen amnestic MCI patients and 20 healthy elderly individuals underwent the fMRI scan. The amplitude of LFF (ALFF) was calculated using REST software. MCI patients showed decreased ALFF in the right hippocampus and parahippocampal cortex, left lateral temporal cortex and right ventral medial prefrontal cortex and increased ALFF in the left temporal–parietal joint (TPJ) and inferior parietal lobule. The ALFF value in the right hippocampus and parahippocampal cortex was positively correlated with the scores of Mini-Mental State Exam. Reduced medial temporal lobe activity may implicate the underlying memory impairment mechanisms in MCI. Increased TPJ and inferior parietal lobule activity may indicate the compensatory mechanism in MCI patients. These findings suggest that ALFF analysis could provide a useful tool in the fMRI study of MCI.

Keywords Mild cognitive impairment · Resting-state functional MRI · Amplitude of low-frequency fluctuation · Medial temporal lobe · Compensation

Riassunto
Le fluttuazioni spontanee a bassa frequenza dell'imaging a risonanza magnetica funzionale (fMRI), ottenuto tramite segnale dipendente dal grado di ossigenazione del sangue (BOLD), hanno dimostrato di rispecchiare l'attività nervosa spontanea. Lo scopo dello studio è stato quello di indagare i cambiamenti funzionali del cervello, in pazienti affetti da deterioramento cognitivo lieve (mild cognitive impairment, MCI), attraverso la misurazione dell'ampiezza dei segnali BOLD. Diciotto pazienti con diagnosi di MCI e 20 controlli anziani sani sono stati sottoposti ad una sessione di fMRI. L'ampiezza delle fluttuazioni a bassa frequenza (AFBF) è stata calcolata utilizzando il software REST. I pazienti con MCI hanno presentato una riduzione dell'AFBF nell'ippocampo di destra, nella corteccia para-ippocampale, nella corteccia temporale laterale di sinistra e nella corteccia pre-frontale ventro-mediale di destra; l'AFBF era aumentata nella giunzione temporo-parietale di sinistra (GTP) e nel lobo parietale inferiore. Il valore dell'AFBF nell'ippocampo di destra e nella corteccia para-ippocampale era positivamente correlato con i punteggi del questionario Mini Mental State. La riduzione dell'attività del lobo temporale mediale potrebbe rappresentare la base dei meccanismi di alterazione della memoria nel MCI. L'incremento dell'attività nella GTP e nel lobo parietale inferiore potrebbe indicare un meccanismo compensatorio nei pazienti con MCI. Queste evidenze suggeriscono che l'analisi delle AFBF potrebbe

essere uno strumento molto utile nello studio fMRI dei pazienti con MCI.

Parole chiave *Deterioramento cognitivo lieve · RM funzionale resting-state · Ampiezza delle fluttuazioni a bassa frequenza · Lobo temporale mediale · Compensazione*

Introduction

Mild cognitive impairment (MCI) is a syndrome with cognitive decline greater than expected for an individual's age and educational level but not interfering notably with activities of daily living [1]. The amnestic subtype of MCI (aMCI) has a high risk of progression to Alzheimer's disease (AD), constituting a prodromal stage of AD [2]. Early medical intervention may block or delay AD progression and improve the patient's quality of life [3]. Therefore, early detection and treatment of aMCI have become very important at present.

Structural MRI has been primarily used to differentiate between AD and healthy elderly individuals and to predict conversion from MCI to AD, relying on volume measurements of the hippocampus and surrounding structures [4] that are closely related to cognitive decline. However, most patients with structural MRI abnormalities often have irreversible pathological damage in the brain. Given that functional alterations might precede structural abnormalities, blood-oxygenation-level-dependent (BOLD) functional MRI (fMRI) may be a promising technique for studying MCI [5–7].

Resting-state fMRI techniques have been used to explore the neurophysiological mechanism underlying MCI. This method does not require the patient to perform any task, thus avoiding any paradigm design and greatly simplifying the fMRI procedure [8]. However, the findings in these studies are inconsistent. For example, medial temporal-lobe activity (MTL) has been suggested to play a critical role in maintaining human memory [9]. Studies have reported decreased activity of the MTL in MCI [10, 11], or increased activity [12] or even no significant change [13]. Furthermore, most resting-state fMRI studies focus on the relationship among different brain areas, e.g. functional connectivity methods based on region of interest (ROI) or independent-component analysis (ICA) rather than amplitude or strength of regional brain activity. Because ROI identification is based on a priori hypothesis, ROI-based analysis is prone to user-introduced bias. Whereas ICA measures BOLD signal synchrony, it is also difficult to pinpoint which area is responsible for the observed abnormality in connectivity. An alternative way of measuring regional brain activity during resting state is to examine the amplitude of low-frequency fluctuation (ALFF) of the BOLD signal [14]. Biswal et al. [15] reported that the reduced low-frequency fluctuation in white matter relative to grey matter by approximately 60% suggests that ALFF is associated with field-potential activity in local brain region. In this case, the ALFF are considered to be the reflection of regional spontaneous neuronal activity [16] and physiological states of the brain [17].

The purpose of this study was to explore the possibility of the altered resting state of brain activity in MCI patients using ALFF analysis and examine possible clinical correlates of ALFF measurements.

Materials and methods

Eighteen aMCI patients and 20 healthy elderly controls participated in the study. Patients were recruited from a memory clinic at the Department of Neurology. Healthy controls were recruited from a community investigation of epidemiological research. All participants provided written informed consent prior to the study, which was approved by the Medical Research Ethics Committee of Tongji Hospital. Prior to resting-state fMRI scanning, examination of each participant included medical history, neurological examination, informant interview, neuropsychological assessment [including Mini-Mental State Exam (MMSE), activity of daily living scale, Hachinski ischaemic scale, and Hamilton rating scale for depression], and structural MRI. Stroke, psychiatric disorders, drug abuse, moderate to serious hypertension and systematic diseases were ruled out. Patients met criteria for MCI, which included reported and neuropsychologically assessed memory impairments and largely intact activities of daily living, and excluded dementia [18]. Memory complaints or neurological deficiencies were not observed in the healthy elderly participants enrolled by normal conventional brain MRI. Demographics and neuropsychological findings of MCI patients and healthy controls are shown in Table 1.

Functional MRIs were obtained on a 1.5-T scanner (Marconi EDGE ECLIPSE). During scanning, all participants were instructed to keep their eyes closed and refrain

Table 1 Demographics and neuropsychological findings of mild cognitive impairment (MCI) patients and healthy elderly controls

Tabella 1 *Dettagli demografici e rilievi neuropsicologici in pazienti con deterioramento cognitivo lieve (MCI) e controlli anziani sani*

	Age	Male/female	Education	MMSE	CDR
aMCI patients (n=18)	67.28±7.87	8/10	12.36±3.18	24.77±3.84*	0.5
Healthy elderly (n=20)	64.65±5.59	9/11	12.24±2.48	28.23±1.77*	0

aMCI, amnestic mild cognitive impairment; *MMSE,* Mini Mental State Exam; *CDR*, clinical dementia rating.
*Values are means±standard deviation: $p<0.01$. There were no significant differences ($p > 0.05$) in age (years), sex and education (years) between groups

aMCI, deterioramento cognitivo lieve in anamnesi; MMSE, punteggio questionario Mini Mental State; CDR, scala Clinical Dementia Rating.
** I valori sono rappresentati come media±deviazione standard: p<0,01. Età (anni), sesso ed educazione (anni) non erano differenti in modo significativo (p>0,05) tra i due gruppi.*

from initiating goal-directed, attention-demanding activity. A T2*-weighted, gradient-recalled echo-planar imaging (FPI) sequence was obtained for functional images: echo time, 40 ms; repetition time, 2,000 ms; slice thickness, 6 mm; gap, 1 mm; flip angle, 90°; field of view, 24 cm; resolution, 64×64 matrix.

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm/). The first ten volumes of the functional images were discarded for signal equilibrium and participants' adaptation to scanning noise. For each participant, functional images were realigned using least-squares minimisation without higher-order corrections for spin history and normalised to the Montreal Neurological Institute (MNI) template. Images were resampled to 3×3×3 mm^3 and smoothed with a 4-mm full width at half maximum.

REST package (REST, http://resting-fmri. sourceforge.net) was used to calculate the ALFF with a voxel-based approach. The time courses were first converted to the frequency domain using fast Fourier transform (FFT), and the power spectrum was obtained by square-rooted FFT and averaged across 0.01–0.08 Hz at each voxel. This averaged square root was taken as the ALFF. To reduce global effects of variability across participants, the ALFF of each voxel was divided by the global mean ALFF value within the whole-brain mask obtained previously. The global mean ALFF was calculated only within the brain, with the background and other tissues outside the brain removed.

Two-sample Student's *t* tests were used to assess differences in age, years of education and MMSE scores between the two groups using SPSS 13.0. To investigate the ALFF difference between the two groups, a two-sample Student's *t* test was executed on the individual normalised ALFF maps. Two statistical results were set: one was a higher ALFF value (cluster size >458 mm^3, $p<0.01$, corrected) in MCI patients compared with healthy controls; another was a lower ALFF value (cluster size >525 mm^3, $p<0.01$, corrected) in MCI patients compared with healthy controls. Linear correlations were calculated between MMSE scores and mean ALFF values across all voxels in the abnormal areas in MCI patients.

Results

The demographics of MCI patients and healthy elderly controls, including age, sex and education years, were matched. In MCI patients, MMSE scores ranged from 21 to 29, with an average of 24.77±3.84. In controls, MMSE scores ranged from 26 to 30, with an average of 28.23±1.77. There was a statistically significant difference in MMSE scores between MCI patients and controls ($|t|=2.36$, $p<0.05$). Compared with healthy controls, MCI patients showed significantly decreased ALFF in the right hippocampus (HC), parahippocampal cortex (PHC), left lateral temporal cortex (LTC) and right ventral medial prefrontal cortex (vMPFC), and increased ALFF in the left inferior parietal lobule (IPL) and left TPJ. (Table 2, Figs. 1 and 2)

To identify the association between altered ALFF and behavioural change of MCI, the average ALFF values of all voxels in the above regions were extracted separately. Significant positive correlations were observed between ALFF values in the right HC, and PHC and MMSE scores ($r=0.34$, $p=0.01$). No significant correlations between ALFF values and MMSE scores were found in other above-mentioned brain regions.

Discussion

Using resting-state fMRI based on ALFF analysis, we found abnormal spontaneous functional activity during the resting state in MCI patients, who showed decreased ALFF compared with controls in the medial temporal lobe, specifically in HC and PHC, and LTC and vMPFC, indicating functional deficiency; and increased ALFF compared with controls in the TPJ and IPL, suggesting functional compensation.

Table 2 Brain areas showing significant amplitude of low-frequency fluctuations (ALFF) differences between mild cognitive impairment (MCI) patients and healthy elderly controls

Tabella 2 *Aree dell'encefalo che mostrano significative differenze dell'ampiezza delle fluttuazioni a bassa frequenza (AFBF) tra il gruppo dei pazienti con deterioramento cognitivo lieve (MCI) e controlli anziani sani*

Related area regions	Brodmann area	Talairach coordinates	T	P	Volume (mm^3)
R HC–PHC	20, 36, 19	22 –20 –26	3.66	0.00023	774
L LTC	21, 22	–60 –24 –18	4.82	0.0042	549
R vMPFC	11, 24, 32	0 26 –18	4.94	0.0027	1043
L IPL	39	–50 –63 29	8.37	0.0016	745
L TPJ	40, 39	–54 –54 28	7.68	0.00034	791

L, R, left, right, and bilateral; *T, P, T* and *P* values from a *t* test of the peak voxel (showing greatest statistical difference within a cluster), which corresponds to a corrected $p<0.01$; *HC*, hippocampus; *PHC*, parahippocampal cortex; *LTC*, lateral temporal cortex; *vMPFC*, ventral medial prefrontal cortex; *IPL*, inferior parietal lobule; *TPJ*, temporal-parietal joint

L, R, sinistra, destra e bilaterale; T, P, T e P, valori ottenuti tramite t test al voxel di picco (il quale presenta la maggiore differenza statistica nel contesto di un cluster), che corrisponde ad una soglia corretta per p<0,01; HC, ippocampo; PHC, corteccia para-ippocampale; LTC, corteccia temporale laterale; vMPFC, corteccia pre-frontale ventro-mediale; IPL, lobo parietale inferiore; TPJ, giunzione temporo-parietale.

Episodic memory damage is the earliest and most prominent cognitive impairment in MCI patients [19]. MTL, including the HC, PHC and entorhinal cortex (EC), is critical for memory function [9], which plays an important role in the process of information storage and retrieval, especially for episodic memory retrieval [20]. Dickerson et al. [21] reported that there was obvious activation in the MTL when MCI patients performed cognitive tasks. Significant bilateral HC and underlying EC coactivation was found in both healthy young and elderly people, as well as unilateral MTL coactivation in the mild AD group [6]. Decreased MTL activity was observed in MCI, with an MMSE score of 26.6 [10] and 28.4 [11], whereas increased MTL activity was observed in mild forms of MCI, with an MMSE score of 29.6 [12]. The results in our study are consistent with some ICA findings: compared with healthy elderly participants, reduced MTL activity was observed in MCI patients with an MMSE score 24.77±3.84. Our correlation analysis linked ALFF values in the HC and PHC to MMSE scores, such that lower ALFF values in the HC and PHC were found in MCI

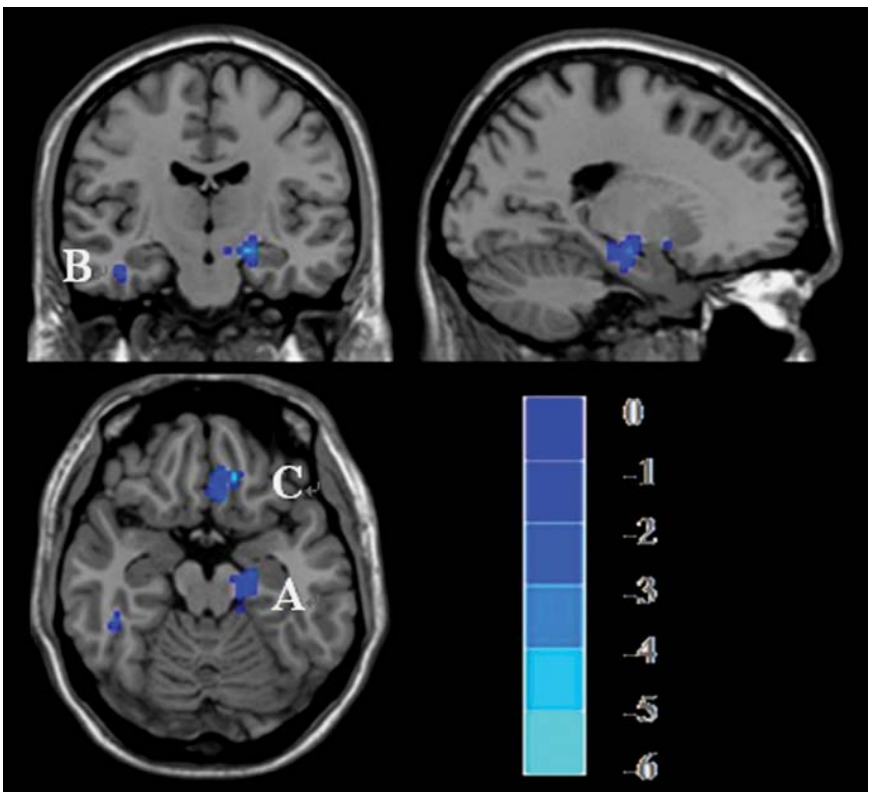

Fig. 1 Regions showing decreased amplitude low-frequency fluctuations (ALFF) in mild cognitive impairment (MCI) patients: *A* right hippocampus (HC) and parahippocampal cortex (PHC); *B* left-lateral temporal cortex (LTC); *C* right ventral medial prefrontal cortex (vMPFC). Threshold was set at $p<0.01$ (corrected). The left hemisphere of the brain corresponds to the left side of the image.

Fig. 1 *Aree che presentano una riduzione in ampiezza delle fluttuazioni a bassa frequenza (AFBF) nei pazienti con deterioramento cognitivo lieve (MCI). A ippocampo di destra (HC) e corteccia para-ippocampale (PHC); B corteccia temporale laterale di sinistra (LTC); C corteccia pre-frontale ventro-mediale di destra (vMPFC). La soglia è stata impostata ad un p<0,01 (corretto). L'emisfero cerebrale di sinistra corrisponde al lato sinistro dell'immagine.*

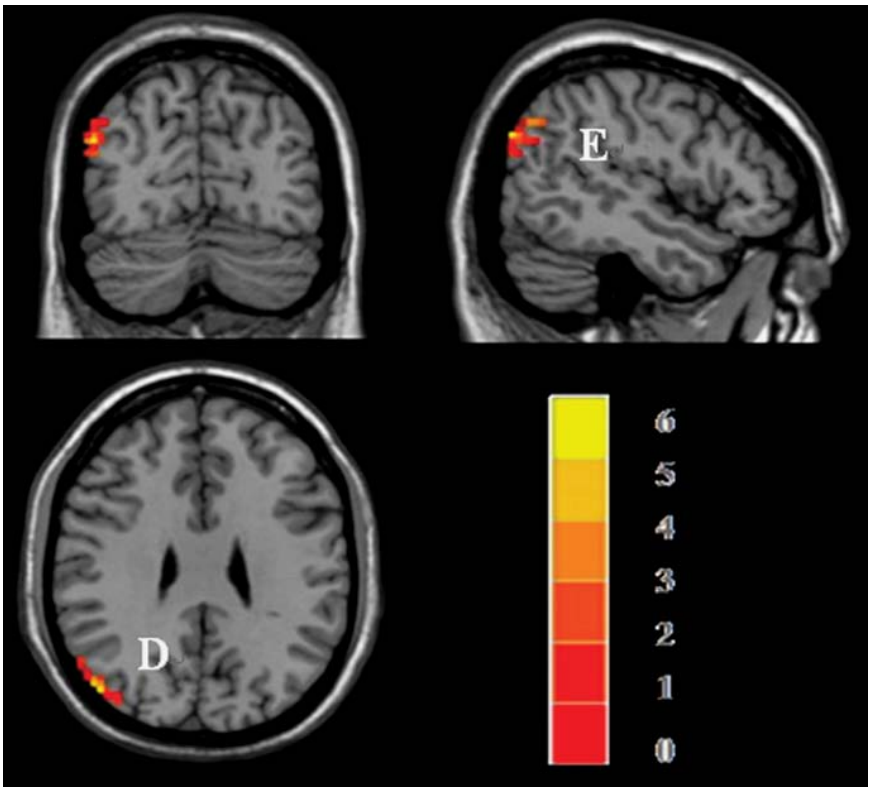

Fig. 2 Regions showing increased amplitude of low-frequency fluctuations (ALFF) in mild cognitive impairment (MCI) patients: *D* left temporal-parietal joint (TPJ); *E* left inferior parietal lobule (IPL). Threshold was set at $p<0.01$ (corrected). The left hemisphere of the brain corresponds to the left side of the image.

Fig. 2 *Aree che presentano un aumento in ampiezza delle fluttuazioni a bassa frequenza (AFBF) nei pazienti con deterioramento cognitivo lieve (MCI). D Giunzione temporo-parietale (TPJ), E lobo parietale inferiore di sinistra (IPL). La soglia è stata impostata ad un p<0,01 (corretto). L'emisfero cerebrale di sinistra corrisponde al lato sinistro dell'immagine.*

patients with lower MMSE scores. These findings suggest that altered MTL activation may be associated with levels of memory impairment seen in MCI patients, and decreased MTL activity could be an imaging-based biomarker to depict MCI.

In our study, there was also decreased ALFF in LTC and vMPFC. The LTC is closely related to episodic memory [22]. Previous studies reported that LTC activity was bilaterally observed in healthy elderly individuals and unilaterally in mild AD patients [6]. The vMPFC is assumed to play a general role in emotional processing, such as attention to emotion, identification or regulation of emotion [23], and guides motivational behaviour by modulating or appraising autonomic emotional responses [24]. MCI patients showed decreased ALFF in multiple brain areas, indicating that there might be many other memory-related brain areas with abnormal activities in the resting state.

In addition to reduced spontaneous activity, increased activity in the left TPJ and IPL was found in MCI patients. The joint of the temporal-parietal-occipital cortex is related to perception, recognition and storage of memory materials. IPL are evoked in working memory and are involved in short-term storage and retrieval of phonology-coded language materials [25] and are obligatorily or unintentionally engaged in the recall of episodic memory information [24]. A previous fMRI study indicated that increased activity in the left prefrontal cortex (PFC) and IPL is found in aMCI patients on the basis of ICA analysis of resting-state fMRI [10]. This phenomenon was considered as a kind of compensatory processes [26]. The compensatory hypothesis is thought to take place in processes of AD, as well as in individuals at risk for AD [27]. Increased functional connectivity between prefrontal regions and other brain regions during memory tasks [28], as well as between the left HC and right dorsolateral prefrontal cortex during resting states [29], was thought to function as compensatory neuronal activity due to cognitive deficits in AD patients. Considering that our patients were enrolled according to strict and uniform standards, the reason that the increased ALFF was caused by clinical symptoms after therapy could be excluded. Cognitive processes rely on optimised use of an increased number of residual healthy synapses or neurons or on alternative brain networks [30]. Therefore, the obviously increased activity might suggest that MCI patients could recruit network resources, primarily from TPJ and IPL, to maintain memory functions following reduced MTL activity.

Several methodological issues concerning the use of ALFF should be considered when interpreting these results. As in all resting-state fMRI studies [24], we reduced but could not eliminate the effects of physiological noise, such as cardiac pulsation, by modelling low-frequency (0.01–0.08 Hz) fluctuations of the BOLD signal, into which cardiac and respiratory noises are aliased because of the relatively low sampling rate (TR=2 s) for multislice acquisitions

[17]. Future studies should record simultaneous cardiac rate to deal with this potential confound.

In conclusion, the abnormal spontaneous brain activity that is closely related to the episodic memory was found in MCI patients. This study suggests that reduced MTL activity could be an imaging-based biomarker to depict MCI. Increased TPJ and IPL activity may indicate a compensatory mechanism in MCI patients. Although rather simple, ALFF analysis may provide a useful tool in fMRI study of MCI.

Acknowledgements This work was supported by the National Natural Foundation of China (Grant 30970818) and the National High-Tech Research and Development Program of China (863 program No: 2008AA02Z302).

Conflict of interest None

References/*Bibliografia*

1. Petersen RC, Smith GE, Waring SC et al (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56:303–308
2. Blennow K, de Leon MJ, Zetterberg H (2006) Alzheimer's disease. Lancet 368:387–403
3. Petrella JR, Krishnan S, Slavin MJ et al (2006) Mild cognitive impairment: evaluation with 4-T functional MR imaging. Radiology 240:177–186
4. Whitwell JL, Przybelski SA, Weigand SD et al (2007) 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain 130:1777–1786
5. Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711
6. Greicius MD, Srivastava G, Reiss AL, Menon V (2004) Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci USA 101:4637–4642
7. Vannini P, Almkvist O, Dierks T et al (2007) Reduced neuronal efficacy in progressive mild cognitive impairment: a prospective fMRI study on visuospatial processing. Psychiatry Res 156:43–57
8. Lui S, Deng W, Huang X et al (2009) Association of cerebral deficits with clinical symptoms in antipsychotic-naive firstepisode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am J Psychiatry 166:196–205
9. Remondes M, Schuman EM (2004) Role for a cortical input to hippocampal area CA1 in the consolidation of a long-term memory. Nature 431:699–703
10. Qi Z, Wu X, Wang Z et al (2010) Impairment and compensation coexist in amestic MCI default node network. Neuroimage 50:48–55
11. Machulda MM, Ward HA, Borowski B et al (2003) Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology 61:500–506
12. Dickerson BC, Salat DH, Greve DN et al (2005) Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 65:404–411
13. Bai F, Zhang Z, Yu H et al (2008) Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: a combined structural and resting-state functional MRI study. Neurosci Let 438:111–115
14. Zang Y, He Y, Zhu C et al (2007) Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 29:83–91
15. Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34:537–541
16. Logothetis NK, Pauls J, Augath M et al (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157
17. Yang H, Long X, Yang Y et al (2007) Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. Neuroimage 36:144–152
18. Petersen RC, Doody R, Kurz A et al (2001) Current concepts in mild cognitive impairment. Arch Neurol 58:1985–1992
19. De Jager CA, Hogervorst E, Combrinck M, Budge MM (2003) Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. Psychol Med 33:1039–1050
20. Buckner RL, Jessica RA, Daniel LS (2008) The brain's default network: anatomy, function, and relevance to disease. Ann NY Acad Sci 1124:1–38
21. Dickerson BC, Salat DH, Bates JF et al (2004) Medial temporal lobe function and structure in mild cognitive impairment. Ann Neurol 56:27–35
22. Grossman M, Koenig P, Glosser G et al (2003) Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. Brain 126:293–311
23. Teasdale JD, Howard RJ, Cox SG et al (1999) Functional MRI study of the cognitive generation of affect. Am J Psychiatry 156:209–215
24. Gusnard DA, Raichle ME (2001) Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2:685–694
25. Jonides J, Schumacher EH, Smith EE et al (1998) The role of parietal cortex in verbal working memory. J Neurosci 18:5026–5034
26. Prvulovie D, Hubl D, Sack AT et al (2002) Functional imaging of visuospatial processing in Alzheimer's disease. Neuroimage 17:1403–1414
27. Bookheimer SY, Strojwas MH, Cohen MS et al (2000) Patterns of brain activation in people at risk for Alzheimer's disease. N Engl J Med 343:450–456

28. Buckner RL (2004) Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 44:195–208

29. Wang L, Zang Y, He Y et al (2006) Changes in hippocampal connectivity in the early stages of Alzheimer's disease: evidence from resting state fMRI. Neuroimage 31:496–504

30. Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc 8:448–460