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Altered spontaneous activity in Alzheimer's disease and mild cognitive impairment revealed by Regional Homogeneity

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ABSTRACT

Alzheimer's disease (AD), the most prevalent cause of dementia in the elderly, is characterized by progressive cognitive and intellectual deficits. Most patients with mild cognitive impairment (MCI) are thought to be in a very early stage of AD. Resting-state functional magnetic resonance imaging reflects spontaneous brain activities and/or the endogenous/background neurophysiological process of the human brain. Regional Homogeneity (ReHo) can provide a fast method for mapping regional activity across the whole brain. Little has been previously published about where or how spontaneous activity differs between MCI and AD, although many previous fMRI studies have shown that the activity pattern is altered in MCI/AD. In the present study, we first used the ReHo method to explore differences in regional spontaneous activities throughout the whole brain between normal controls (NC) and people with MCI and with AD. A one-way ANOVA was performed to determine the regions in which the ReHo differs between the three groups, and then a post hoc analysis was performed to evaluate differences in the pattern among the three groups. Finally a correlation analysis was done between the ReHo index of these regions and clinical variables in order to evaluate the relationship between ReHo and cognitive measures in the AD and MCI groups. An exploratory classification analysis also demonstrated that ReHo measures were able to correctly separate subjects in 71.4% of the cases. Altered brain spontaneous activations were found in the medial prefrontal cortex, the bilateral posterior cingulate gyrus/precuneus and the left inferior parietal lobule (IPL) in both MCI and AD. In MCI, the ReHo index in the left IPL was higher than that of the NC, which could indicate the presence of a compensatory mechanism in MCI. More obviously, the correlation analysis indicated that the lower the memory and other cognitive abilities, the lower the ReHo in patients with MCI and AD. Combining our findings with the results in earlier studies, we propose that the spontaneous activity pattern in the resting state could potentially be used as a clinical marker for MCI/AD.

Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder in which the pathophysiological process consists of the presence of amyloid aggregations and neurofibrillary tangles together with a loss of cortical neurons and synapses (Nestor et al., 2004). Clinically, AD is characterized by cognitive and intellectual deficits and behavioral disturbances (Blennow et al., 2006; Kukull and Bowen, 2002; Sperling et al., 2011). Typically, the earliest and most salient cognitive damage in AD is difficulty in the formation and maintenance of episodic memory (Johnson, 1994). Mild cognitive impairment (MCI) refers to a transitional state between the cognitive changes of normal aging and the fully developed clinical features of dementia (Petersen et al., 1999). MCI is an important condition associated with AD because it is often considered to be a prodromal phase of AD. Individuals with MCI have AD-like symptoms such as reduced memory and other cognitive functions and are at a high risk of conversion to AD (Almkvist et al., 1998; Petersen, 2007). Roughly half of them will convert to AD within 3–5 years (Petersen et al., 1999, 2001). Several other longitudinal studies have suggested that patients with MCI convert to AD at annual rates ranging from 15 to 26% (Landau et al., 2010; Petersen, 2009; Pozueta et al., 2011; Rami et al., 2007). Hence, MCI seems to represent the early symptomatic stage of AD (Bennett et al., 2005; Petersen, 2009; Sperling

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et al., 2011), a possibility that has attracted much attention from neurologists, neuroscientists and neuroradiologists, though whether MCI may progress to other dementia types is still under debate (Fischer et al., 2007; Landau et al., 2010; Molano et al., 2010; Petersen et al., 2009; Petersen, 2011).

Functional magnetic resonance imaging (fMRI) provides a primary method of mechanism detection, diagnostic assessment or therapeutic monitoring of MCI and AD (Buckner et al., 2008; Fornito and Bullmore, 2010; Zhang and Raichle, 2010). Many previous studies that were based on task-state fMRI have found that the activity patterns changed in both MCI/AD patients during the performance of various tasks (Celone et al., 2006; Pariente et al., 2005; Rombouts et al., 2005a, 2005b). Resting-state fMRI signals reflect spontaneous neuronal activity (Biswal et al., 1995; Wang et al., 2008) and/or the endogenous/background neurophysiological process of the human brain (Fox and Raichle, 2007; Raichle et al., 2001; Zhang and Raichle, 2010). Recently, because neither stimulation nor response is required, resting-state fMRI has received increasing interest in AD and MCI related studies (Chen et al., 2011; Greicius et al., 2004; Han et al., 2011; He et al., 2007; Li et al., 2002; Liu et al., 2008; Qi et al., 2010; Wang et al., 2006, 2007; Xu et al., 2008).

Zang et al. (2004) proposed a measure called Regional Homogeneity (ReHo), which can effectively evaluate resting-state brain activity. Based on the hypothesis that brain activity is more likely to occur in clusters rather than in a single voxel, ReHo is calculated using Kendall's coefficient of concordance (KCC) (Kendall and Gibbons, 1990), which evaluates the similarity between the time series of a given voxel and its nearest neighbors. Therefore, ReHo can rapidly map the level of regional activity across the whole brain of an individual (Kiviniemi, 2008).

Several previous studies have investigated the regional spontaneous activity patterns in AD or MCI patients. For example, He et al. (2007) found that AD patients showed significant decreases in the ReHo value in the posterior cingulate/precuneus cortex (PCC/PCu) and increases in the ReHo index of other brain regions, including the bilateral cuneus, the left lingual gyrus and the right fusiform gyrus, when compared with normal controls (NC). Bai et al. (2008) found that in amnestic MCI, the ReHo indices were decreased in regions that included the PCC/PCu, the right anterior cingulate gyrus, the right inferior frontal region, the right superior temporal gyrus and the bilateral cuneus, and were increased in the right inferior parietal lobule, the right fusiform gyrus and the bilateral putamen. A possible explanation for these differences is the different stages of disease (AD and amnestic MCI, respectively) recruited in these two similar studies. However, these differences highlight the fact that the spontaneous brain activity patterns between AD, MCI and NCs across the whole brain are still poorly understood.

We hypothesized that the ReHo index would be different between NCs and people with either MCI or AD, and that the differences in ReHo would be associated with differences in cognitive ability. To address these questions, we first used the ReHo method to explore differences in regional spontaneous activity in the whole brain between NC, MCI and AD subjects. A one-way ANOVA was used to identify regions in which the spontaneous activity pattern was different between the NC, MCI and AD groups. A post hoc analysis was then performed to compare the ReHo index between each pair of groups. Then, a correlation analysis was performed between the ReHo index of the identified regions and various clinical variables (i.e., Mini-Mental State Examination (MMSE) scores, Auditory Verbal Learning Test (AVLT) Immediate Recall/Delay Recall and Recognition scores) in the AD and MCI groups to evaluate the relationship between the ReHo scores and the cognitive abilities of the MCI and AD patients.

Materials and methods

Subjects

All the participants were recruited by advertisement (http://www.301ad.com.cn , Chinese version) and evaluated at the Chinese PLA General Hospital, Beijing, China. All subjects did not accept any medication that may influence cognition during the scans. This study was approved by the Medical Ethics Committee of the PLA general hospital. Written consent forms were obtained from all subjects or their legal guardians. Before they were selected for this study, all participants had general physical, psychological and laboratory examinations. All subjects were right handed and underwent a neuropsychological test battery that included the Mini-Mental State Examination (MMSE), Auditory Verbal Learning Test (AVLT), Geriatric Depression Scale (GDS) (Yesavage et al., 1982), Clinical Dementia Rating (CDR) (Morris, 1993) and the Activities of Daily Living scale (ADL). In brief, in the present study, the AVLT consisted of one learning trial in which a list of 10 Chinese double-character words was read and the subject was asked to immediately recall as many items as possible. After that, the trial was repeated twice and the Immediate Recall score was the average accurate recall of the words three times. Q5 After a 5-minute delay, each subject was asked to recall the words from the initial list (AVLT-Delay Recall). Then the subjects were told to identify the 10 studied words mixed with 10 novel words (AVLT-Recognition). The demographic and neuropsychological details for the included subjects are shown in Table 1.

The diagnostic criteria for MCI was as stated in Peterson et al. (1999) including: (1) memory complaints, lasting at least 6 months; (2) CDR = 0.5; (3) intact functional status and ADL<26; and (4) without dementia according to International Classification of Diseases, 10th Revision (ICD-10). Q6

The recruited AD patients fulfilled the following inclusion criteria: (1) diagnosed using the ICD-10 criteria for AD; (2) CDR = 1 or 2; (3) receiving no nootropic drugs such as anticholinesterase inhibitors; and (4) able to perform the neuropsychological test and tolerate the MR scanning.

The criteria for NC comprised the following: (1) normal general physical status; (2) CDR = 0; and (3) without memory complaint.

Excluding conditions for all subjects included the following: (1) metabolic conditions such as hypothyroidism or vitamin B12 or folic acid deficiencies; (2) psychiatric disorders such as schizophrenia, or depression; (3) infarction or brain hemorrhage, as indicated by MR/CT imaging; and (4) Parkinsonian syndrome, epilepsy and other nervous system diseases that can influence cognitive function. Of course, anyone with a metallic foreign body, such as cochlear implants or heart stents or other MR scanning relevant contraindications was excluded from the study.

Data acquisition

MR images were acquired with a 3.0 T GE MR system using a standard head coil. None of the subjects were taking any medications at

Table 1
Demographic, clinical and neuropsychological data in normal control (NC), mild cognitive impairment (MCI) and Alzheimer's disease patients (AD).

	NC (n = 21)	MCI (n = 19)	AD (n = 23)	*P* value
Gender (M/F)	12/9	10/9	7/16	0.163
Age (year)	70 ± 7	76 ± 8	73 ± 9	0.060
MMSE	29 ± 1	27 ± 2[a]	20 ± 4[a,b]	<0.001
CDR	0	0.5	1.26 ± 0.45	–
AVLT-Immediate Recall[c]	5.9 ± 1.2	5.0 ± 1.0	2.6 ± 1.6[a,b]	<0.001
AVLT-Delay Recall[c]	5.5 ± 2.0	2.6 ± 1.9[a]	0.4 ± 0.7[a,b]	<0.001
AVLT-Recognition[c]	9.2 ± 1.1	8.1 ± 1.9	5.8 ± 3.7[a,b]	<0.001

Chi-square was used for gender comparisons.
One-way ANOVA with Bonferroni post hoc test was used for age, and neuropsychological tests comparisons.
MMSE, Mini-Mental state Examination; CDR, Clinical Dementia Rating; AVLT, auditory verbal learning test.
[a] Significant compared to NC.
[b] Significant compared to MCI.
[c] Two AD subjects refuse to continue this test.

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the time of the scans. Tight but comfortable foam padding was used to minimize head motion, and ear plugs were used to reduce scanner noise. Resting-state fMRI scans were performed by an echo planar imaging (EPI) sequence with scan parameters of repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, matrix = 64 × 64, field of view (FOV) = 220 × 220 mm^2, slice thickness = 3 mm and slice gap = 1 mm. Each brain volume comprised 30 axial slices and each functional run contained 200 volumes. During the fMRI scans, all subjects were instructed to keep their eyes closed, relax and move as little as possible. Sagittal structural images with a resolution of 0.94 × 0.94 × 1.2 mm were acquired using a magnetization prepared rapid gradient echo (MP-RAGE) three-dimensional T1-weighted sequence (TR = 2000 ms; TE = 2.6 ms; FA = 9°).

Data preprocessing

All preprocessing steps were carried out using statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of each functional time series were discarded from analysis to allow for magnetization equilibrium and for the adaptation of the subjects to the scanning situation. The remaining 190 volumes were corrected for the acquisition time delay between the different slices and were also corrected for geometrical displacements according to the estimated head movement and were realigned to the first volume. Head motion parameters were computed by estimating the translation in each direction and the angular rotation on each axis for each volume. Any subject who had a maximum displacement in any of the cardinal directions (x, y, z) that was larger than 3 mm, or a maximum spin (x, y, z) larger than 3°, was excluded. All data were then spatially normalized to the standard EPI template and resampled to 2 × 2 × 2 mm cubic voxels. Several sources of spurious variances including the estimated motion parameters, the linear drift, and the average time series in the cerebrospinal fluid and white matter regions were removed from the data through linear regression. After that, a temporal filter (0.01–0.08 Hz) was performed to reduce the effect of low-frequency drifts and high-frequency uninteresting signals. Finally, the filtered images were smoothed with a 6-mm full width at half maximum to reduce spatial noise.

Nine subjects (1 NC, 2 MCI and 6 AD) who exhibited large amounts of head motions during scanning were also excluded. The demographic and neuropsychological details for the remaining 63 subjects are shown in Table 1.

ReHo measure and statistical analysis

Regional Homogeneity (ReHo) can provide a fast method for mapping regional activity across the whole brain (Zang et al., 2004) (details about this process can be found in Appendix A). In order to reduce the effect of individual variability, we normalized the ReHo value of each voxel by dividing it by the mean ReHo of the whole brain for each subject (Liu et al., 2011; Wu et al., 2009), that's for each voxel $\mathrm{ReHo}_{\mathrm{normlized}} = \mathrm{ReHo}(x, y, z)/\mathrm{Mean}(\mathrm{ReHo})$.

A one-way ANOVA with age and gender as covariances was performed to identify the differences between the MCI, AD and NC groups. The resultant F value map was then thresholded using $P<0.01$ ($F = 4.991$, $df = (2, 58)$) for each voxel and a cluster size of at least 100 voxels, resulting in a corrected threshold of $P_{\mathrm{alpha}}<0.05$, as determined by a Monte Carlo simulation (see AlphaSim in AFNI http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf; parameters were: single voxel $P = 0.01$, FWHM = 6 mm, with automated anatomical labeling (AAL, http://www.cabiatl.com/mricro/) template as mask). Subsequently, the regions that showed significant differences were extracted as regions of interest (ROI) and the mean ReHo values were used for a post hoc analysis after regressing out age and gender effects. Statistical comparisons of the mean fitted ReHo values between each pair of groups were performed using a two-sample two-tailed t-test at a threshold of $P<0.05$ (FDR corrected, with groups times number of significant brain regions).

Relationship between ReHo and the clinical variables

In order to determine whether the ReHo index varied with disease progression in the MCI and AD patients, correlation analyses between the fitted ReHo index and each of the clinical variables (MMSE scores, AVLT-Immediate/Delay Recall and Recognition scores) were performed after regressing out age and gender effects. Because these analyses were exploratory in nature, we used a statistical significance level of $P<0.05$ (uncorrected).

Exploratory classification analysis

In order to measure the potential of this method for possible future use in diagnosis, the ReHo measures were tested to see if they could be used as a feature that could separate patients from normal controls. To test this, we took the mean fitted ReHo measures of each subject as features and introduced the Fisher's linear discriminate functions to get a group classification model using Statistical Product and Service Solutions software (SPSS 13.0). Thus, we took the mean ReHo index of the identified regions for each subject in the three groups (NC, MCI and AD) as features in the discrimination analysis. To test the robustness of the results, we also validated the results by using the leave-one-out cross-validation method (Shi et al., 2007; Wang et al., 2006).

Results

Group differences

First, a one-way ANOVA was used to determine the regions in which the ReHo index was significantly altered among the MCI, AD and NC groups. We found that the ReHo index was significantly different in the following regions: the medial prefrontal cortex (MPFC), the bilateral posterior cingulate gyrus/precuneus (PCC/PCu) and the left inferior parietal lobule (IPL) at $P<0.01$ (Alphasim corrected, $P_{\mathrm{alpha}}<0.05$ at a cluster size at least 100 voxels) between the NC, MCI and AD populations (Table 2 and Fig. 1). Next, we obtained the fitted mean ReHo index of each identified region after regressing out the age and gender effects. A two-sample two-tailed t-test was then performed to determine differences in the pattern between the fitted mean ReHo indices of each pair of the NC, MCI and AD groups.

As Fig. 2 shows, the fitted mean ReHo values in the MPFC, the bilateral PCC/PCu and the left IPL decreased significantly ($P<0.05$, FDR corrected) in the AD population (blue dots) compared with the NCs (red dots) and the MCI group (green bar). In addition, the fitted mean ReHo value in the left IPL significantly increased ($P<0.05$, FDR corrected) in the MCI population compared with the NC group.

Relationship between ReHo and clinical variable

Correlations between the fitted ReHo index of the identified regions and each of the clinical variables were computed for the AD and MCI groups so that we could evaluate the relationship between differences in spontaneous brain activity and cognitive ability in the patients.

As Fig. 3 shows, all the identified regions, that is, the MPFC, the bilateral PCC/PCu and the left IPL, showed significant correlations with the MMSE in the MCI and AD populations ($P<0.05$). Specifically, the lower the MMSE, the lower the ReHo value in these regions.

As Fig. 4 shows, all the identified regions, that is, the MPFC, the bilateral PCC/PCu and the left IPL, showed significant correlations with the AVLT-Immediate Recall scores in the MCI and AD groups ($P<0.05$). Specifically, the lower the AVLT-Immediate Recall ability

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Table 2
Brain areas with significant difference ReHo in the MCI and AD ($P<0.01$, 100 voxels, Alphasim corrected).

Brain region	BA	Cluster size	Voxel F	Voxel equivZ	MNI x, y, z
MPFC	9/10	117	15.05	4.40	−8 60 −8
			9.94	3.55	0 62 −2
			8.12	3.16	−16 60 −6
			7.15	2.93	−24 58 −8
			6.08	2.65	−18 58 −10
			5.73	2.55	−16 66 −6
Pcc\Pcu .L	31	271	11.55	3.85	−8 −64 24
			11.08	3.76	−8 −60 14
			10.42	3.64	−12 −58 22
			10.41	3.64	−6 −52 20
			7.51	3.02	0 −60 16
			7.31	2.97	−8 −56 8
Pcc\Pcu.R	23/31	154	11.25	3.79	8 −36 30
			11.13	3.77	10 −52 20
			8.05	3.15	8 −42 34
			7.45	3.01	10 −48 8
			7.01	2.90	8 −42 22
			6.40	2.74	14 −60 26
IPL.L	40	243	10.39	3.64	−38 −58 34
			9.45	3.45	−44 −62 44
			9.31	3.42	−50 −50 38
			8.74	3.30	−48 −64 42
			8.67	3.29	−40 −58 44
			8.49	3.25	−52 −48 42

MPFC: medial prefrontal cortex; Pcc/Pcu: posterior cingulate gyrus/precuneus; IPL: inferior parietal lobule. Please see Fig. 1 for the regions with slice view.

in the patients with MCI/AD, the lower the ReHo value in these identified brain regions.

As Fig. 5 shows, the MPFC, the left PCC/PCu and the IPL, showed significant correlations with the AVLT-Delay Recall scores in the MCI and the AD patient groups ($P<0.05$). Specifically, the lower the AVLT-Delay Recall ability, the lower the ReHo value in these identified brain regions.

We did not find significant correlations between the ReHo index in the identified regions and the AVLT Recognition scores in the MCI and AD patients.

Exploratory classification analysis based on identified region

We found the fitted mean ReHo values in the MPFC, the bilateral PCC/PCu and the left IPL altered significantly ($P<0.05$, FDR corrected) between the AD, MCI and NC (Fig. 2). Then, we had 4 features ($F1$, $F2$, $F3$, $F4$, mean ReHo index in the identified regions separately) for each subject in the three groups (NC, MCI and AD) in the discrimination analysis. Our results show that the discriminate scores can be calculated by the following two functions:

$$Function\ 1 = 6.189\times F1 + 0.041\times F2 + 5.293\times F3 + 7.055\times F4 - 22.157 \quad (1)$$

$$Function\ 2 = 2.483\times F1 + 5.614\times F2 + 6.279\times F3 - 14.065\times F4 - 0.017. \quad (2)$$

Using these two functions, we were able to correctly distinguish the patients from the NCs in 74.6% of the cases (Table 4 and Fig. 6). The leave-one-out cross-validation results also showed that 71.4% of subjects were able to be correctly classified among the three groups (Table 4). We also found that the mean specificity and sensitivity were higher than 80% in each pair of subgroups between AD, MCI and NC groups (Table 5).

Discussion

To the best of our knowledge, this is the first study to investigate the ReHo of brain spontaneous activity in both MCI and AD patients as well as to compare them with NCs. Significant differences were found in the ReHo scores in various brain regions, that is, the MPFC,

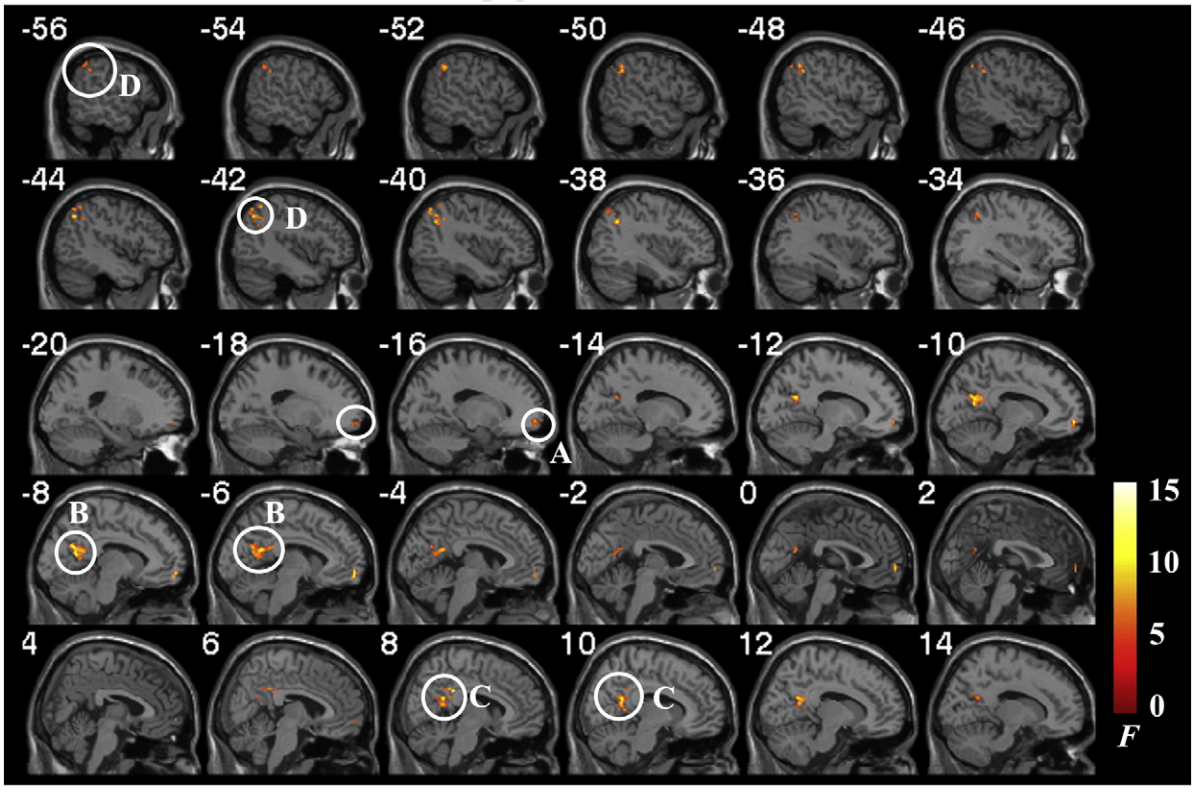

Fig. 1. Brain areas with significant differences in the ReHo in both MCI and AD patients ($P<0.01$, 100 voxels, Alphasim corrected). A—MPFC; B—left Pcc/Pcu; C—right Pcc/Pcu; D—left IPL.

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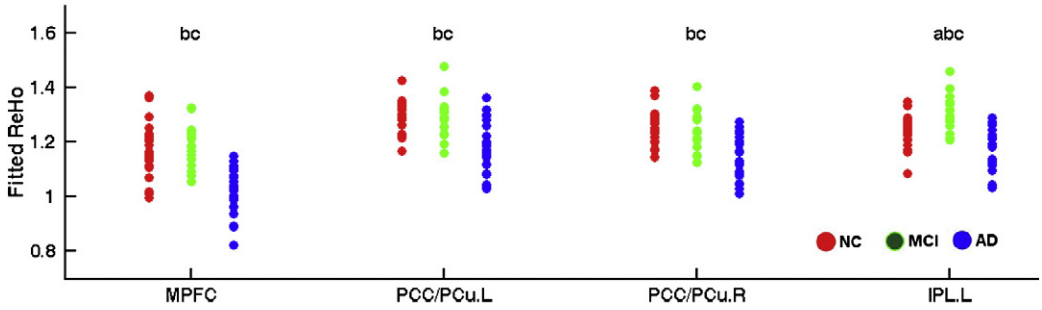

Fig. 2. Plot of ReHo index among NC (red), MCI (green) and AD (blue) in the identified regions ($P<0.05$, FDR corrected). a—the ReHo index is significantly different comparing the NC and MCI; b—the ReHo index is significantly different between the NC and the AD; c—the ReHo index is significantly different between the MCI and the AD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web of this article.)

the bilateral PCC/PCu, and the left IPL in the NC, MCI and AD subjects (Table 1, Fig. 2). More importantly, the ReHo index in these identified brain regions showed a significant correlation with clinical variables in the MCI and the AD populations (Figs. 3–5).

Altered ReHo value in brain regions within the default network

All of the significantly different regions (the MPFC, the bilateral PCC/PCu and the left IPL) are involved in the default network that

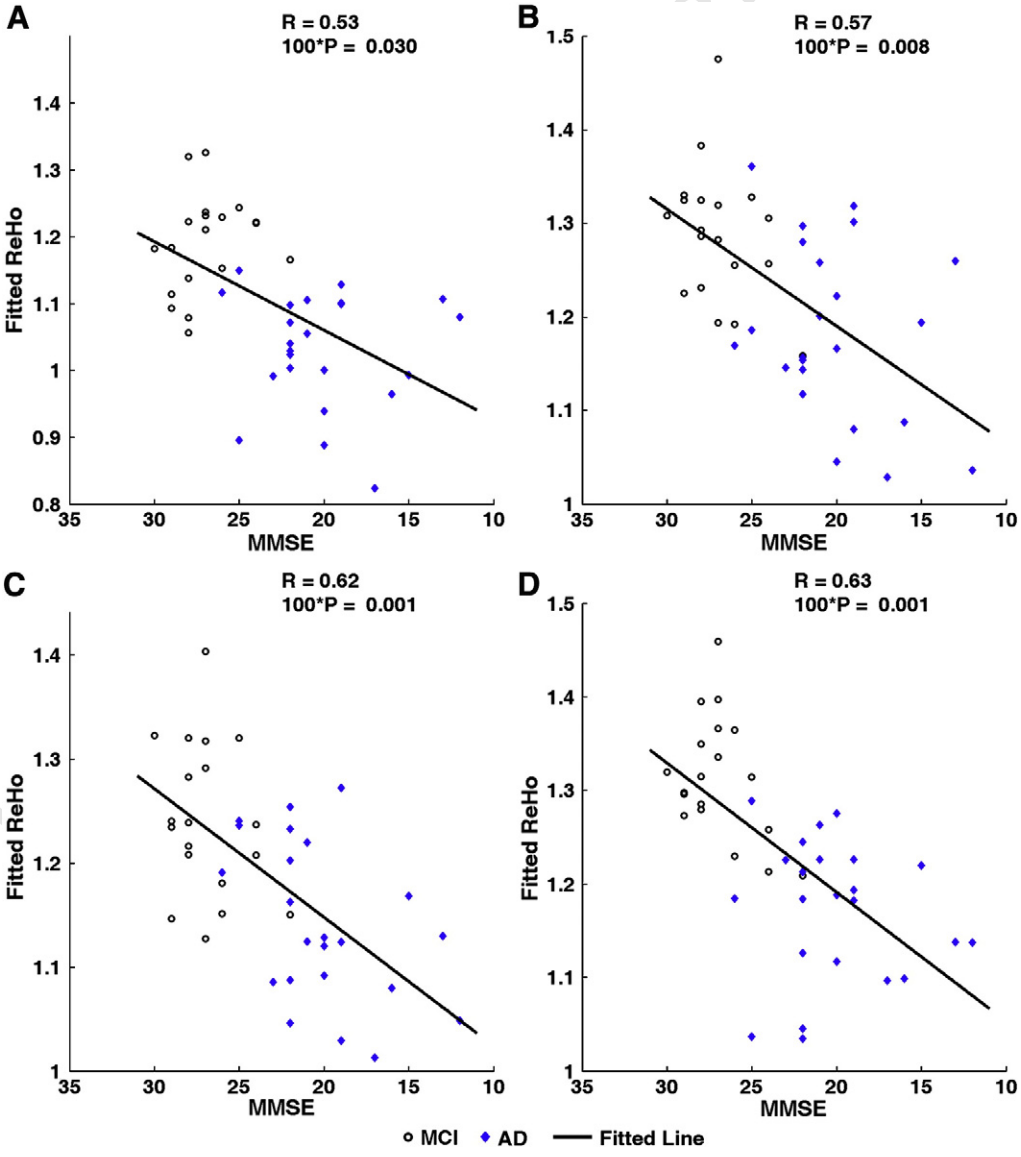

Fig. 3. Correlation between the mean fitted ReHo index and the MMSE in both MCI and AD patients ($P<0.05$). A—MPFC; B—left PCC/Pcu; C—right PCC/Pcu; D—left IPL.

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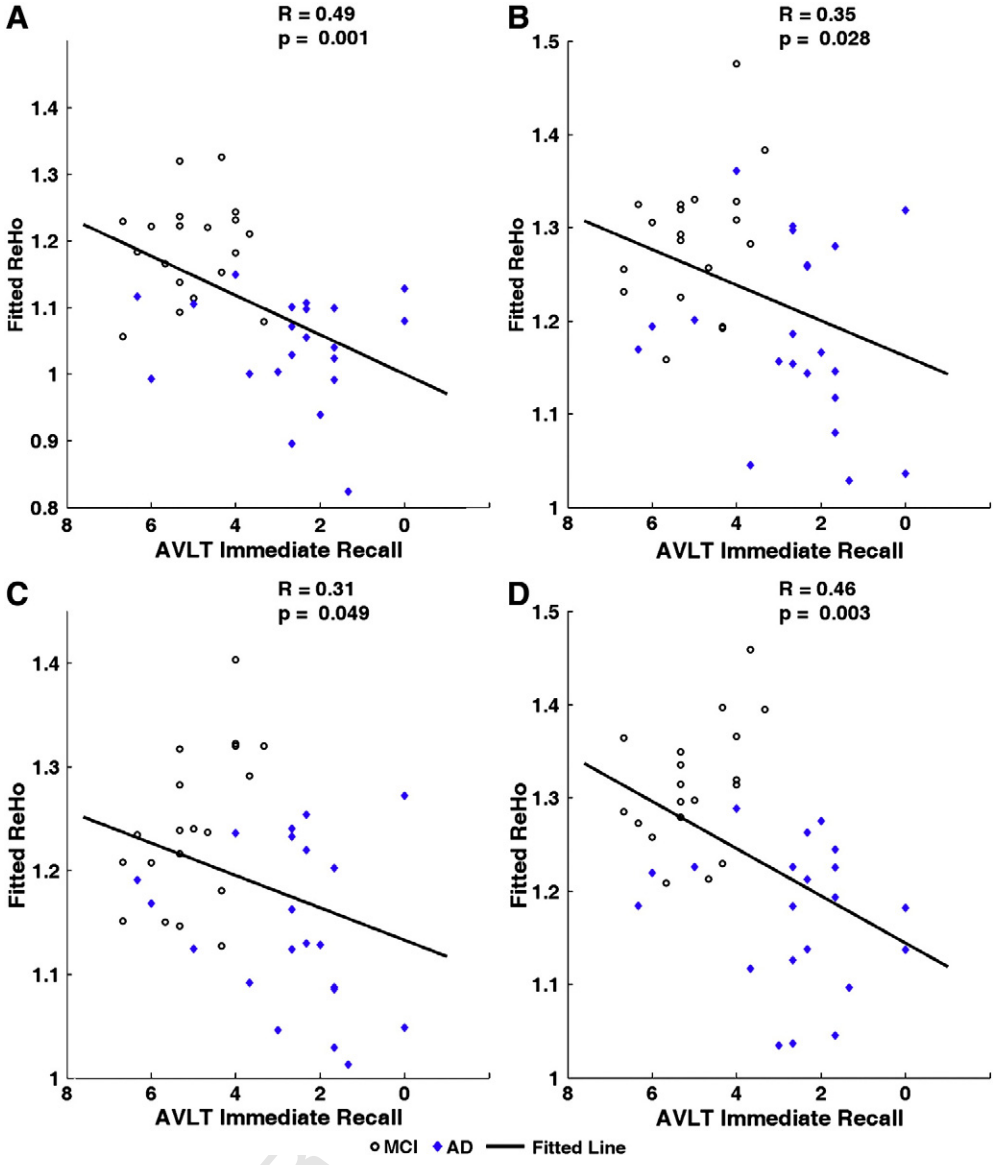

Fig. 4. Correlation between the mean fitted ReHo index and the AVLT-Immediate Recall ability in both MCI and AD patients ($P<0.05$). A—MPFC; B—left PCC/Pcu; C—left IPL.

characterizes resting-state brain activity (Buckner et al., 2008; Raichle et al., 2001). The default network has been suggested as being engaged in internally focused tasks, including autobiographical memory retrieval and envisioning the future, when individuals are not focusing on the external environment. Recently, the default network has been found to be a sensitive hallmark that is injured in MCI/AD patients (Buckner et al., 2008; Dickerson et al., 2009; Greicius et al., 2004; Qi et al., 2010).

Many studies have demonstrated that the PCC/PCu has the highest metabolic rate (Raichle et al., 2001; Shulman et al., 1997) and is an important node in the memory network in healthy subjects (Buckner et al., 2008). Functional connectivity studies have also illustrated that the PCC/PCu may play a pivotal role in mediating the intrinsic activity that sustains a sense of self-consciousness and referential mental thoughts in the default network (Fox and Raichle, 2007; Fransson and Marrelec, 2008; Greicius et al., 2004). Moreover, previous studies have shown morphological abnormalities, hypo-metabolism and altered functional patterns in this region in AD patients (Chetelat et al., 2003; Chetelat et al., 2008; Greicius et al., 2004; Lustig et al., 2003). Recent resting-state fMRI studies on MCI/AD populations have consistently revealed that spontaneous brain activities in the PCC/PCu were reduced in MCI/AD patients (Bai et al., 2009a; Han et al., 2011; He et al., 2007; Qi et al., 2010). Our results increase the evidence for AD-related changes in the PCC/PCu and further indicate that ReHo values in the PCC/PCu can reflect the disrupted global cognitive function in patients with MCI/AD. This correlation was supported by the positive relationship between ReHo index values in the PCC/PCu and scores on the MMSE (Fig. 3). However, unlike previous studies (Bai et al., 2008; Qi et al., 2010), we did not find a significant difference between the MCI population and the normal controls in this study (Fig. 3). Nevertheless, the ReHo index in this region was significantly correlated with AVLT-Immediate/Delay Recall scores in the MCI/AD populations. This indicates that the broken memory systems induced by MCI/AD can be reflected by coherence in the regional activity of the PCC/PCu. This further implies an important role for the PCC/PCu in the memory network. Taken together, the decreasing spontaneous activity of the PCC/PCu seems to be the most robust alteration in the MCI/AD disease process.

We also found a decreased ReHo index in the MPFC (BA 9/10) in the AD patients compared with the NC and MCI groups (Fig. 1). The MPFC (BA 9/10/24/32) has also been identified as a critical node in the default network (Buckner et al., 2008; Raichle et al., 2001) and has been associated with autobiographical memory and self-referential processing as well as supporting attention toward the external environment and

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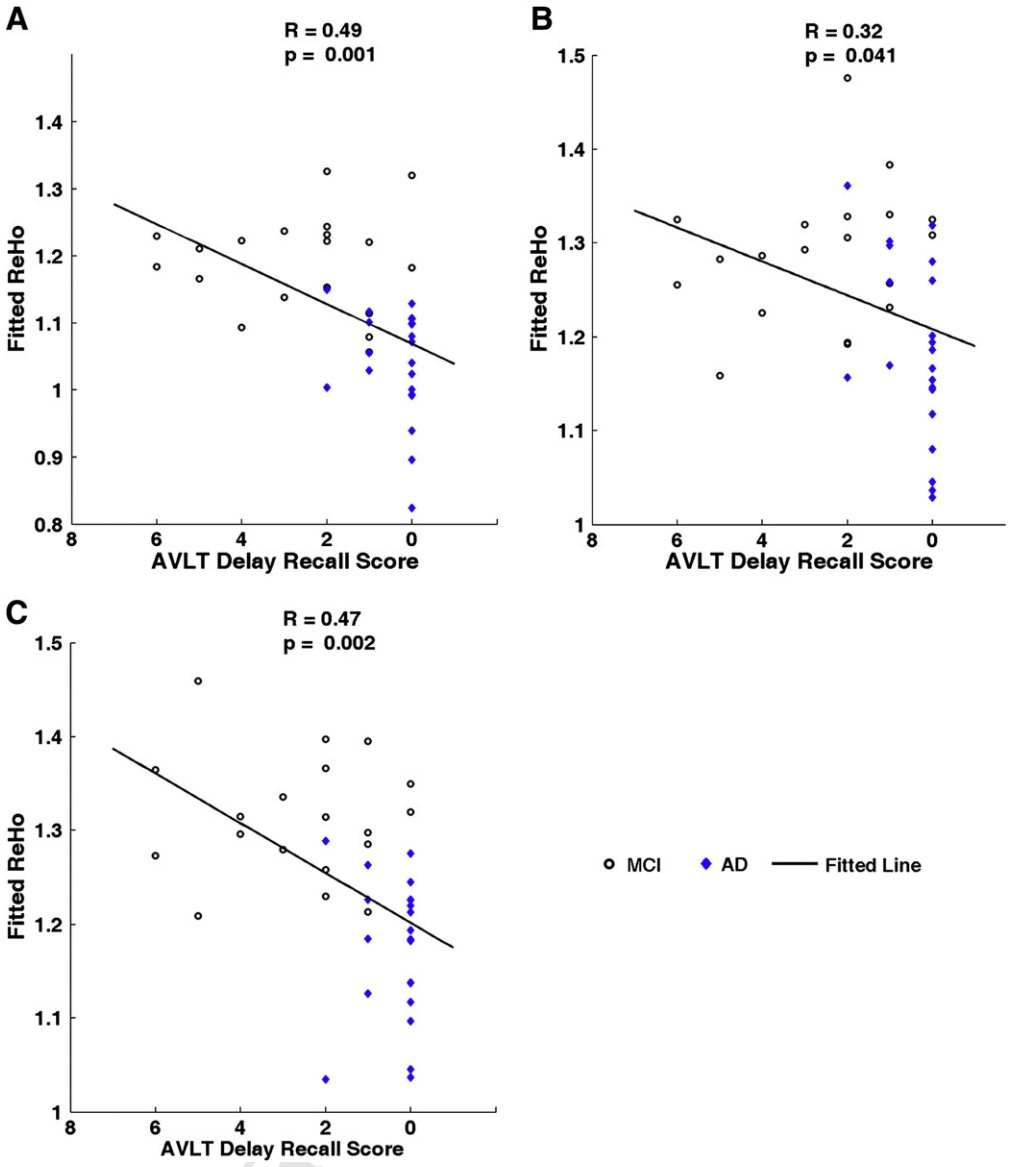

Fig. 5. Correlation between the mean fitted ReHo index and the AVLT-Delay Recall ability in both MCI and AD patients ($P<0.05$). A—MPFC; B—left Pcc/Pcu; C—right Pcc/Pcu; D—left IPL.

facilitating performance by task-related fMRI (Cabeza et al., 2004; Gilbert et al., 2006; Spreng and Grady, 2010). Consistent with our findings, Rombouts et al. found task-induced decreased resting-state activity in the MPFC that was associated with working memory load in AD patients (Rombouts et al., 2005b). Similarly, decreased spontaneous activations in this region were observed in the MPFC

Table 3
Summary of correlation between the mean fitted ReHo index and various clinical variables (MMSE, AVLT-Immediate Recall/Delay Recall) in both MCI and AD, also in MCI, AD and NC groups separately ($P<0.05$).

	Brain area	AD and MCI		MCI		AD		NC	
		R	*P*	*R*	*P*	*R*	*P*	*R*	*P*
MMSE	MPFC	0.531	**0.0003**	−0.255	0.291	0.073	0.742	0.286	0.209
	Pcc/Pcu.L	0.571	**7.9e-05**	0.338	0.157	0.293	0.175	−0.156	0.499
	Pcc/Pcu	0.622	**1.1e-05**	0.240	0.321	0.449	**0.032**	0.029	0.901
	IPL.L	0.626	**9.3e-06**	0.394	0.095	0.106	0.629	0.213	0.354
AVLT-Immediate Recall	MPFC	0.493	**0.0012**	−0.102	0.677	0.128	0.581	0.199	0.387
	Pcc/Pcu.L	0.348	**0.0278**	−0.327	0.172	0.140	0.545	−0.392	0.079
	Pcc/Pcu	0.313	**0.0490**	−0.533	**0.0189**	0.177	0.444	−0.158	0.495
	IPL.L	0.458	**0.0029**	−0.421	0.0730	0.177	0.460	0.224	0.329
AVLT-Delay Recall	MPFC	0.490	**0.0013**	0.010	0.969	0.259	0.257	0.261	0.254
	Pcc/Pcu.L	0.324	**0.0412**	−0.259	0.284	0.450	**0.041**	−0.140	0.545
	Pcc/Pcu	0.232	**0.1493**	−0.329	0.169	0.147	0.526	−0.205	0.373
	IPL.L	0.473	**0.0020**	0.0449	0.855	0.052	0.822	0.008	0.974

MPFC: medial–prefrontal cortex; Pcc/Pcu: posterior cingulate gyrus/precuneus; IPL: inferior parietal lobule.

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Table 4
Summary of exploratory classification results of NC, MCI and AD groups.

		Group	Predict group			Total
			NC	MCI	AD	
Original	Classify count	NC	14	4	3	
		MCI	5	13	1	
		AD	3	0	20	
	Correct ratio (%)	NC	**66.7**	19	14.3	
		MCI	26.3	**68.4**	5.3	
		AD	13	0	**87.0**	**74.6**
Cross-validated[a]	Classify count	NC	14	4	3	
		MCI	6	12	1	
		AD	4	0	19	
	Correct ratio (%)	NC	**66.7**	19	14.3	
		MCI	31.6	**63.2**	5.3	
		AD	17.4	0	**82.6**	**71.4**

[a] Here we used the leave-one-out cross-validation method.

Table 5
Summary of each pair of group between the NC, MCI and AD groups.

	Group	Predict group			Total correct ratio (%)		Ratio (%)
		NC	MCI	AD			
Original	NC	**17**	4			Specificity	81
	MCI	6	**13**		**75.0**	Sensitivity	68.4
	NC	**18**		3		Specificity	85.7
	AD	4		**19**	**84.1**	Sensitivity	82.6
	MCI		**19**	**0**		Specificity	100
	AD		2	**21**	**95.2**	Sensitivity	91.3
Cross-validated[a]	NC	**15**	6			Specificity	71.4
	MCI	7	**12**		**67.5**	Sensitivity	63.2
	NC	**17**		4		Specificity	81
	AD	4		**19**	**84.1**	Sensitivity	82.6
	MCI		**16**	3		Specificity	84.2
	AD		3	**20**	**85.7**	Sensitivity	87

[a] Here we used the leave-one-out validation method to do cross-validation.

in an MCI group (Han et al., 2011) and in AD patients (Bai et al., 2008) compared with healthy controls. Furthermore, we found that decreased ReHo values were significantly correlated with cognitive decline, as indicated by MMSE and AVLT-Immediate/Delay Recall scores (Figs. 3–5). Therefore, we conclude that these decreasing activations in the MPFC may be reflective of the damaged default network and memory system in AD patients, and thus that, in addition to the PCC/PCu, the MPFC may be an important vulnerable region in the AD population.

In the present study, the left IPL (BA 40) was the only region that was able to be used to distinguish the three groups, the MCI, the AD and the NC, from each other. The IPL acts to integrate information from different sensory modalities and plays an important role in a variety of higher cognitive functions (Caspers et al., 2006; Dickerson et al., 2009). Structural MRI studies have demonstrated that atrophy of the IPL is associated with MCI/AD (Desikan et al., 2009; Greene and Killiany, 2010) and that this atrophy in the IPL may act as a predictor of progress from MCI to AD or of aggravation of the disease (Im et al., 2008; Karas et al., 2008). So, the IPL is a notably sensitive marker for changes in MCI and the early stages of AD. Even in pre-symptomatic individuals at high risk for AD, hypo-metabolism and atrophy in the IPL have already occurred (Mosconi et al., 2006). In the current study, the left IPL exhibited a significantly increased ReHo in the MCI population and a significantly decreased ReHo in the AD group compared with the NC and MCI groups (Fig. 2). The increase in spontaneous activity in the IPL in MCI patients may reflect a coherent compensatory recruitment. Consistent with our findings, Bai et al. (2008) and Qi et al. (2010) described compensatory increased spontaneous activity in the IPL in amnestic MCI. In addition, the MCI/AD-related compensatory mechanisms indicated by the increasing activations in this region were also observed in task fMRI studies during memory or mental processing (Acosta-Cabronero et al., 2010; Bokde et al., 2010; Pariente et al., 2005; Yassa et al., 2008). Combining the previous findings with our results, we speculate that increases in ReHo values in the IPL in the MCI patients may reflect compensatory recruitment, whereas the decreased ReHo index in the IPL in AD patients indicated disease related alterations, but this speculation needs to be further tested in the future.

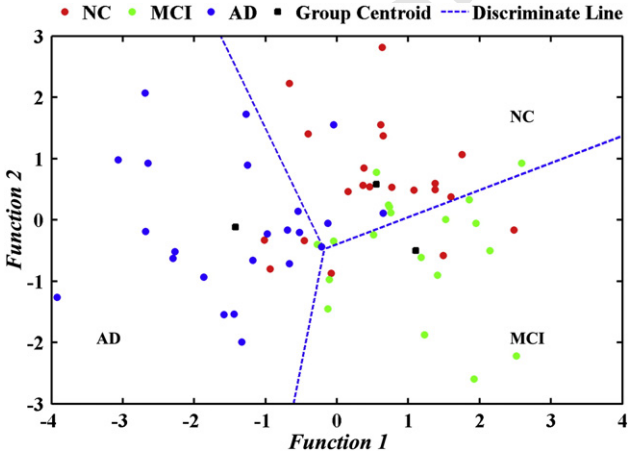

Fig. 6. Exploratory classification results of NC (red), MCI (green) and AD (blue) groups, the discriminate scores calculated using function 1 are on the x axis, the discriminate scores calculated using function 2 are on the y axis. The black square is the centroid of each group; the blue line represents the edge of each group, which was derived by dividing the distance between the centroids in half and extending it from the midpoint of the values. (For interpretation of the references to colour in this figure legend, the reader is referred to the web of this article.)

Correlation between the ReHo index and clinical variables

A novel finding in this study was the identification of a positive correlation between the identified brain regions and the performance on neuropsychological tests. The MMSE, which involves multiple cognitive domains and reflects the global function of the brain, can quantify cognitive function and screen for cognitive loss. The AVLT-Immediate Recall consists of trials of a list learning task and indicates verbal short-term memory, which transfers information into long-term storage, whereas the AVLT-Delay Recall test is often used to measure episodic memory. The ReHo values in the identified regions (i.e., the MPFC, the bilateral PCC/PCu and the left IPL) were significantly correlated with the MMSE and AVLT-Immediate/Delay Recall scores (Figs. 3–5). All these demonstrated that the lower the MMSE or the lower ability in the AVLT-Immediate/Delay Recall, the lower the ReHo index in the identified brain regions.

These findings, indicating that the neuronal substrate breaks down in the course of MCI/AD, confirmed a clinically relevant role for the default network, a finding which is consistent with previous literature (Bai et al., 2009b; Buckner et al., 2008; Han et al., 2011; He et al., 2007; Liu et al., 2008; Qi et al., 2010). Correlations between the ReHo values in the identified regions and the clinical variables (i.e., MMSE and AVLT-Immediate/Delay Recall scores) suggest that the ReHo measurement may be considered to be a predictor of disease progression and an available marker for underlying disease. Note that the ReHo in the bilateral PCC/PCu and the MPFC was relatively constant in the MCI group but was significantly lower in the AD patients compared to the NC group (Fig. 2). This finding was similar to our finding for the AVLT-Immediate and Recognition score (Table 1). This similarity suggested that a reduction in the ReHo score in the bilateral PCC/PCu and the MPFC can represent a decline in learning ability and beyond that in the progress of the diseases. In addition, these positive correlations indicate that the default

network regions are involved in short-term and episodic memory (AVLT-Immediate/Delay Recall) and global cognitive function (MMSE). Taken together, the decreased spontaneous activity in the default network seems to be the most robust change in MCI/AD and indicates that this decreased activity could be a potential marker for classifying patients and distinguishing them from normal controls.

Is the ReHo index a good feature

One of the ultimate goals of our study was to find objective and quantitative indexes for the early diagnosis and therapeutic evaluation of AD patients. Based on exploratory classification analyses, we were able to discriminate the subjects as to stage (NC, MCI, or AD) at a rate that was 71.4% correct (Tables 4, 5 and Fig. 6). In addition, if we only used the ReHo index in the identified regions to distinguish AD from NC or MCI, we were able to obtain a higher correct ratio (about 85% correct) and the mean specificity and sensitivity were higher than 80% in each pair of AD, MCI and NC (Table 5). Note, also, that a definitive diagnosis of AD currently depends on a histopathologic confirmation (Dubois et al., 2010; Li et al., 2002). To confirm our study, however, since histopathologic evidence is not available, we will follow up the imaging and clinical changes of these subjects for the next few years to validate the imaging markers. Several studies have used features from resting-state fMRI to distinguish AD from normal controls and have achieved a percent correct that is comparable to that found in the current study (Chen et al., 2011; Greicius et al., 2004; Li et al., 2011, 2002; for review see Liu et al., 2008; Wang et al., 2006). However, including the current study, all of the above studies only used a small sample size, so the statistical power is limited. Using larger sample sizes will help to reduce individual effects on the classification results and will allow us to develop effective and applicable biomarkers for AD and MCI. In the future such a classification system, based on large sample size, should be able to be introduced to form a clinical diagnostic method based on brain imaging.

Methodological issues and comparison discussion

ReHo is proposed based on the hypothesis that brain activity seems likely to occur in clusters rather than as a single voxel, thus Kendall's coefficient of concordance has been used to evaluate the similarity among the time series of a given voxel and its nearest neighbors (Zang et al., 2004). The pattern of resting-state brain activities obtained by the ReHo method is very similar to that observed by a PET scan in healthy subjects, which indicates that ReHo is a promising measurement for resting-state local brain activities (Zang et al., 2004). Because it is a rank order statistic, the ReHo index is also insensitive to differences in the overall magnitude of the BOLD response. In previous studies, the ReHo index has been successfully applied to the study of a variety of neurological and psychiatric diseases (such as Parkinson's disease, schizophrenia, blindness etc.) and has provided new findings that are disease related (He et al., 2007; Liang et al., 2011; Liu et al., 2011; Mankinen et al., 2011; Shukla et al., 2010; Wang et al., 2011; Wu et al., 2009; Yang et al., 2010).

Consistent with two previous AD/MCI studies (Bai et al., 2008; He et al., 2007), our results support the hypothesis that ReHo is a robust and significant index for evaluating spontaneous activity in MCI and AD patients. He et al. (2007) used the ReHo index to investigate the pattern of regional coherence of spontaneous activity in AD patients and found that these patients showed significant decreases compared with healthy subjects in ReHo in the PCC/PCu. They also found that the ReHo index of the PCC/PCu correlated significantly with MMSE scores. The AD patients also showed an increased ReHo in the bilateral cuneus, left lingual gyrus and right fusiform gyrus compared with healthy subjects. These regions are consistent with previous findings of AD-related increased activation during cognitive tasks, as explained in terms of a compensatory recruitment hypothesis (He et al., 2007). Bai et al. (2008) found that the brain regions in the default network included the PCC/PCu, anterior cingulate gyrus, superior temporal gyrus and bilateral cuneus. Conversely, compared with the control subjects, amnestic MCI subjects were observed to have an elevated ReHo in the right inferior parietal lobule, right fusiform gyrus and bilateral putamen. These higher ReHo levels may also reflect compensation for damage to the medial temporal regions and limbic structures (Bai et al., 2008). In contrast with these two previous studies that are most related to our work, we also found a decreased ReHo index in the PCC/PCu in both the MCI and the AD patients. Note that the identified regions used in these three studies do not exactly match. The most likely explanation for this difference is that these studies focused on different disease types and different conditions at various severity levels. For example almost all of He's sample focused on a greater disease severity and included only diagnosed AD patients, whereas Bai et al.'s study focused on amnestic MCI patients. However, for the first time, the current study identified the regions in which spontaneous activity was significantly altered in both MCI and AD patients. More importantly, the current study also demonstrated that the ReHo index is significantly correlated with the MMSE, AVLT-Immediate/Delay Recall ability in both MCI and AD patients. These findings make us believe that altered spontaneous activity could be used as a trait marker to identify early MCI patients and to separate them from those with AD and from others who are undergoing normal aging.

In contrast with the previous two studies that are most closely related to ours, (Bai et al., 2008; He et al., 2007), we found no significant differences in the ReHo indices in the medial temporal lobe (the MTL, including the entorhinal cortex, hippocampus and parahippocampal gyrus) between the three groups of subjects in the current study. The MTL may be an early and profoundly involved area of amyloid deposits and neurofibrillary tangles, so a considerable amount of work on examining the anatomic basis for memory impairment in AD has focused on the hippocampus and other MTL structures (Arnold et al., 1991; Braak and Braak, 1991; Wolk and Dickerson, 2011). Additionally, many studies have demonstrated that the MTL, especially the hippocampus, is an important node in the memory network (Buckner et al., 2008; Celone et al., 2006; Chetelat et al., 2008; Prince et al., 2005; Ranganath and D'Esposito, 2001). Increased or decreased spontaneous activations in the MTL of AD/MCI patients have been obtained using resting fMRI experiments (Han et al., 2011; He et al., 2007; Li et al., 2002; Qi et al., 2010). The reasons why the activity pattern during rest in these regions is different in different studies remains unclear. The absence of different ReHo values between the three groups of subjects in the MTL in our study may be explained because we recruited patients who were in an early stage and were in a relatively mild state. However, if we thresholded the cluster using a size of 30 voxels at $P<0.01$, the ReHo index in the hippocampus was found to differ between the MCI and AD populations (details can be found in Fig. S1 in Part I of the supplemental material). Petrella et al. (2007) also reported that the MTL, as observed by fMRI, was less vulnerable and sensitive than other regions, such as the PCC/PCu, in AD and MCI patients.

Another issue is the effect of brain atrophy on the fMRI measures. In a previous study, by taking into account regional atrophy as a covariate, He et al. (2007) have found that statistical significance was reduced in both between-group differences in the PCC/PCu and in the correlation between the PCC/PCu ReHo and the MMSE scores. This finding implies that the AD-related fMRI results can be at least partly explained by regional atrophy (He et al., 2007). We have also found a similar pattern in our data after controlling for age, gender and gray matter volumes, that is that the mean statistical F value decreased in a manner that was similar to the results reported by the He et al. (2007) (details can be found in part II of the supplemental material). Considering that previous studies have also shown that some brain structure measures, such as gray matter volumes, cortical thickness, gray matter density etc., are significantly correlated with age (Luders et al., 2009; Narr et al., 2005; Taki et al., 2004), we believe

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that controlling for age might also reduce the effect of gray matter volumes. The material on the effect of the gray matter volumes can be found in part II of the supplemental material.

Notwithstanding the fact that substantial regional activations during the resting state were identified in this study, the relationships of the AD- and MCI-related changes to the deficit of special cognitive function have not been defined in detail. We found that the patients' clinical variables (MMSE, AVLT-Immediate/Delay Recall) were significantly correlated with the ReHo values from various regions. Such correlations indicate a general relationship between abnormal regional spontaneous activity and cognitive function in the patients' groups. However, when we evaluated the correlation between the altered ReHo measure and the clinical variables within AD or MCI, we found lower correlations than when we took the MCI and AD patients together (Table 3). This could be due to the fact that the discriminatory ability of the clinical variables is low because the range is narrow as well as that the between-patient variability is relatively high for both the clinical variables and the ReHo index. More detailed correlations between cognitive domain-specific impairment and region-specific spontaneous activity in the resting brains of MCI/AD patients should be further investigated.

Conclusion

In summary, the present study demonstrated that spontaneous activity in the brain regions in the default network was significantly different in both AD and MCI patients when compared to a NC group. More importantly, the altered ReHo index was significantly correlated with clinical variables in the MCI and AD populations. In the AD group, spontaneous activations were reduced in all of the implicated regions compared with normal controls and the MCI group. This finding may indicate a relationship between an impaired default network and cognitive functioning in AD. In the MCI patients, the ReHo values in the left IPL were higher than those of normal controls, which might indicate the presence of a compensatory mechanism. The significant correlation between the ReHo index and clinical variables indicates that differences in spontaneous activity could provide a novel perspective that could also be used to provide a more sensitive marker than has previously been available. Combining our findings with results from previous related studies, we propose that the spontaneous activity pattern in the resting state could potentially be used as a marker for clinical diagnoses of MCI/AD.

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Appendix A

ReHo measurement

Zang et al. (2004) has proposed using the KCC to measure the similarity of the time series of a given voxel to those of its nearest neighbors in a voxel-wise manner. For a given voxel,

$$\mathrm{ReHo} = \frac{\sum (R_i)^2 - n(\bar{R})^2}{K^2(n^3 - n)/12}$$

where the ReHo is calculated using the KCC (Kendall and Gibbons, 1990). The ReHo ranges from 0 to 1; and the higher the ReHo, the higher the similarity of the local activity of a given voxel to that of its neighbors. $R_i = \sum_{j=1}^{k} r_{ij}$ is the sum rank of the *i-th* time point and r_{ij} is the rank of the *i-th* time point of the *j-th* voxel; $\bar{R}$ is the mean of the; n is the length of the time series; and k is the number of voxels ($k = 27$ in the present study) within the measured cluster. An individual ReHo map was obtained voxel by voxel for each subject.

Appendix B. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.08.049.

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