Brain Imaging and Behavior (2018) 12:188–200
DOI 10.1007/s11682-017-9680-4

ORIGINAL RESEARCH

Alteration of regional homogeneity and white matter hyperintensities in amnestic mild cognitive impairment subtypes are related to cognition and CSF biomarkers

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Published online: 24 February 2017
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Abstract Amnestic mild cognitive impairment can be further classified as single-domain aMCI (SD-aMCI) with isolated memory deficit, or multi-domain aMCI (MD-aMCI) if memory deficit is combined with impairment in other cognitive domains. Prior studies reported these clinical subtypes presumably differ in etiology. Thus, we aimed to explore the possible mechanisms between different aMCI subtypes by assessing alteration in brain activity and brain vasculature, and their relations with CSF AD biomarkers. 49 healthy controls, 32 SD-aMCI, and 32 MD-aMCI, who had undergone structural scans, resting-state functional MRI (rsfMRI) scans and neuropsychological evaluations, were identified. Regional homogeneity (ReHo) was employed to analyze regional synchronization. Periventricular white matter hyperintensities (PWMH) and deep WMH (DWMH) volume of each participant was quantitatively assessed. AD biomarkers from CSF were also measured. SD-aMCI showed decreased ReHo in medial temporal gyrus (MTG), and increased ReHo in lingual gyrus (LG) and superior temporal gyrus (STG) relative to controls. MD-aMCI showed decreased ReHo, mostly located in precuneus (PCu), LG and postcentral gyrus (PCG), relative to SD-aMCI and controls. As for microvascular disease, MD-aMCI patients had more PWMH burden than SD-aMCI and controls. Correlation analyses indicated mean ReHo in differenced regions were related with memory, language, and executive function in aMCI patients. However, no significant associations between PWMH and behavioral data were found. The Aβ level was related with the ReHo value of STG in SD-aMCI. MD-aMCI displayed different patterns of abnormal regional synchronization and more severe PWMH burden compared with SD-aMCI. Therefore aMCI is not a uniform disease entity, and MD-aMCI group may show more complicated pathologies than SD-aMCI group.

Keywords Alzheimer's disease · Cognition · Mild cognitive impairment · CSF · White matter hyperintensities · Magnetic resonance imaging · Precuneus

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Introduction

Amnestic mild cognitive impairment (aMCI) has been conceptualized as an intermediate stage between normal aging and Alzheimer's disease (AD) (Petersen et al. 2001). According to the recent classification criteria, aMCI patients can be further divided into two subtypes: single-domain aMCI (SD-aMCI), characterized by selective episodic memory impairment, and multi-domain aMCI (MD-aMCI), presenting substantial deficits in memory and at least one other cognitive

domain, such as language, executive function, or visuo-spatial abilities (Winblad et al. 2004). There are evidences that MD-aMCI is much more likely to convert to dementia compared with SD-aMCI (Bermejopareja et al. 2016; Bozoki et al. 2001; Lopez et al. 2003).

In addition to clinical evidence of higher conversion rates, neuroimaging techniques demonstrated that MD-aMCI have more "AD-like" features compared to SD-aMCI. To be specific, SD-aMCI shows confined atrophy in medial temporal lobe (MTL) while MD-aMCI exhibits atrophy spreading from MTL into posterior cingulate cortex (PCC) compared to controls(Brambati et al. 2009; Whitwell et al. 2007; Zhang et al. 2012b). Global topological organization of white matter networks are significantly disrupted in MD-aMCI but not in SD-aMCI (Shu et al. 2012). Functionally, during encoding memory, SD-aMCI displays decreased activation confined in sub-gyral regions while MD-aMCI exhibits a more widespread decreased activation of brain regions relative to controls (Li et al. 2013b). Besides, MD-aMCI displays decreased intrinsic brain activity, mostly in DMN regions, compared with SD-aMCI (X. Li et al. 2014). Although previous studies already had advanced understandings of the mechanisms of two aMCI subtypes, the association between intrinsic brain activity and AD neuropathology (e.g., β-amyloid1–42 and tau levels from CSF), which can help for understanding pathophysiologic substrates of these aMCI subtypes, has not yet been fully characterized.

Apart from well-known AD neuropathology, vascular risk factors, such as chronic cerebral hypoperfusion, may also play a primary role in AD pathogenesis (Brickman et al. 2014). Based on MRI, demyelination and axonal loss caused by chronic cerebral hypoperfusion is best visualized in vivo as white matter hyperintensities (WMH) on T2-weighted imaging (Kim et al. 2008). Only Two studies had assessed the differences in WMH severity between different MCI subtypes. While both studies reported negative results, these two studies used visual rating rather than quantitative measure of WMH volume (Bombois et al. 2007; van de La et al. 2009). It should be noted that, visual rating scales have some limitations, including nonlinearity of data, lack of sensitivity to small changes, relative to quantitative measurements (Melhem et al. 2003). The spatial distribution of WMH may have distinctive influence on neurobehavioral outcomes; cognitive abilities such as executive function or processing speed are preferentially associated with periventricular WMH (PWMH, which are attached to the ventricular system) rather than deep WMH (DWMH, which are located apart from cerebral ventricle in subcortical white matter) (Brickman et al. 2014; Kim et al. 2008; Prins et al. 2004). Based on different neuropsychological characteristics between aMCI subtypes, we hypothesized MD-aMCI may have increased PWMH burden relative to SD-aMCI. Conclusively, studies to quantitatively assess PWMH and DWMH in aMCI subtypes are warranted.

In this study, we assessed intrinsic brain activity using a data-driven method, Regional Homogeneity (ReHo), which can quickly measure individual's local coherence of spontaneous brain activity without priori assumption, and is sensitive to detect aberrant local functional connectivity of brain regions in MCI and AD patients (Bai et al. 2008; Y. He et al. 2007; Zang et al. 2004; Zhang et al. 2012a). Besides, we quantitatively assessed vascular risk by separately measuring PWMH and DWMH burden. The aim of present study was to: 1) investigate alteration of regional brain synchronization during resting state and severity of chronic hypoperfusion in these two aMCI subtypes; 2) explore associations of these measures with cognition/CSF AD biomarkers.

Material and Method

Alzheimer's Disease Neuroimaging Initiative

Data used in this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians in developing new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

Participants

The study was approved by the Institutional Review Boards of all of the participating institutions, and informed written consent was obtained from all participants at each site. Using ADNI GO and ADNI 2 database, 49 right-handed cognitively intact healthy participants and 64 aMCI patients, who had undergone structural scans, rsfMRI scans, and neuropsychological evaluation, were identified. Study data were downloaded from the ADNI publically available database prior to April 15, 2016. For the ADNI, to be classified as healthy controls, the subject had a Mini-Mental State Examination (MMSE) between 24 and 30 (inclusive), a clinical dementia rating (CDR) score of 0. Additionally, no signs of depression (Geriatric Depression Scale, GDS < 6) or dementia were present. To be classified as aMCI, the subject had an MMSE

between 24 and 30 (inclusive), a memory complaint, objective evidence of abnormal memory, CDR score of 0.5, general cognition preserved such that a diagnosis of AD could not be made, stable medication, and no signs of depression (GDS score < 6).

Additionally, all subjects were screened and excluded for a history of obvious head trauma, other neurological or major psychiatric disorder and alcohol/drug abuse. Individuals were excluded from participation if they had a significant vascular disease risk history, defined as Hachinski Ischemia Scale (HIS) > 4.

Neuropsychological testing and diagnosis of MCI subtypes

All subjects underwent extensive neuropsychological tests to assess general mental status (MMSE and CDR, mentioned above) and other cognitive domain (Shu et al. 2012), including memory function (Auditory Verbal Learning Test, AVLT, including AVLT 1–5 total and AVLT 30 min recall; Wechsler Memory Scale-Logical Memory, WMS-LM, including immediate and delayed score), processing speed (Trail-Making Test, Part A, TMT-A) (Miner and Ferraro 1998), visuospatial function (Clock-Drawing Test, CDT), executive function (Trail-Making Test, Part B, TMT-B), language (Boston Naming Test, BNT; Semantic Verbal Fluency, SVF).

The aMCI patients were classified into the following subtypes on the basis of the performance in cognitive domain cited previously: SD-aMCI, if there was impairment in memory alone, MD-aMCI, if there was impairment in memory and at least another cognitive domain. Impairment was defined by the presence of a test scoring 1.5 standard deviations (SD) below the average score of age and education matched healthy controls from ADNI (Shu et al. 2012). Specifically, the total number of healthy controls from ADNI is 198, mean age is 73.03 ± 6.20, and mean education attainment is 16.47 ± 2.45. There is no significant difference of age and education ($P > 0.05$) between ADNI controls and aMCI subjects (mean age: 73.33 ± 5.69; education: 15.84 ± 2.45). Finally, in the current study, 49 out of 198 ADNI controls that undergone structural scans, rsfMRI scans, and neuropsychological evaluation were enrolled for subsequent analyses. Meanwhile, 32 MD-aMCI and 32 SD-aMCI patients were left for final analyses.

There were 24 participants (48.9%) of healthy controls with first-degree relatives suffering from AD, and there were 7 participants (21.8%) of SD-aMCI patients and 13 (40.6%) of MD-aMCI patients with first-degree positive AD family history. The reason may attribute to the healthy controls that had positive family history have relatively higher motivation to take part in research than those had negative family history. Our two-sample T tests showed that no significant differences of cognitive ability and WMH volume between subjects who had positive family history and those had negative family history (in both groups or in subgroup level).

CSF samples and quantification of β-amyloid and tau

CSF data set was downloaded from the ADNI website. Levels of $A\beta_{1-42}$, total tau (t-tau) and phosphorylated tau ($p\text{-}tau_{181}$) were measured from CSF samples, which were obtained using the standardized ADNI protocol as previously described (Shaw et al. 2011). Meanwhile, participants with CSF levels outside 3 SD above or below the mean were excluded. It should be noted that not all subjects in present study have the CSF sample because lumbar puncture is an invasive procedure and not obligatory for healthy subjects. Thus, the final samples for CSF analyses included 26 out of 49 healthy controls, 30 out of 32 SD-aMCI and 28 out of 32 MD-aMCI patients.

Data acquisition

Both the structural scans and rsfMRI scans were downloaded from the ADNI database. All participants were scanned using a 3.0-Tesla Philips MRI scanner Structural images were acquired using a 3D MPRAGE T1-weighted sequence with the following parameters: repetition time (TR) =2300 ms; echo time (TE) =2.98 ms; inversion time (TI) =900 ms; 170 sagittal slices; within plane FOV = 256 × 240 mm^2; voxel size = 1.1 × 1.1 × 1.2 mm^3; flip angle = 9°; bandwidth = 240 Hz/pix. The rsfMRI images were obtained using an echo-planar imaging sequence with the following parameters: 140 time points; TR = 3000 ms; TE = 30 ms; flip angle = 80°; number of slices = 48; slice thickness = 3.3 mm; spatial resolution = 3.31 × 3.31 × 3.31 mm^3; matrix = 64 × 64. The T2 FLAIR scans were obtained using an echo-planar imaging sequence with the following parameters: TR = 9000 ms, TE = 90 ms, and TI = 2500 ms. According to the human scan protocol of ADNI database, all subjects should keep their eyes open with fixation (focus on a point on the mirror) during the entire resting-state fMRI scan.

Imaging preprocessing

Data preprocessing was performed using the Data Processing Assistant for Resting-state fMRI, DPASF (http://www.rfmri.org/DPARSF), which is based on the Statistical Parametric Mapping software (SPM8) package (http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Trust Center for Neuroimaging, University College London, United Kingdom) and Resting-State fMRI Data Analysis Toolkit, REST (http://www.restingfmri.sourceforge.net/). The first 10 image volumes of rsfMRI scans were discarded for the signal equilibrium and subject's adaptation to the scanning noise. The remaining 130 images were corrected for timing differences between each slice and

head motion (six-parameter rigid body). Datasets with more than 2.0 mm maximum displacement in any of the x, y, or z directions or 2.0° of any angular motion were discarded. Subsequently, based on through rigid-body transformation, the T1-weighted image was co-registered to the mean rsfMRI image, and spatially normalized to the Montreal Neurological Institute (MNI) stereotactic space, then re-sampled into of 3 mm × 3 mm × 3 mm cubic voxels. Finally, linear trends and temporally filter (0.01 Hz < f < 0.08 Hz) were performed. To remove any residual effects of motion and other non-neuronal factors, six head motion parameters, WM signal, cerebrospinal fluid signal were used as nuisance variables in the functional connectivity analysis. The output of these preprocessing steps was a 4D residual functional volume in native functional space, for each participant. These 4D native data were registered to the MNI152 space with 2 mm resolution based on the affine transformation. Given the disputation of removing the global signal in the pre-processing of rsfMRI data, we omit regress the global signal out.

ReHo analyses

According to the hypothesis that intrinsic brain activity appear in the form of a mass or region made up of many cluster volumes, Zang et al. proposed to analyze characteristics of regional brain activity and to evaluate the similarity between the adjacent cluster volume's brain activities using the Regional Homogeneity (ReHo) method (Zang et al. 2004). Specifically, measurement of ReHo is accomplished on a voxel-by-voxel basis by calculating Kendall's coefficient of concordance (KCC) of time series of a given voxel with those of its nearest neighbors (by Kendall 2010). A larger value for a given voxel indicates a higher regional coherence within a cluster made up of the voxel and its nearest neighbors.

It has been noted that spatial smoothing before ReHo calculation dramatically increases the ReHo value. To prevent this, preprocessed 4D rsfMRI data without spatial smoothing was used for ReHo analysis. All individual ReHo maps were computed and standardized into ReHo Z-value by subtracting the mean voxel-wise ReHo obtained for the entire brain (i.e., global ReHo), and then dividing the resultant value by the standard deviation. This subject-wise ReHo normalization has been demonstrated to improve normality and reliability across subjects (Zuo et al. 2013). Finally, generated ReHo maps were spatially smoothed with a 6 mm full width at half maximum (FWHM) Gaussian kernel.

WMH segmentation and quantification

For each subjects, their 3D T1-weighted scans and T2 FLAIR scans were normalized to MNI space. Then the Lesion Segmentation Toolbox (LST) in SPM8 was used to create the WMH lesion segmentation maps based on 3D T1-weighted scans and T2 FLAIR scans. Automatically created lesion maps were further manually checked for misclassification by 2 experienced neuroradiologist (M. M ZHANG and P. Y Huang). The segmented WMH maps were manually divided in to periventricular WMH and deep WMH using ITK-SNAP software. PWMH were defined as WMHs contiguous with the margins of each lateral ventricle and DWMHs as those separate to it (Seo et al. 2011). Then the volume of PWMH and DWMH for each subjects were calculated by multiplying the voxel number by 1 mm^3.

Statistical analysis

Quantitative variables were presented as mean and standard deviation. Categorical variable were given as absolute and relative frequencies. All statistical analyses were performed using IBM SPSS19 statistical software on Windows.

The TMT-A/B and BNT performance were log-transformed due to positively skewed distribution. Group differences in age, education attainment, neuropsychological scores, CSF data, and WMH burden (including PWMH and DWMH) were examined by one-way analyses of variance (ANOVA). Using Bonferroni correction, post-hoc pair-wise T-test was performed if ANOVA was significant ($P < 0.05$). Sex and first-degree family history were analyzed by using a Chi-square test.

The statistical analyses of ReHo were performed using REST software (www.restfmri.net). Firstly, ANOVA was conducted to identify the ReHo differences among the controls, SD-aMCI, and MD-aMCI groups. The statistical map was corrected for multiple comparisons at a significance level of $P < 0.05$ by combining the individual voxel $P < 0.05$ with cluster size >85 using Monte Carlo simulations; For those clusters displaying significant differences of ReHo among three groups, Post-hoc 2-sample t-tests were further performed, the statistical map was also corrected for multiple comparisons, at a significance level of $P < 0.01$ by combining the individual voxel $P < 0.05$ with cluster size >23 using Monte Carlo simulations.

Finally, we investigated the associations of imaging measures and behavioral data/AD biomarkers from CSF in the 3 groups separately and in aMCI patients. It should be noted the correlations were performed only within the regions exhibiting significant ReHo or WMH differences among three groups. The statistical significance level of correlation analyses were chosen as $p < 0.05$ (uncorrected) since these analyses were exploratory in nature.

Results

Demographics, neuropsychological testing and CSF AD biomarkers

The demographic information, neuropsychological characterizations and AD-related CSF biomarkers for each group are shown in Table 1. There were no significant differences of age, education, first-degree family history and sex distribution among three groups ($p > 0.05$). The MMSE scores were significantly lower in MD-aMCI patients than in SD-aMCI patients ($P < 0.01$) and controls ($P < 0.001$). For neuropsychological testing scores, the group effects were significant for all cognitive domains, with the best performance in healthy controls, intermediate performance in SD-aMCI patients, and worst performance in MD-aMCI patients.

With regard to CSF biomarkers, there were no significant differences of $A\beta_{1-42}$ and p-tau_{181} among three groups. However, there was significant difference of t-tau level among three groups. MD-aMCI patients had significantly increased t-tau relative to SD-aMCI and controls.

ReHo

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: left parahippocampal (PHG), right middle temporal gyrus (MTG), left lingual gyrus (LG), and right postcentral gyrus (PCG).

Then, post-hoc t-test was performed. SD-aMCI showed significantly decreased ReHo in right MTG and inferior temporal gyrus (ITG) and increased ReHo in left LG and right superior temporal gyrus (STG) when compared to controls. MD-aMCI showed significant decreased ReHo in right precuneus (PCu) when compared to controls. And MD-aMCI showed significant decreased ReHo in left LG and right PCG relative to SD-aMCI. The detailed results are shown in Table 2 and Figure 1.

White matter hyperintensities

The frequency maps of WMH in three groups are shown in Figure 2. The one-way ANOVA was used to determine the regions in which WMH was significantly altered among three groups. We found that the total WMH and PWMH burden was significantly different in three groups (Figure 3). Then, *post-hoc* t-test was performed. There is no significant difference of WMH between SD-aMCI and controls. In contrast, MD-aMCI showed significantly increased total WMH and PWMH burden when compared to SD-aMCI and controls ($P < 0.05$, corrected by least significant difference (LSD) for multiple comparisons).

Correlations between ReHo and cognition/CSF biomarkers

In both aMCI subgroups, the correlation analysis showed ReHo of LG was significantly related with log-transformed TMT-A ($r = -0.44$, $p < 0.001$), log-transformed TMT-B ($r = -0.47$, $p < 0.005$), CDT ($r = 0.30$, $p < 0.01$); ReHo of right PCG was significantly related with CDT ($r = 0.29$, $p < 0.05$) , SVF ($r = 0.37$, $p < 0.005$), log-transformed TMT-A ($r = -0.31$, $p < 0.01$), log-transformed TMT-B ($r = -0.34$, $p < 0.005$). The correlation analyses were subsequently performed in subgroup level. In SD-aMCI, ReHo of STG was significantly related with MMSE ($r = -0.52$, $p < 0.005$) and Aβ1–42 ($r = -0.48$, $p < 0.005$). In MD-aMCI, ReHo of left LG was significantly related with AVLT ($r = -0.54$, $p < 0.05$). Unexpectedly, no correlations between the WMH (PWMH and total-WMH) burden and the behavioral data existed. Besides, there was still no significant correlation between WMH (PWMH and total-WMH) volume and CSF biomarkers in three groups.

Given that age, education, sex and first-degree family history of AD (mirroring the influence of known and unknown susceptibility genes and other non-genetic risks (Trachtenberg et al. 2012)) may affect the ReHo value and cognitive abilitiy, subsequent association analyses were performed after controlling for these factors. In both aMCI subgroups, the correlation analysis showed ReHo of LG was significantly related with log-transformed TMT-A ($r = -0.43$, $p < 0.001$), log-transformed TMT-B ($r = -0.37$, $p < 0.005$), CDT ($r = 0.335$, $p < 0.01$). ReHo of right PCG was significantly related with CDT ($r = 0.36$, $p < 0.005$) and SVF ($r = 0.35$, $p < 0.01$). The correlation analyses were subsequently performed in subgroup level. In SD-aMCI, ReHo of STG was significantly related with MMSE ($r = -0.58$, $p < 0.005$) and $A\beta_{1-42}$ ($r = -0.45$, $p < 0.05$). In MD-aMCI, ReHo of PCu was significantly related with log-transformed TMT-A ($r = -0.45$, $p < 0.05$), log-transformed TMT-B ($r = -0.40$, $p < 0.05$), CDT ($r = 0.34$, $p < 0.05$) and total AVLT ($r = 0.29$, $p < 0.05$). There were no correlations between the WMH (PWMH and total-WMH) burden and the behavioral data existed. Besides, there was still no significant correlation between WMH (PWMH and total-WMH) volume and CSF biomarkers in three groups. The scatter plots are shown in Figure 4.

Discussion

To the best of our knowledge, this is the first research to investigate both alteration of intrinsic brain activity and vascular risk in patients with different aMCI subtypes. The present study yielded evidence for different patterns of changed regional synchronization in aMCI subtypes relative to

Table 1 Comparison of demographic information, behavioral data, CSF AD-related biomarkers among three groups

Characteristic	Normal Controls (n = 49)	SD-aMCI (n = 32)	MD-aMCI (n = 32)	F/χ2 Value	P Value
Age	73.33 ± 4.60	72.43 ± 4.25	74.90 ± 5.27	2.3	0.11
Education	16.24 ± 2.60	16.47 ± 2.24	15.25 ± 2.65	2.2	0.12
Gender (Female/male)	31/18	15/17	15/17	3	0.22
First-degree relative with AD	24 (48.9%)	7 (21.8%)	13 (40.6%)	6.04	0.05
HIS	0.59 ± 0.71	0.47 ± 0.76	1.09 ± 1.06	5.21	0.01
MMSE	29.02 ± 1.20	28.34 ± 1.68	27.16 ± 1.71	15.03	<0.001[bc]
Memory					
WMS-LM immediate	14.73 ± 2.76	9.88 ± 3.17	7.88 ± 2.83	60.49	<0.001[abc]
WMS-LM delayed	13.96 ± 2.99	7.97 ± 2.78	5.75 ± 3.06	84.93	<0.001[abc]
AVLT-Total	43.22 ± 9.01	37.34 ± 9.63	31.25 ± 8.78	16.85	<0.001[abc]
AVLT-30Min	6.84 ± 3.47	4.50 ± 3.94	3.16 ± 3.61	10.52	<0.001[ab]
Visuo-spatial					
CDT	4.76 ± 0.48	4.75 ± 0.44	3.78 ± 1.18	19.68	<0.001[bc]
Language					
SVF	20.84 ± 4.75	21.44 ± 3.55	14.66 ± 3.76	27.37	<0.001[bc]
Log-transformed BNT	1.46 ± 0.02	1.45 ± 0.03	1.41 ± 0.12	3.98	0.02[b]
Executive					
Log-transformed TMT-B	1.86 ± 0.16	1.86 ± 0.13	2.19 ± 0.16	51.75	<0.001[bc]
Processing speed					
Log-transformed TMT-A	1.51 ± 0.12	1.47 ± 0.08	1.66 ± 0.15	23.82	<0.001[bc]
CSF					
Aβ(ng/L)	182.81 ± 50.73	178.29 ± 62.45	170.79 ± 51.60	0.33	0.72
T-tau (ng/L)	61.45 ± 30.15	90.74 ± 58.99	97.55 ± 55.62	3.86	0.03[b]
P-tau (ng/L)	39.51 ± 29.73	40.36 ± 22.23	49.48 ± 28.11	1.19	0.31

Data are presented as mean ± SD;

Abbreviations: MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, single-domain amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; WMS-LM, Wechsler memory scale-logical memory; CDT, clock drawing test; SVF, semantic verbal fluency; AVLT, auditory verbal learning test. TMT-A, trail-making test, part A; TMT-B, trail-making test, part B

[a] Post hoc paired comparisons showed significant group differences between NC and SD-aMCI, after Bonferroni correction.[b] Post hoc paired comparisons showed significant group differences between NC and MD-aMCI, after Bonferroni correction.[c] Post hoc paired comparisons showed significant group differences between SD-aMCI and MD-aMCI, after Bonferroni correction

controls. Besides, unlike SD-aMCI cases who displayed no significant different of WMH burden from that of controls, MD-aMCI showed significantly increased total WMH and PWMH burden relative to SD-aMCI and controls. More importantly, these measures showed a significant correlation with both behavioral data and AD biomarkers from CSF.

Abnormal ReHo in patients with SD-aMCI and MD-aMCI

Firstly, we detected that SD-aMCI have significantly decreased ReHo in right ITG/MTG and increased ReHo in left LG and right STG than controls. Several rsfMRI studies using same method have consistently shown decreased ReHo area in ITG/MTG and increased ReHo area in LG relative to controls in aMCI patients (Bai et al. 2008; Yuan et al. 2016). Regions of ITG/MTG are involved in semantic memory processing (Onitsuka et al. 2007). Thus, it may be reasonable to assume that ITG/MTG play an important role in the disruption of memory function in SD-aMCI. Of note, both STG and LG exhibited significantly increased regional synchronization in SD-aMCI. As for STG region, it includes the primary and secondary auditory cortices and a language-related area (Dikker et al. 2014; Tomasino et al. 2014). Meanwhile, LG is part of the visual association cortex that is linked to processing vision, and LG is also a structure in relation to recognition of words (Mechelli et al. 2000). On the basis of evidence that no significant differences of additional cognitive abilities (other than memory function) between SD-aMCI and controls were present, we hypothesized that increased ReHo in STG and LG indicate the presence of a compensatory mechanism. Specifically, additional increased regional synchronization in STG and LG may comnpensant for the language or visuo-spatial function that should have been disrupted. This

Table 2 Brain areas with significant ReHo difference among normal controls, SD-aMCI and MD-aMCI patients

Region	MNI Coordinate			Cluster Voxels	Peak Intensity
	X	Y	Z		
Controls VS. SD-aMCI					
R-Inferior/Middle Temporal Gyrus	63	-48	-9	25	-3.56
L-Lingual Gyrus	0	-90	-3	50	3.67
R-Superior Temporal Gyrus	60	-60	21	37	4.03
Controls VS. MD-aMCI					
R-Precuneus	3	-48	12	31	-3.52
SD-aMCI VS. MD-aMCI					
L-Lingual Gyrus	-3	-66	6	248	-5.12
R-Postcentral Gyrus	51	-21	39	60	-3.62

Abbreviations: MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, single-domain amnestic mild cognitive impairment; MNI, Montreal Neurological Institute. The X, Y, Z coordinates of the primary peak locations in the MNI space

assumption could be further supported by the negative correlation between ReHo of STG and MMSE in SD-aMCI patients. Although SD-aMCI patients had increase regional synchronization in STG, our results indicated that the impairment of general cognitive ability in SD-aMCI patients has already started and it was linked to the degree of compensatory effects.

PCu is involved in processing information integration and tightly linked to cognitive abilities including long-term memory (via working in concert with the medial temporal lobe), executive function as well as processing speed. In the current work, MD-aMCI showed significantly decreased ReHo in right PCu when compared to controls (Randy L. Buckner et al. 2009). Previous studies using same methods also reported that AD patients had significantly lower ReHo value in PCC/PCu (Y. He et al. 2007; Zhang et al. 2012a). Meanwhile, one recent meta-analysis reported (based on 36 task-based fMRI studies), during the processes of memory encoding, the AD patients exhibited altered brain activity in PCu (H. J. Li et al. 2015). Our results extended prior findings by demonstrating that abnormal regional functional synchronization in patients with MD-aMCI was similar to the abnormalities in AD patients. Furthermore, there were significant brain-behavior associations between the ReHo of PCu and memory, which may account for the neural bases underlying serious memory deficits in MD-aMCI.

We observed MD-aMCI exhibited decreased ReHo in PCG relative to SD-aMCI patients. In general, the major function of the PCG is somatosensory processing, such as the somatic sensation of external stimuli (Nelson and Chen 2008). However, it should be noted that parietal cortex has extensive connections with the frontal lobe region (i.e., parieto-frontal circuit), which could send rich sensory information not only for movement controls, but also for other cognitive abilities, especially in executive function (R. L. Buckner et al. 2008; O'Sullivan et al. 2001; Xiao et al. 2016). As a result, a decreased ReHo of motor system in MD-aMCI might indicate the disruption of parieto-frontal functional connections. There are several supportive evidence from microstructural studies. Li and Liang reported MD-aMCI groups have significantly reduced FA in right PCG when compared to SD-aMCI groups (Li et al. 2013a). Meanwhile, using diffusion spectrum imaging (DSI), Chang et al. demonstrated that MD-aMCI groups have more impairment in the inferior cingulum bundle than SD-aMCI groups, which anatomically reach(connected with) parietal cortex (Chang et al. 2015). Subsequent correlation analyses in our study indicated ReHo of PCG was significantly related with CDT and SVF. It is common known that performance of CDT and SVF are needed to modulate executive function, which is compatible with our assumption as well (Troyer et al. 1998).

We noted that MD-aMCI displayed significantly decreased ReHo in left LG relative to SD-aMCI. Similarly, Li et al. detected the differences in the alteration of intrinsic brain activity between the subtypes of aMCI, they also observed that MD-aMCI had significantly decreased ALFF in the LG than SD-aMCI patients (Li et al. 2013b). Correlation analyses showed that ReHo value of LG was significantly related with log-transformed TMT-A/TMT-B, CDT in both aMCI groups. These results were supported by previous work documenting that LG is part of the visual association cortex that is linked to processing vision (Mechelli et al. 2000). In conclusion, our results suggested abnormal regional synchronization of LG and PCG contribute to a more severe impairment of visuo-spatial function, executive function, language and information processing speed in MD-aMCI than SD-aMCI.

Unexpectedly, the current study did not find significant difference of ReHo value in the PCC between SD-aMCI and MD-aMCI patients. Previous relevant studies have shown that the PCC of MD-aMCI have smaller volume (J. He et al. 2009; Whitwell et al. 2007), reduced fractional anisotropy (FA) (Li

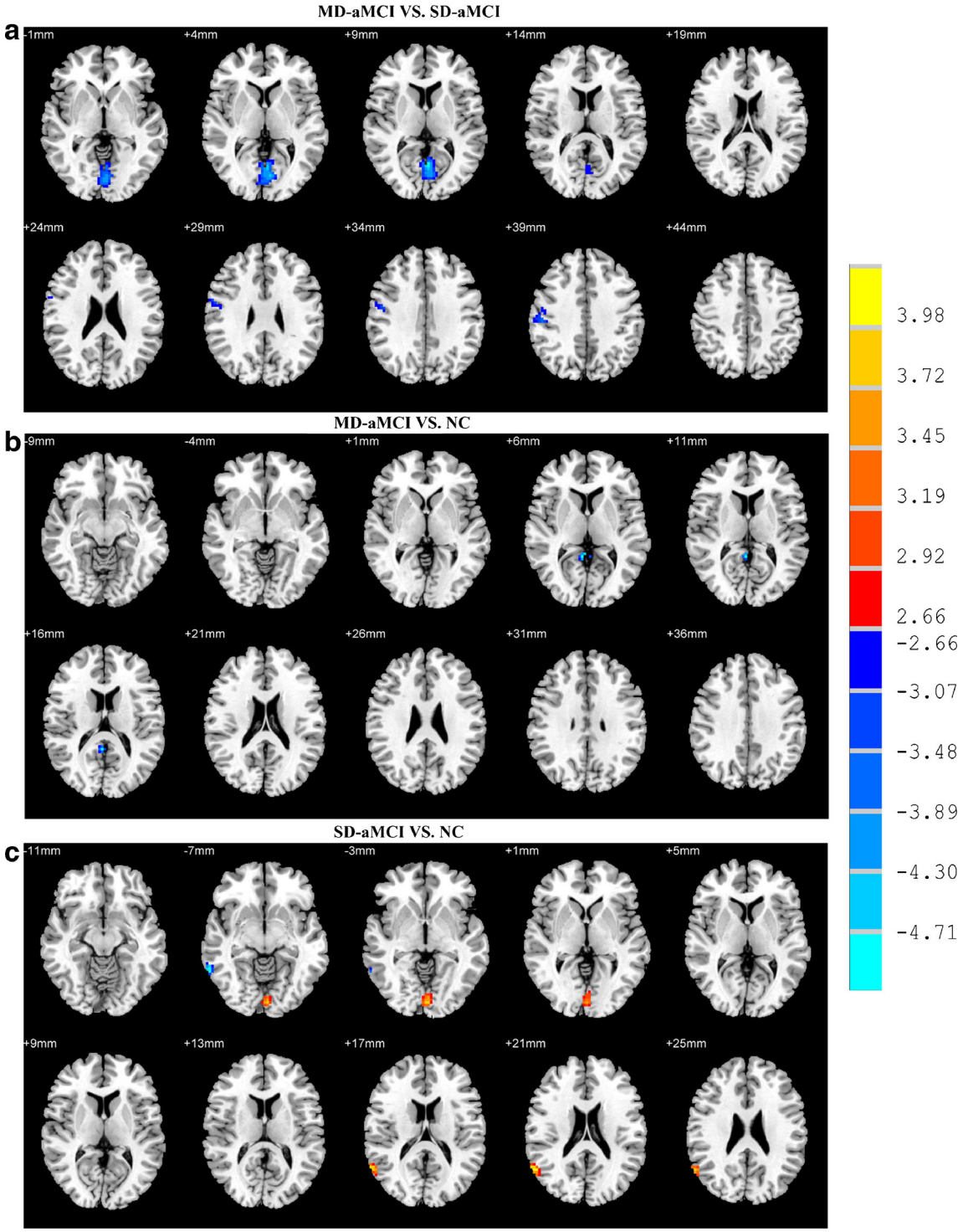

Fig. 1 shows t-statistical difference map between (**a**) SD-aMCI and MD-aMCI, (**b**) normal controls and MD-aMCI, and (**c**) normal controls and SD-aMCI. T-score bars are shown on the right. Warm and cold colors indicate ReHo increased and decreases, respectively

et al. 2013a), hypometabolism (Caffarra et al. 2008) and decreased memory-encoding related brain activity (Li et al. 2013b) relative to SD-aMCI. Difference of mean age of samples may account for this inconsistence. The mean age of sample of current work was 73.5 ± 4.8y, which was higher than the age of samples in work mentioned above. This age difference may affect the intrinsic functional connectivity and metabolites of PCC (Campbell et al. 2013; Reyngoudt et al. 2012). Although there were no significant differences of cognitive ability between subjects who had positive family history and those had negative family history in both groups or in subgroup level, another possibility is that the control group

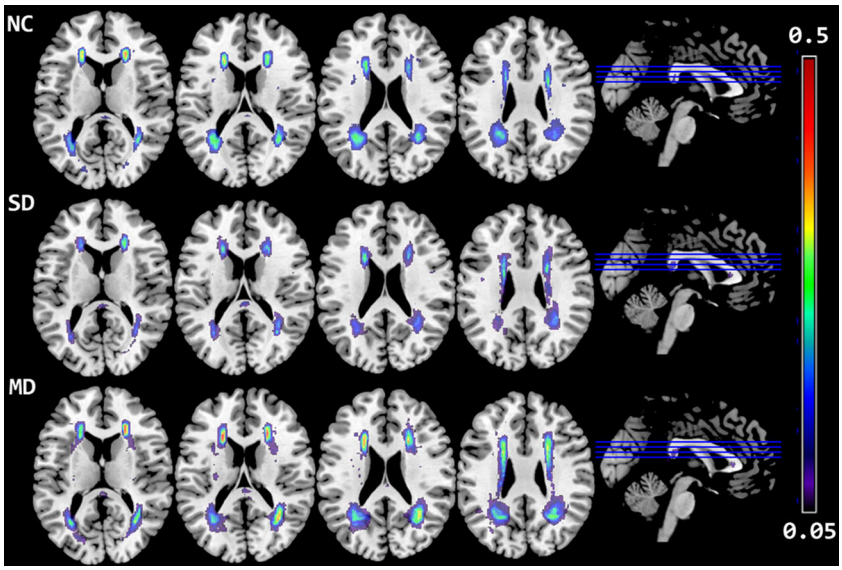

Fig. 2 shows cumulative WMH map in normal controls (NC), SD-aMCI patients (SD) and MD-aMCI patients (MD). Only areas with WMH in at least 5% of the patients are shown. Compared with the SD-aMCI patients and controls, MD-aMCI patients have more WMH burden, especially in PWMH

has many participants with first-degree family history of AD (48.9%). As a result, the first-degree family history may be another factors that caused our result to differ from previous ones. Thus, future studies of MCI should take the one-degree AD family history into consideration, because it may represent a complicated risk factor, mirror the influence of know and unknown susceptibility genes and other non-genetic risk (Trachtenberg et al. 2012).

Abnormal WMH burden in patients with SD-aMCI and MD-aMCI

With regard to the MRI-derived chronic hypoperfusion biomarker, there was no significant difference of WMH burden between SD-aMCI and controls. In contrast, MD-aMCI exhibited significantly increased WMH burden, particular in PWMH, when compared to SD-aMCI and controls. From the perspective of hemodynamics, the difference of WMH

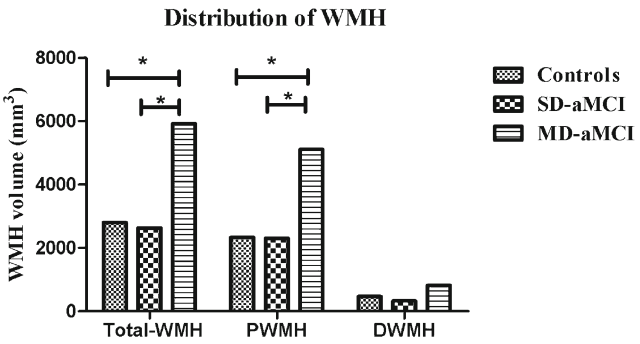

Fig. 3 shows regional distribution of mean WMH volume across groups. The histogram showing MD-aMCI patients had significantly increased WMH burden in PWMH relative to SD-aMCI patients and controls. *represents $P < 0.05$, corrected by least significant difference (LSD)

burden in these two aMCI subtypes further support the notion that aMCI is not a uniform disease entity. Previous studies have reported dichotomization of WMH into PWMH and DWMH have a substantial functional relevance. To be specific, cognitive impairment, rate of cognitive decline are preferentially associated with PWMH while risk and outcomes of mood disorders are preferentially associated with DWMH (Brickman et al. 2014; Krishnan et al. 2006; Prins et al. 2004). Unexpectedly, in present study, there were no significant correlations between PWMH burden and any behavioral data in aMCI patients. There are two primary possibilities that may explain these results. Firstly, we speculated that severe cognitive impairment in MD-aMCI patients may primarily result from alteration of neural activity mentioned above, rather than vascular risk factors, and increased PWMH may reflect Wallerian-type degeneration secondary to primary pathology in cerebral cortex (Khan et al. 2014). Alternatively, ADNI study was designed to parallel procedures employed in a clinical trial and thus only included participants who were in good medical health. Notably, individuals were excluded from participation if they had a significant vascular disease risk history, defined as HIS greater than 4 (Hachinski et al. 1988). Thus, it is very possible that the relatively low HIS in our sample influenced WMH burden, and further, weakened the statistical power to detect the associations.

In contrast with our results, there are two previous studies using visual rating of WMH, which had found no significant difference of WMH among patients with different aMCI subtype (Bombois et al. 2007; van de La et al. 2009). A possible reason is that the differences in measuring method (mentioned above) and field strength of MRI machine (Kim et al. 2008). These two studies were performed on a 1.0 or 1.5-T MRI machine. In contrast, our MRI data were acquired from

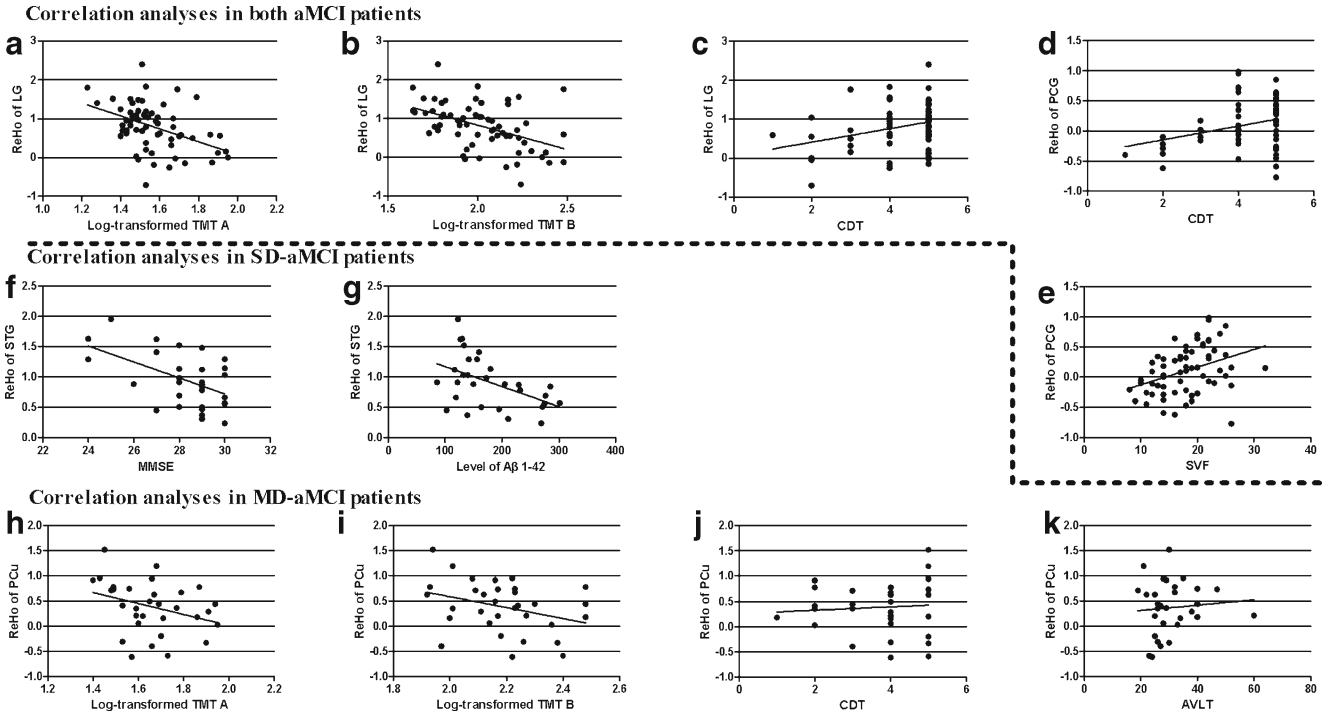

Fig. 4 shows correlation between ReHo and neuropsychological scores/CSF biomarkers in both aMCI subgroups (**a-e**), in SD-aMCI patients (**f-g**), and in MD-aMCI patients (**h-k**). Abbreviations: MD-aMCI, multiple-domain amnestic mild cognitive impairment; SD-aMCI, single-domain amnestic mild cognitive impairment; LG, lingual gyrus; PCG, postcentral gyrus; STG, superior temporal gyrus; PCu, precuneus; CDT, clock drawing test; SVF, semantic verbal fluency; AVLT, auditory verbal learning test

3.0 T-MRI scanners. It is known 3.0 T MRI have increased sensitivity to small WMH or early WMH compared to 1.0/1.5 T MRI (Keiper et al. 1998; Sicotte et al. 2003).

Possible physiology interpretation of abnormal imaging measures

CSF biomarkers, including Aβ1–42, t-tau and p-tau181, are well established pathologic hallmarks of AD as they are intimately related to amyloid plaques, neuronal death and accumulation of neuronal fibrillary tangles respectively (Blennow and Hampel 2003; Braak et al. 2006). Early studies examining CSF have demonstrated that elevated concentrations of t-tau, p-tau181 and decreased concentrations of Aβ1–42 in AD relative to controls (for review, see (Babić et al. 2014)). Consistently, in present study, we observed that MD-aMCI patients had elevated t-tau level than SD-aMCI patients and controls.

As an exploratory analysis, we further examined the relationship between mean ReHo in regions with significant differences between groups and CSF biomarker. It is interesting to note that, in SD-aMCI patients, the ReHo of STG was significantly and negatively related to Aβ1–42. This association suggests the alteration of ReHo in aMCI patients might result from accumulation of amyloid plaques. According to histopathologic studies, STG is one of the brain regions are susceptible to amyloid plaques, accumulated amyloid plaques thus may disrupt local gray matter structure, and further impair the neuropil (Braak et al. 2006). In order to maintain normal cognitive abilities (language or visuo-spatial function) in SD-aMCI patients, the affected brain region exerts compensatory increased regional synchronization. However, without histological data, such interpretation should be made with caution. Additionally, no significant association between PWMH and CSF AD biomarkers was found, which further suggested the presence of PWMH, may be independent of amyloid plaques or tau-protein related NFT to some extent. Indeed, previous histopathologic studies have demonstrated that PWMH is closely associated with patchy rarefaction of myelin, which are ischemic in nature (Thomas et al. 2003).

There are several limitations of this study. First, our study was cross-sectional in its design and therefore limited in assessing the role of abnormal regional synchronization and increased PWMH in the subsequent development of dementia. Longitudinal studies are needed to investigate the conversion of aMCI subtypes to AD and to evaluate clinical values of ReHo and PWMH to predict AD. Secondly, the exact histopathological processes leading to changes in ReHo and PWMH are complex, thus, appropriate animal models where MRI assessments can be directly correlated with histological samples will be meaningful. Thirdly, the controls with first-degree relatives suffering from AD are relatively higher than SD-aMCI and MD-aMCI patients. The reason may be attribute to the health control who had positive family history will

have relatively higher motivation to take part in research than those who had negative family history. Future studies should conduct in "purified" subjects to reduce confounding factors. Finally, not all subjects in present study have CSF sample because lumbar puncture is an invasive procedure. CSF material is available of 87.5% among MD-aMCI, 93.0% among SD-aMCI and 53.1% among controls. These may have influenced statistical tests sensitivity.

Conclusion

Conclusively, our study used a combination of neuroimaging markers (ReHo and WMH) to support the notion of biological heterogeneity between two aMCI subtypes and suggested that MD-aMCI group may show more mixed pathologies than the SD-aMCI group.

Acknowledgements This study was funded by the 12th Five-year Plan for National Science and Technology Supporting Program of China (Grant No. 2012BAI10B04), Zhejiang Provincial Natural Science Foundation of China (Grant No. LZ14H180001 and Grant No. Y16H090026).

Data collection and sharing for this project was funded by the Alzheimer"s Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.;Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; ElanPharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliatedcompany Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen AlzheimerImmunotherapy Research & Development, LLC.; Johnson & Johnson PharmaceuticalResearch & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; MesoScaleDiagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis PharmaceuticalsCorporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; andTransition Therapeutics. The Canadian Institutes of Health Research is providing funds tosupport ADNI clinical sites in Canada. Private sector contributions are facilitated by theFoundation for the National Institutes of Health (www.fnih.org). The grantee organization isthe Northern California Institute for Research and Education, and the study is coordinatedby the Alzheimer"s Disease Cooperative Study at the University of California, San Diego.ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Compliance with ethical standards

Funding This study was funded by National Key Research and Development Program of China (No. 2016YFC1306600), Zhejiang Provincial Natural Science Foundation of China (Grant No. LZ14H180001 and Grant No. Y16H090026).

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval "All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent Written informed consent was obtained from all participants and/or authorized representatives and the study partners before any protocol-specific procedures were carried out in the ADNI study.

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