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Interhemispheric functional connectivity for Alzheimer's disease and amnestic mild cognitive impairment based on the triple network model*

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Abstract: The purpose of this study was to explore the differences in interhemispheric functional connectivity in patients with Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) based on a triple network model consisting of the default mode network (DMN), salience network (SN), and executive control network (ECN). The technique of voxel-mirrored homotopic connectivity (VMHC) analysis was applied to explore the aberrant connectivity of all patients. The results showed that: (1) the statistically significant connections of interhemispheric brain regions included DMN-related brain regions (i.e. precuneus, calcarine, fusiform, cuneus, lingual gyrus, temporal inferior gyrus, and hippocampus), SN-related brain regions (i.e. frontoinsular cortex), and ECN-related brain regions (i.e. frontal middle gyrus and frontal inferior); (2) the precuneus and frontal middle gyrus in the AD group exhibited lower VMHC values than those in the aMCI and healthy control (HC) groups, but no significant difference was observed between the aMCI and HC groups; and (3) significant correlations were found between peak VMHC results from the precuneus and Mini Mental State Examination (MMSE) and Montreal Cognitive Scale (MOCA) scores and their factor scores in the AD, aMCI, and AD plus aMCI groups, and between the results from the frontal middle gyrus and MOCA factor scores in the aMCI group. These findings indicated that impaired interhemispheric functional connectivity was observed in AD and could be a sensitive neuroimaging biomarker for AD. More specifically, the DMN was inhibited, while the SN and ECN were excited. VMHC results were correlated with MMSE and MOCA scores, highlighting that VMHC could be a sensitive neuroimaging biomarker for AD and the progression from aMCI to AD.

Key words: Voxel-mirrored homotopic connectivity; Alzheimer's disease; Amnestic mild cognitive impairment; Default mode network; Salience network; Executive control network
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1 Introduction

Alzheimer's disease (AD) is an age-associated, neurodegenerative disease characterized by progressive memory decline and other cognitive function impairments (Menon, 2011; Liu et al., 2015). Amnestic mild cognitive impairment (aMCI) is an early

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stage of AD that manifests as memory decline and cognitive deterioration in the elderly, but does not meet the standard for dementia. The conversion rate of aMCI to AD is 10%–15% per year (Petersen et al., 2001). Plenty of studies based on resting-state functional magnetic resonance imaging (rs-fMRI) have shown that AD is a "disconnection syndrome", which develops from aMCI, an even earlier stage. Aberrant functional connectivity could be a neuroimaging biomarker for AD.

Many studies have demonstrated abnormal connectivity in different brain regions and networks, such as the default mode network (DMN), salience network (SN), and executive control network (ECN). The brain regions involved include the parietal cortex, precuneus, posterior cingulate cortex (PCC), hippocampus, medial prefrontal cortex (MPFC), dorsal anterior cingulate cortex (dACC), thalamus, and dorsolateral prefrontal cortex (dlPFC). The aberrant activity and functional connectivity of the above brain regions and networks were considered to be associated with the onset and progression of AD (Menon, 2011; Zhong et al., 2014; Blautzik et al., 2016; Lu et al., 2017).

The DMN and its core brain regions play a key role in monitoring the internal mental environment (Lehmann et al., 2015). The SN is anchored mainly in the dACC and is responsible for perceiving biological and cognitive-related environmental stress or events, and in working memory and higher-level cognitive management (Menon and Uddin, 2010). The ECN, anchored in the dlPFC and lateral parietal cortex, represents the frontoparietal system (Cai et al., 2017). "The ECN is essential to actively maintain and manipulate information in working memory, rule-based problem solving, and decision-making based on goal-oriented behavior" (Francx et al., 2015; Li et al., 2018). The three networks are thought to form a large-scale model associated with AD, which provides a general framework to detect the stability and reliability of large-scale connections (Menon, 2011). Many studies have examined the nodes in the three networks in AD and demonstrated that the activity of PCC, dACC, and dlPFC is changed in AD and mild cognitive impairment (MCI) (Joo et al., 2016). Our previous study also demonstrated that aberrant connectivity could be used as a highly-sensitive neuroimaging biomarker for the identification of aMCI based on the triple network model, the functional connections in the DMN displayed as inhibitory functions and the connectivity within the SN and ECN demonstrated by excitatory functions (Yu et al., 2017).

Many studies focusing on intrahemispheric functional connectivity did not pay attention to the aberrant activity and connectivity of interhemispheric connections (Jiang, 2005). It has been suggested that the interhemispheric integration of information is impaired in the process of cognition in AD (Lakmache et al., 1998). Deciphering such functional connectivity and cognition correlations would be helpful for revealing the pathogenesis of AD and aMCI. Therefore, the connectivity of homotopic sites should be studied further, especially in the two hemispheres.

Voxel-mirrored homotopic connectivity (VMHC) has been used to examine the connectivity between two homotopic sites in the two hemispheres based on voxel-wise image analysis. Using this method, Wang et al. (2015) found that the VMHC values in the forebrain areas, including the prefrontal cortex and subcortex, of patients with AD and MCI decreased, showing a trend of AD<MCI<normal cognition (CN), while the VMHC values in patients with MCI in the posterior brain areas were significantly higher than those in patients with AD and CN (Wang et al., 2015). Nevertheless, they did not examine other important networks such as the ECN and SN. In addition, the correlation between the extent of cognitive impairment and interhemispheric VMHC is still not fully elucidated. Other studies have demonstrated that VMHC could be used to reflect the connectivity disruptions in autism (Anderson et al., 2011), cocaine addiction (Kelly et al., 2011), schizophrenia (Hoptman et al., 2012), multiple sclerosis (Zhou et al., 2013), and depression (Wang et al., 2013). This suggests that VMHC could be an effective method to measure the specific mode of interhemispheric aberrant connections and could reflect the functional changes in pathological lesions caused by these diseases.

We hypothesized that the interhemispheric functional connectivity could be inhibited at the DMN level, but excited at the SN and ECN levels in AD and aMCI patients compared with normal cognition healthy controls (HCs). Furthermore, we evaluated the correlation between cognition and the VMHC results in AD and aMCI. The ultimate purpose of the present analysis was to investigate aberrant interhemispheric

functional connectivity and its association with cognition impairments in the three networks.

2 Materials and methods

2.1 Demographic and clinical assessment

AD and aMCI patients came from the Memory Clinic of Zhejiang Provincial People's Hospital, Hangzhou, China. The study was approved by the hospital ethics committee (permit number: 2012KY002), and their families (spouses or children) with signed written informed consent.

All participants were included in our previous studies on intrahemispheric functional connectivity in AD and aMCI based on fMRI and the three networks (Yu et al., 2017). Details of inclusion and exclusion criteria, data acquisition and processing, and quality control are available in that previous study (Yu et al., 2017).

AD and aMCI patients were recruited between Jan. 2013 and Dec. 2015. The HC subjects came mainly from the health promotion center of the hospital. All participants were right-handed. All AD patients met the revised National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD (McKhann et al., 2011). Patients with aMCI fulfilled the diagnostic criteria described by Petersen et al. (2001).

The standards of the HC subjects were: (1) no neurological deficiencies such as visual or hearing impairment; (2) no psychiatric or neurological disease such as depression, stroke, or epilepsy; and (3) no infarctions or focal lesions on conventional brain MRI scans.

The neuropsychological level of the subjects was tested using the Mini Mental State Examination (MMSE), whose factor scores included orientation, recall, attention and calculation, delayed recall, and language and reading. The subjects were also evaluated using the Montreal Cognitive Assessment (MOCA), whose factor scores included visuospatial ability and executive function, attention, calculation, language, abstraction, delayed recall, and orientation. The MOCA was administered at least 30 min after the MMSE to avoid a possible learning effect. MMSE scores of AD patients were ≤24 and MOCA scores ≤26. Patients with aMCI displayed memory decline but did not meet the standard of dementia, with MMSE scores of >24 and ≤27, and MOCA scores of ≤26. The HC subjects had normal memory performance with MMSE scores of >28 and MOCA scores of >27.

For all participants (AD, aMCI, and HC groups), the exclusion criteria were: (1) large head motions (>2 mm); (2) imaging artifacts; (3) incomplete demographic data.

2.2 MRI acquisition protocol

All participants were scanned using a Siemens Trio3-Tesla scanner equipped with a 12-channel phased-array head coil (Siemens, Erlangen, Germany) located at the hospital. All participants were asked to remain quiet and to relax during the scanning, with eyes closed, and to think of nothing, but not to fall asleep. The echo-planar imaging (EPI) was designed for accessing resting-state functional image data. Details of the specific setup mode and parameters are available in our previous study (Yu et al., 2017).

2.3 Data preprocessing

The fMRI image data were preprocessed by DPARSFA v2.3 and REST v1.8 based on SPM8 with MATLAB 2012a. The preprocessing consisted of steps such as elimination of the first four time points, slice timing correction, and head motion correction. Details of specific steps and parameters are available in our previous study (Yu et al., 2017). Images with a head movement greater than 2 mm of translations or 2° of rotation in any direction were excluded.

2.4 Voxel-mirrored homotopic connectivity

To account for VHMC, we adopted the method of calculation used by Kelly et al. (2011). We examined global and regional group differences in VMHC. Global VMHC was calculated by averaging VMHC values across all brain voxels within a unilateral hemispheric gray matter mask. The mask was created using the MNI152 gray matter tissue. We excluded medial voxels to minimize artificially increased VMHC caused by blurring. The regions of interest (ROIs) were placed at the peak point of the VMHC results.

2.5 Statistical analyses

The Kolmogorov Smirnov test was used to test the normality of continuous data. Homoscedasticity was tested using the Breusch-Pagan test, and sphericity

using Mauchly's test. A comparison of age, education level, and MMSE scores in the AD, aMCI, and HC groups was performed using one-way analysis of variance (ANOVA) with the Bonferroni post-hoc test. A two-sample independent *t*-test was used to compare the MOCA scores between the AD and aMCI groups. The gender ratio was tested using Fisher's exact test. $P<0.05$ was considered to be significantly different in all tests. All analyses were performed by a trained biostatistician.

We performed voxel-wise group comparisons using one-way ANOVA to investigate the potential differences in VMHC between the groups. Monte Carlo simulations were performed using the AlphaSim program to obtain an appropriate combination of significant voxels and the cluster size required to achieve the corrected significance threshold of $P<0.05$. The simulations used 1000 iterations (Liu et al., 1998; Mueller-Bierl et al., 2007) and showed a voxel-significance level of $P<0.05$ and a minimum cluster extent of 228 continuous significant voxels to reach the significance level of $P<0.05$ using AlphaSim correction.

To further analyze the differences among the groups, the brain regions that represented significant differences in the above-mentioned ANOVA were set as ROI, with the peak voxel as the center and a 6-mm radius. The VMHC values were extracted from each ROI, and ANOVA with group as a factor (three groups: AD, aMCI, and HC) was used to test for significant differences among the three groups. Post-hoc two-sample, two-sided tests of AD vs. aMCI, AD vs. HC, and aMCI vs. HC were assessed, with *P*-values set at a significance level of 0.05.

To estimate the correlation between interhemispheric functional connectivity and neuropsychological level, we explored by regression analysis the the correlation between *Z* scores in each ROI and the MMSE scores, MOCA scores, and their factor scores in the AD, aMCI, and AD plus aMCI groups, with a statistical significance level of $P<0.05$ (uncorrected).

3 Results

3.1 Demographic and clinical data

A total of 86 individuals were screened for participation. After excluding participants with large head motions (n=4, 1, and 1 for the AD, aMCI, and HC groups, respectively) and imaging artifacts (n=12, 2, and 2 for the AD, aMCI, and HC groups, respectively), as per the data preprocessing criteria, the data of 30 AD (mean age, (72.8±9.3) years; 15 males; MMSE, 15.9±5.3), 14 aMCI (mean age, (68.8±9.0) years; 9 males; MMSE, 26.0±0.9), and 18 HC (mean age, (73.8±9.9) years; 6 males; MMSE, 29.6±0.5) participants were used in the subsequent analyses. The demographic and clinical data are listed in Table 1. There were no significant differences in gender, age, or level of education among the three groups (all $P>0.05$). As expected, the MMSE total scores were significantly different among the three groups and the MOCA total scores were significantly different between the AD and aMCI groups ($P<0.05$).

3.2 VMHC analysis

Fig. 1 shows the statistically significant brain regions of the three groups based on the VMHC results. The significantly aberrant brain regions involved in the three networks were the DMN-related brain regions (i.e. precuneus, calcarine, fusiform, cuneus, lingual gyrus, temporal inferior gyrus, and hippocampus), SN-related brain regions (i.e. frontoinsular cortex), and ECN-related brain regions (i.e. frontal

Table 1 Demographic and neuropsychological data of the Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), and healthy control (HC) groups

Group	Age (year)	Gender (M:F)	Education (year)	MMSE score	MOCA score
AD (n=30)	72.8±9.3	15:15	6.9±3.7	15.9±5.3	10.6±4.9
aMCI (n=14)	68.8±9.0	9:5	9.6±4.9	26.0±0.9	22.3±1.9
HC (n=18)	73.8±9.9	6:12	7.4±4.9	29.6±0.5	
Group comparison *P*-value	0.29	0.21	0.16	<0.001*	<0.001*

Data of age, education, MMSE, and MOCA are expressed as mean±standard deviation (SD). One-way ANOVA with Bonferroni post-hoc test was used for age, education, and MMSE comparison. A two-sample independent *t*-test was used for MOCA scores. A chi-square test was used for gender comparison. * $P<0.05$ for the significant differences among groups. Reprinted from Yu et al. (2017), with kind permission from Springer Science+Business Media New York

middle gyrus and frontal inferior). The peaks of the VMHC values from the DMN and ECN networks were extracted as ROI1 and ROI2, respectively. ROI1 was in the right precuneus (peak *Z*-VMHC centered at *x*=12, *y*=−69, *z*=33) and ROI2 was in the right frontal middle gyrus (peak *Z*-VMHC centered at *x*=48, *y*=30, *z*=6) (Table 2). Because the regions from the SN network did not reach a minimum cluster extent of 228, we could not set an ROI.

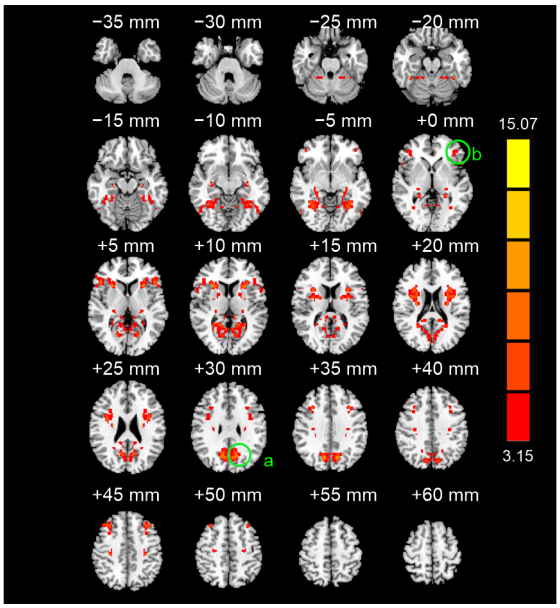

Fig. 1 Significant differences in the VMHC results (red) The *F*-test was used, with the threshold set to $P<0.05$ with AlphaSim correction (individual $P<0.05$, cluster size of >228 mm^3) with the color scale reflecting the ranges of values. The abnormal regions involved in the three networks included the precuneus, calcarine, fusiform, cuneus, lingual gyrus, temporal inferior gyrus, and hippocampus in the DMN, the frontal middle gyrus and frontal inferior Tri/Oper in the ECN, and the frontoinsular cortex and corpus striatum in the SN. a: precuneus set as ROI1, extracted from the DMN (centered at *x*=12, *y*=−69, *z*=33). b: frontal middle gyrus set as ROI2, extracted from the ECN (centered at *x*=48, *y*=30, *z*=6)

Fig. 2 shows the differences in VMHC values among the three groups in ROI1 and ROI2 ($P<0.0001$ and $P=0.0087$, respectively). Post-hoc analyses showed that VMHC values in the ROI1 were markedly lower in the AD group than in the aMCI and HC groups ($P<0.0001$ and $P=0.0004$, respectively), whereas no significant differences were observed between the values for the aMCI and HC groups.

VMHC values in the ROI2 were significantly lower in the AD group than in the HC group, but no significant differences were observed between those in the AD and aMCI groups or aMCI and HC groups (Fig. 2).

3.3 Correlation between peak values of VMHC and MMSE, MOCA, and their factor scores

The peak results of significantly different VMHC values from ROI1 and ROI2 were analyzed for correlation with the MMSE and MOCA total scores, and factor scores in the AD, aMCI, and AD plus aMCI groups. The VMHC of ROI1 was significantly correlated with the MMSE_ and MOCA_delayed recall factor scores in the aMCI patients (Figs. 3a and 3b). The linear correlation between ROI2 and the MOCA_ abstraction factor score was also significant (Fig. 3c). At the overall cognition level, the higher VMHC from ROI1 (Fig. 4) was correlated with higher MMSE/MOCA total scores and their factor scores in the AD plus aMCI group ($P<0.05$). The MMSE factor scores

Table 2 Significant differences in VMHC results from the triple network in the AD, aMCI, and HC groups

Network	Region	ROI	BA	Number of voxels	Peak activation strength, *F*	Peak coordinates		
						x	*y*	*z*
DMN	Precuneus, calcarine, fusiform, cuneus, lingual gyrus, temporal inferior gyrus, hippocampus	Precuneus	7/31	637	15.0738	12	−69	33
ECN	Frontal middle gyrus, frontal inferior Tri/Oper	Frontal middle gyrus	8/9	490	9.7414	48	30	6
SN	Frontoinsular cortex, corpus striatum							

The *F*-test was used, with the threshold set to $P<0.05$ with AlphaSim correction (cluster size >228 mm^3). Averaged VMHC values were extracted from the triple network, including the default mode network (DMN), salience network (SN), and executive control network (ECN). A two-sample *t*-test was used for between-group comparisons of VMHC values, with the *P* value set at a significance level of 0.05. The aberrant regions included the bilateral precuneus, calcarine, fusiform, cuneus, lingual gyrus, temporal inferior gyrus, hippocampus, and frontal middle inferior Tri/Oper. The ROI1 was from the DMN and was extracted from the right precuneus (centered at *x*=12, *y*=−69, *z*=33). The ROI2 was from the ECN and was extracted from the right frontal middle gyrus (centered at *x*=48, *y*=30, *z*=6). BA: Brodmann's area

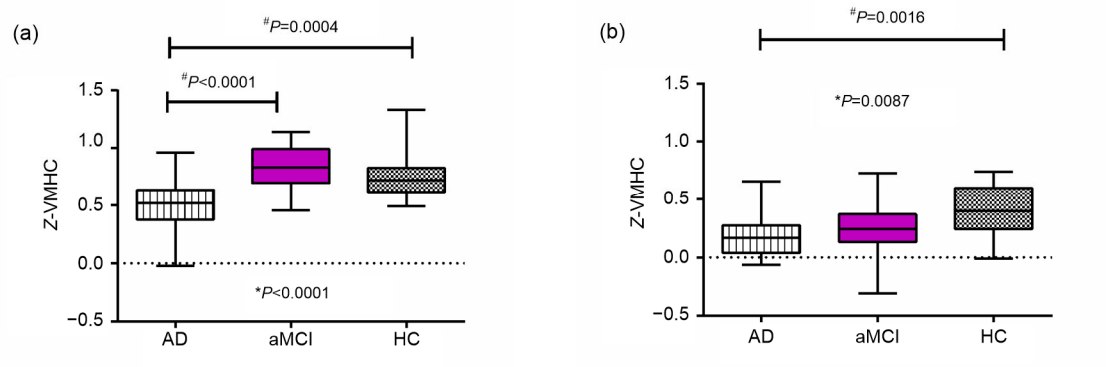

Fig. 2 Analysis of VMHC results

One-way ANOVA and unpaired *t*-test for significant VMHC values extracted from ROI1 (a) and ROI2 (b) among the AD, aMCI, and HC groups. $^{*}P$, one-way ANOVA, comparison among three groups. $^{\#}P$, unpaired *t*-test of one-way ANOVA

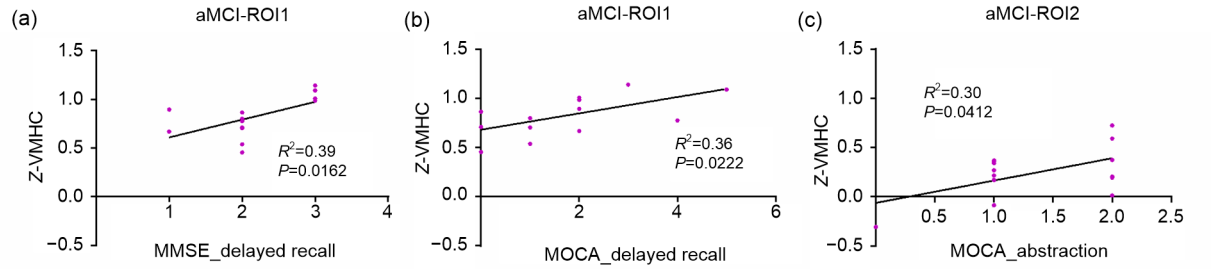

Fig. 3 Regression analysis of the peak *Z*-VMHC values extracted from the two ROIs and the MMSE and MOCA factor scores of the aMCI group

(a) ROI1 and MMSE factor score; (b) ROI1 and MOCA factor score; (c) ROI2 and MOCA factor score

included orientation, attention and calculation, recall, language and reading. The MOCA factor scores included attention, language, delayed recall, and orientation (Figs. 4a and 4b). There were no significant linear correlations between the VMHC from ROI2 and the MMSE/MOCA scores and factor scores.

4 Discussion

By measuring the VMHC using fMRI, we observed that the significant brain regions in two homotopic sites of the two hemispheres were scattered in three core networks: the DMN, SN, and ECN. The peak points of interhemisphere VMHC centered in the precuneus (ROI1) and frontal middle gyrus (ROI2) were extracted from the DMN and ECN, respectively. In ROI1, the AD group presented significantly lower VMHC than the aMCI and HC groups. In ROI2, AD patients showed lower VMHC values compared only with the HC group. Regression analyses showed significant correlations between VMHC values of ROI1 and ROI2 and the total MMSE and MOCA scores and their factors in the AD, aMCI, and AD plus aMCI groups.

Lustig et al. (2003) found that in early-stage dementia of the Alzheimer type (DAT), equivalent to the aMCI stage, the activity of the inferior parietal lobule and mesial temporal lobe was enhanced. Menon (2011) proposed that three crucial brain networks (i.e. ECN, DMN, and SN) may underlie neuropsychiatric disorders, including dementia. In our previous study we also found that the three networks showed aberrant intrahemisphere changes in AD and aMCI patients (Yu et al., 2017). Nevertheless, how functional connectivity is changed in the symmetrical brain regions in the three networks is unknown. The present study suggests that widespread functional connections between the symmetrical brain regions in the two hemispheres are disrupted because of AD. Previous studies using diffusion tensor imaging (DTI) found integrity failures in the structures of midline

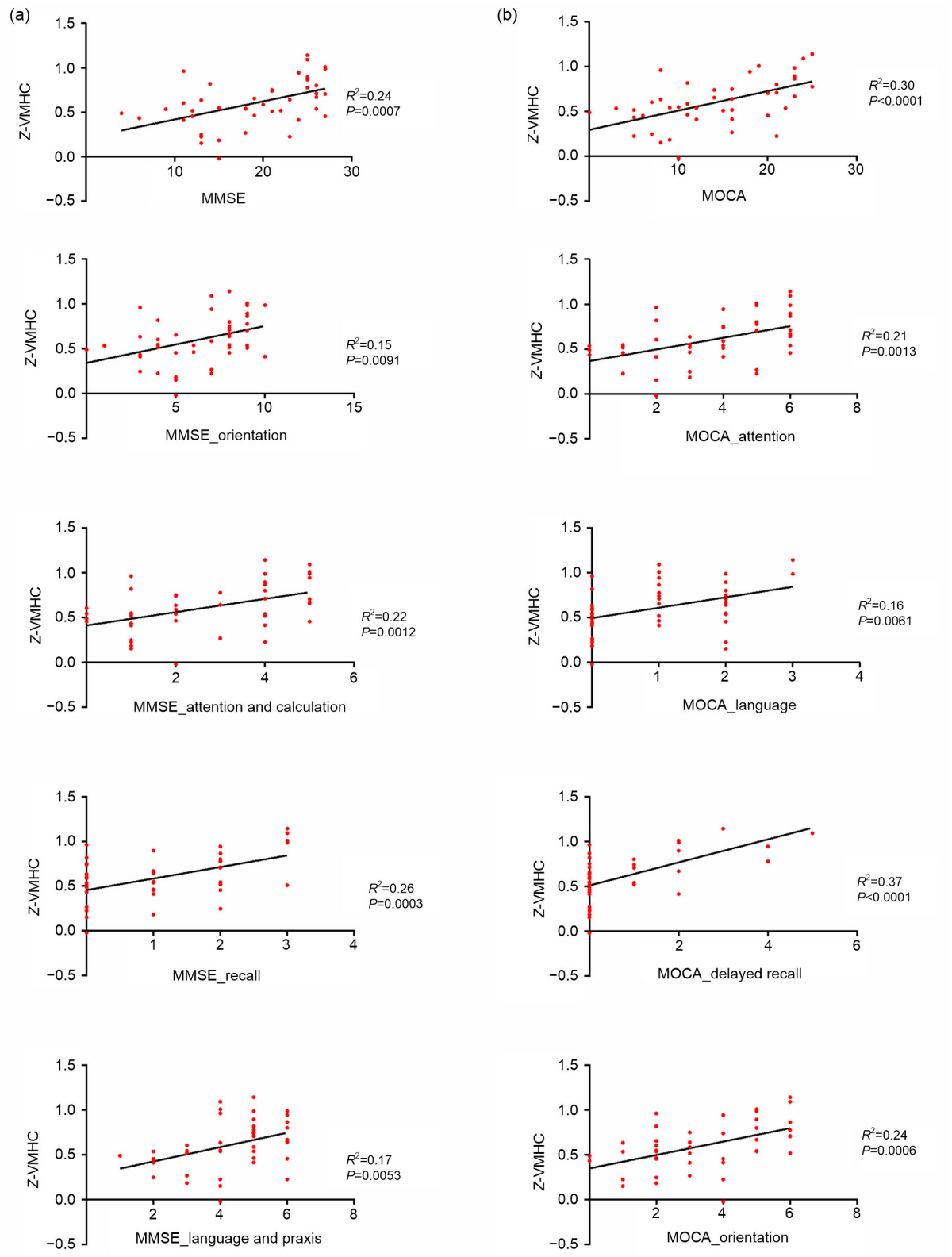

Fig. 4 Regression analysis of the peak *Z*-VMHC values extracted from ROI1 and the MMSE and MOCA factor scores in all AD and aMCI patients

(a) MMSE and factor scores; (b) MOCA and factor scores

white matter in AD associated with changes in hemispherical functional connectivity (Wang et al., 2015). Those findings support our results and the concept that within the three networks, VMHC values may be a sensitive biomarker for AD.

Aberrations in the lower symmetrical regions in the DMN (such as the precuneus and fusiform) could be the principal reason for memory decline. These regions play an important role in visual information processing of AD patients (Chang et al., 2015; Xu et al., 2016). Buckner et al. (2005) also observed that disruption of the medial temporal lobe contributed to memory impairment. Zhan et al. (2016) suggested that functional connections within the right fusiform gyrus (rFG) and between the rFG and right precuneus were affected in aMCI patients compared with HC patients. Our study showed significantly higher connectivity in the fusiform gyrus and precuneus in the aMCI group. The higher VMHC in aMCI may reflect a potential abnormal hemispheric connection as a compensatory pathological mechanism (Donchin et al., 1998) and indicates a progressive recession from MCI to AD in interhemispheric connectivity (Wang et al., 2015). In addition, in aMCI, the functional disruption may involve only a single hemisphere. As the VMHC analysis presented a significant difference in AD, but not in aMCI, it could be a more sensitive biomarker for AD than aMCI.

The other lower interhemisphere connections were distributed in the ECN. The ECN showed aberrant changes during problem solving and abnormal behavior. More than 99% of AD patients show mental and behavioral symptoms at different stages of the disease, associated with frontal lobe injury (Perri et al., 2014). In this study, we found that the VMHC value of the middle frontal gyrus of AD patients was significantly lower than that of HC patients, and not significantly different from that of the aMCI group. The differences among the three groups could be used to characterize the abnormalities of AD patients.

The fMRI images showed some damages in the white matter. A study by Burns et al. (2005) indicated that white matter lesions are common in the early stages of AD. The presence of these white matter lesions influences cognitive decline in the earliest stage of AD (Burns et al., 2005). Nevertheless, the exact impact of white matter lesions on the three networks and AD development still needs to be determined.

The SN plays an important role in processing advanced cognitive functions including social and affective information (Botvinick et al., 2004). For example, anxiety disorder has been correlated with abnormal activity in the SN (Stein et al., 2007). In AD, anxiety and depression are the most common behavioral and psychological symptoms of dementia (Orgeta et al., 2015). Although our study found that there were differences in the frontoinsular cortex and corpus striatum among the three groups, no further analysis could be conducted because voxel values were not greater than 225. Nevertheless, our results suggest that the SN also had aberrant functional connectivity in AD patients.

Regression analyses of VMHC peak values and total MMSE and MOCA scores and their factor scores revealed that in the aMCI group, the VMHC values of the precuneus were positively correlated with the total MMSE score and the MOCA factor of delayed recall, while the VMHC peak values of the frontal middle gyrus were positively correlated with the MOCA factor of abstraction. In the AD plus aMCI group, only the precuneus exhibited a significant correlation with the MMSE and MOCA total scores and their factor scores such as recall, orientation, and language. Thus, the lower the capability for these skills, the lower were the VMHC values. These findings were consistent with the results among the three groups in ROI1 and ROI2, where the VMHC values of the AD group were the lowest. Delayed recall and abstraction reduction can appear in aMCI and are reported to be an important signal of AD progression (Russo et al., 2017). Therefore, we believe that VMHC within the three networks not only can be used as a neuroimaging biomarker in aMCI, but also can provide tendency changes for AD.

Functional connectivity obtained from VMHC can differentiate interhemisphere connections among the three networks, which is a sensitive indicator for AD. This indicator can also reveal tendency changes at the stage of disease progression when no obvious cognitive function decline is found in aMCI. Therefore, VMHC analysis based on the triple network theory provides a new insight into large-scale neural networks of intrinsic connection in AD and aMCI. We believe that such analysis may provide sensitive neuroimaging biomarkers for AD.

Our study has some limitations. The statistical analyses were challenging because of the relatively

small sample size and inexact matching of subjects, especially in the aMCI and HC groups. Thus, the findings of this study should be interpreted with caution and the study results should be replicated. Future studies are needed to investigate the correlation between changes in cognitive function and disease degree based on the Wisconsin Card Sorting Test, trail making test, and language fluency test. In addition, a longitudinal study would track the changes in AD more thoroughly over time and show how they correlate to changes in the severity of AD based on the triple network model.

It is difficult to translate research findings obtained from fMRI to bedside clinical use for diagnostic and treatment purposes because of the large equipment involved, high cost incurred, and limitations of body position (Ho et al., 2016). Functional near infrared spectroscopy (fNIRS) is a non-invasive and cost-effective neuroimaging technology that maps the functions of the cerebral cortex by measuring hemodynamics (Zhu et al., 2014). The results of this study should be replicated in fNIRS studies or be combined with those from fMRI, to increase understanding of the integrity of functional characteristics in AD and aMCI (Lai et al., 2017).

5 Conclusions

Using the VMHC analytical technique, we revealed significant variation in interhemispheric functional connectivity among the three core networks (lower connectivity for DMN, and higher connectivity for SN and ECN) in AD and aMCI patients. The VMHC value of the AD group was significantly lower than those of the aMCI and HC groups in the DMN and ECN networks. Results showed that impaired interhemispheric functional connectivity affected a wide range of brain regions including the two networks, and that VMHC could be a sensitive neuroimaging biomarker for AD. In addition, significant correlations were found between peak VMHC results from ROI1 and MMSE and MOCA scores and their factor scores in all four groups, and between ROI2 and a MOCA factor score in the aMCI group. Our findings suggest that the combination of VMHC and MMSE or MOCA scores could be a sensitive neuroimaging biomarker for the progression to AD.

Compliance with ethics guidelines

Zheng-luan LIAO, Yun-fei TAN, Ya-ju QIU, Jun-peng ZHU, Yan CHEN, Si-si LIN, Ming-hao WU, Yan-ping MAO, Jiao-jiao HU, Zhong-xiang DING, and En-yan YU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients' families (spouses or children) for being included in the study.

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中文概要

题　目：基于三网络模式的阿尔茨海默病和遗忘型轻度认知功能障碍的半球间功能连接研究

目　的：探讨阿尔茨海默病（AD）和遗忘型轻度认知功能障碍（aMCI）在默认脑网络（DMN）、突显网络（SN）和执行控制网络（ECN）这三个脑网络中的半球间脑功能连接的差异性。

创新点：利用体素镜像同伦功能连接（VMHC）来观察AD和aMCI在多个脑网络基础上的半球间功能连接特点。

方　法：该研究纳入了浙江省人民医院就诊的30例AD患者、14例aMCI患者和18例老年健康对照者，均给予静息态功能磁共振扫描，利用VMHC进行数据分析，联合简易智力状态检查量表（MMSE）和蒙特利尔认知评估量表（MOCA）进行相关分析。

结　论：（1）位于三个脑网络的异常半球功能连接主要存在于AD组，可以作为AD诊断的一个敏感性指标；（2）VMHC值可以作为预测AD进展包括aMCI发展为AD的一个敏感性指标。

关键词：体素镜像同伦功能连接；阿尔茨海默病；遗忘型轻度认知功能障碍；默认脑网络；突显网络；执行控制网络