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Altered structural and functional homotopic connectivity associated with the progression from mild cognitive impairment to Alzheimer's disease

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ABSTRACT

The progressive mild cognitive impairment (pMCI) is associated with an increased risk of Alzheimer's disease (AD). Many studies have reported the disrupted brain alteration during the imminent conversion from pMCI to AD. However, the subtle difference of structural and functional of inter-hemispheric between pMCI and stable mild cognitive impairment (sMCI) remains unknown. In the present study, we scanned the multimodal magnetic resonance imaging of 38 sMCI, 26 pMCI, and 50 healthy controls (HC) and assessed the cognitive function. The voxel-mirrored homotopic connectivity (VMHC) and volume of corpus callosum were calculated. A structural equation modeling (SEM) was established to determine the relationships between the corpus callosum, the inter-hemispheric connectivity, and cognitive assessment. Compared to sMCI, pMCI exhibited decreased VMHC in insular and thalamus, and reduced volume of corpus callosum. SEM results showed that decreased inter-hemispheric connectivity was directly associated with cognitive impairment and corpus callosum atrophy, and corpus callosum atrophy indirectly caused cognitive impairment by mediating inter-hemispheric connectivity in pMCI. In conclusion, the destruction of homotopic connectivity is related to cognitive impairment, and the corpus callosum atrophy partially mediates the association between the homotopic connectivity and cognitive impairment in pMCI.

1. Introduction

Alzheimer's disease (AD) is clinically characterized by progressive cognitive impairment and impaired ability of daily living, and is the most common type of dementia (McKhann et al., 1984). The etiology and pathogenesis of AD have not yet been fully elucidated, and there is currently no cure for AD. Mild cognitive impairment (MCI) is considered a prodromal stage of AD, which manifests as an intermediate stage between normal age-related cognitive decline and dementia (Petersen et al., 1999). Longitudinal studies have revealed that about 8.3% to 34% of MCI converts to AD (Mitchell and Shiri-Feshki 2008; Petersen et al., 2001), however, many MCI patients still maintain long-term stable cognitive function without progression (Yang et al., 2021). The National Institute on Aging and the Alzheimer's Association (NIA-AA) proposed the AT(N) framework, which refined diagnostic staging based on the characteristics of pathological markers (Jack et al., 2018). Diagnostic

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classification based on the staging of pathological markers more clearly distinguishes MCI patients who are at high risk of transforming to AD. However, in a previous study, it was shown that pathological markers and clinical manifestations were not linear, that is, the existence of pathological markers was not fully consistent with the conversion of AD (Wallace et al., 2019). The complicated and unclear underlying mechanism of progression makes it difficult to accurately identify which patients will progress to AD dementia. Therefore, identifying markers that are related to AD progression not only provides perspectives for early diagnosis of AD, but also provides novel insights into the development of targeted interventions in clinical practice. The aim of this study was to elucidate neuropathological features of MCI that convert to AD (referred to as progressive MCI or pMCI) or not (referred to as stable MCI or sMCI) over the next few years, and its accuracy in distinguishing pMCI.

Functional separation and integration of the cerebral cortex can rapidly extract information and generate coherent brain states to generate complex cognitive function (Sporns et al., 2004). Intracortical connections require coordination across different regions of the brain, not only within the hemispheres, but also for long-range functional connection between hemispheres (Zuo et al., 2010). Most previous studies have focused on the functional connectivity (FC) within the cerebral hemisphere, and it is easy to ignore the abnormal activity and connectivity between hemispheres in AD (Banks et al., 2018). Bilateral hemisphere activity imbalance and lateralization may be related to the severity and progression of AD. In a previous study that focused on different tasks, it was revealed that AD patients perform poorly when performing tasks that require inter-hemisphere communication, and perform normal when performing tasks that require intra-hemisphere processing (Lakmache et al., 1998). Moreover, in an electroencephalography (EEG) study, it was shown that AD patients showed decreased synergy between hemispheres during photic stimulation (Kikuchi et al., 2002). The above-mentioned studies indicated that failure of information integration between the two hemispheres may be associated with the pathogenesis of AD. Thus, exploring the changes in the connections between the hemispheres in the AD continuum is essential for a deeper understanding of the occurrence and development of AD. At present, the mechanism underlying the inter-hemispheric disruption in AD remains unclear. Asymmetric inter-hemispheric deposition of the Aβ protein in PET and autopsy studies has suggested that the deposition of pathological proteins may promote the disturbance of inter-hemispheric connectivity (Frings et al., 2015; King et al., 2015; Stefanits et al., 2012). Structural and functional magnetic resonance imaging (MRI) indirectly reflects neuron and synaptic damage by quantifying alterations in gray/white matter volume and functional activity (Xue et al., 2021). Voxel-mirrored Homotopic Connectivity (VMHC) is a validated method that allows for the detection of FC changes between inter-hemispheric regions by quantifying the high degree of synchrony in spontaneous activity between each voxel in the cerebral hemisphere and the corresponding voxel in the mirror hemisphere (Zuo et al., 2010). In a previous study, it was shown that AD and MCI patients have a specific pattern of VMHC values changes between hemispheres compared to the HC group, thereby indicating that VMHC can indeed be used as a biomarker for the degradation of connectivity between hemispheres in the AD continuum (Liao et al., 2018). The pathophysiological characteristics of AD begin decades before cognitive symptoms; therefore, it is of utmost importance to assess whether functional connectivity between hemispheres is affected at an early stage, and whether it can be used as a predictor of disease progression.

The corpus callosum is the main channel for transmitting information between hemispheres and involves bilateral sensory information integration and various advanced cognition (Fox et al., 2014; Garnier-Crussard et al., 2020; Lewis et al., 2021; Paul et al., 2003; Wertz et al., 2020). In previous studies, it was found that AD patients have corpus callosum atrophy, and corpus callosum atrophy was associated with cognitive decline in AD patients (Pantel et al., 1999; Sui et al., 2018; Van Schependom et al. 2018). Moreover, it was found that the integrity of the corpus callosum was related to specific changes of FC between the hemispheres in AD patients (Wang et al., 2015). However, changes in the corpus callosum volume in pMCI and sMCI patients are unclear. In addition, previous studies on the relationship between corpus callosum volume and inter-hemispheric functional connectivity were conducted using correlation analysis methods, which did not allow for examining the causal relationship between the two and cognitive function. Therefore, in this study, structural equation modeling (SEM) was used to investigate the direct or indirect causal relationship between inter-hemispheric functional connectivity, corpus callosum volume, and cognitive impairment in pMCI and sMCI patients.

Therefore, this study aimed to explore the potential disruption and relationship between inter-hemispheric connectivity and the corpus callosum volume, as well as their relationship with cognitive function in sMCI and pMCI patients. Furthermore, the relationship between inter-hemispheric connectivity and amyloid-β (PET AV45) was explored. We hypothesized that there was a distinct pattern of changes in functional connectivity between hemispheres and corpus callosum volume in sMCI and pMCI patients. The SEM method was used to verify the hypothetical model that the atrophy of the corpus callosum leads to the interruption of functional connection between hemispheres, which may be conducive to cognitive impairment. In addition, the significance of the application of multiple functional feature combinations was explored to accurately diagnose and identify sMCI and pMCI patients.

2. Methods

2.1. Participants

All MCI patients and healthy control (HC) subjects were obtained from the AD Neuroimaging Initiative (ADNI, http://adni.loni.usc.edu) database. In 2003, the ADNI was launched as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment could be combined to measure the progression of MCI and early AD. For up-to-date information, visit www.adni-info.org. The ADNI recruited participants from 55 to 94 years from a multicenter study conducted at 59 locations in North America.

The diagnostic criteria of MCI in the ADNI database were as follows: (1) memory complaints; (2) objective evidence of memory decline, Clinical Dementia Rating (CDR) scores=0.5; (3) Mini-Mental State Examination (MMSE) scores between 24 and 30; (4) no dementia and no signs of severe depression. The diagnostic criteria for converting from MCI to AD status were based on the NINCDS-ADRDA criteria (McKhann et al., 1984). In this study, pMCI was defined as a diagnostic status converting from MCI to AD within 4 years, and sMCI patients were defined as a diagnostic status maintaining the MCI diagnosis for at least 4 years. The diagnostic criteria of HC subjects in the ADNI database were as follows: (1) no memory complaints; (2) normal cognitive performance, MMSE between 24 and 30; (3) CDR=0. More detailed HC and MCI inclusion and exclusion criteria can be obtained from the ADNI website: http://adni.loni.usc.edu/data-samples/access-data/.

According to the above-mentioned criteria, 31 pMCI, 41 sMCI, and 50 matched HC were included in the study. Due to poor image quality and large head movements, 5 pMCI and 3 sMCI patients were excluded from the study. Finally, 26 pMCI patients, 38 sMCI patients, and 50 HC were included in this study.

2.2. Neuropsychological assessment

General cognitive ability was evaluated by the Montreal Cognitive Assessment (MOCA). Episodic memory was evaluated by the composite score of the Rey Auditory Verbal Learning Test, the Alzheimer Disease Assessment Scale-Cognitive, Logical Memory, and MMSE. Executive

function was assessed by the composite score of Category Fluency, WAIS-R Digit Symbol, Trails A & B, Digit Span Backwards, and clock drawing. All neurocognitive assessments are available on the ADNI website (https://ida.loni.usc.edu/pages/access/studyData).

2.3. MRI data acquisition

Both structural and functional MRI images were acquired on a 3.0T scanner from Siemens (Munich, Germany), General Electric (Cleveland, OH, USA) and Philips (Best, the Netherlands). Detailed information about image acquisition parameters (structural MRI image and rest functional MRI image) has been reported in detail in a previous study (Chen et al., 2021).

2.4. Preprocessing of structural MRI

Structural images were preprocessed using the Data Processing and Analysis of Brain Imaging (DPABI) based on the Statistical Parametric Mapping 8 (SPM 8, https://www.fil.ion.ucl.ac.uk/spm/) program, which was implemented in MATLAB2013b (http://www.mathworks.com/products/matlab/). Original DICOM format images were converted to the NIFTI format and spatially normalized. Then, the gray matter, white matter, and cerebrospinal fluid images, obtained by segmenting the MPRAGE images, were standardized to the Montreal Neurological Institute (Montreal Neurological Institute, MNI) standard space (1.5mm×1.5 mm×1.5 mm). Subsequently, the smoothing kernel with a full width at half maximum (FWHM) of 8 mm×8 mm ×8 mm was used to obtain maps of the gray matter and white matter. For subsequent analyses, the obtained voxel-wise gray matter volume maps were resampled to a setting of $3 \times 3 \times 3$ mm^3 voxels, and voxel-based gray matter volume correction.

To obtain the volume of corpus callosum, a prior region of interest (ROI) of the corpus callosum was created as a structural mask using the WFU PickAtlas Tool (The Functional MRI Laboratory, Wake Forest University School of Medicine, Winston-Salem, NC, USA; http://www.ansir.wfubmc.edu).

2.5. Preprocessing of resting-state fMRI data

Resting-state fMRI data were preprocessed using DPABI implemented in MATLAB2013b (http://www.mathworks.com/products/matlab/). Steps are summarized as follows: (1) the first 10 vol were discarded to increase the stability of the MRI signal; (2) slice timing correction and head movement correction were performed. Images of a subject were excluded if the translation or rotation exceeded 3 mm and 3°; (3) images were spatially normalized to the MNI echo-planar imaging template and resampled to a default setting ($3 \times 3 \times 3$ mm^3 voxels); (4) nuisance covariate regression of 24 motion parameters, global signal, white matter signal, and cerebrospinal fluid signal; (5) a $6 \times 6 \times 6$ mm FWHM were used to reduce high spatial frequency noise; (6) the filtering frequency was 0.01−0.08 Hz.

To obtain VMHC maps, all normalized T1 images were averaged to create a mean normalized T1 image. Then, a group-specific symmetrical template was created by averaging left-right symmetric version of the mean image. Next, homotopic resting state FC was computed as the resting state FC between any pair of symmetric inter-hemispheric voxels. Subsequently, the Pearson's correlation coefficient was computed between the residual time series of each voxel and its contralateral hemispheric counterpart. Finally, the correlation values were performed by the Fisher Z-transformed.

2.6. Florbetapir positron emission tomography images

Aβ deposition was measured by the florbetapir Positron Emission Tomography (PET) technology. Detailed descriptions of acquisition and preprocessing on florbetapir-PET imaging are available at http://adni.loni.usc.edu/updated-florbetapir-av-45-pet-analysis-results/. The florbetapir-PET standardized uptake value ratios were calculated by the average values of six cortical regions using the whole cerebellum as a reference, including medial orbital frontal, parietal, temporal, precuneus, posterior cingulate, and anterior cingulate cortex. Florbetapir-PET images were spatially normalized to a standard MNI atlas space template using automatic affine. Then, the alignment of the patient's PET brain/cerebellum was visually compared with the template brain/cerebellum to check the registration results. Situations that needed to improve the results of automatic registration were manually adjusted, including translation, scaling, rotation, and shearing. In this study, 25 pMCI patients, 35 sMCI patients, and 36 HC subjects underwent Florbetapir-PET scans.

2.7. Statistical analysis

Statistical analysis was performed by the Statistical Package for the Social Sciences (SPSS) software version 22.0 (IBM, Armonk, New York, NY, USA). Demographic data and differences in neuropsychological scales between the three groups were analyzed by analysis of variance (ANOVA) and chi-square test. Bonferroni correction was employed for post-hoc comparison, and $p<0.05$ was considered statistically significant.

One-way ANOVA was performed to obtain a voxel-based comparison of VMHC maps among the three groups, thereby controlling for the effects of age, gender, education level, and gray matter (GM) volume. The permutation test with Threshold-Free Cluster Enhancement (TFCE) and the familywise error (FWE) correction was set to 1000, a p-value<0.05 was considered significant. Next, a two-sample *t*-test was used for post-hoc comparison with age, gender, education level, and GM volume as covariates (TFCE-FWE corrected, $p<0.05$).

One-way ANOVA was conducted to compare the corpus callosum volume across the three groups with age, gender, education level, and total intracranial volume as covariates (permutation 1000, TFCE-FWE, $p<0.05$). The discrepant brain regions obtained in the above-mentioned analysis were used as the mask to extract the corpus callosum volume. Subsequently, one-way ANOVA was employed to compare the corpus callosum volume of the three groups in SPSS, and the Bonferroni correction was used for post-hoc comparisons. For all analyses, $p<0.05$ was considered statistically significant.

The partial correlation analysis was used to explore the relationships between altered VMHC values and corpus callosum volume as well as cognitive domains. In addition, the relationship between altered VMHC values and Aβ deposition was explored. The false discovery rate (FDR) was used for multiple comparisons ($P<0.05$). For all analyses, age, gender, and education level as covariates were removed.

SEM is a statistical method to analyze the relationship between variables based on the covariance matrix of the variables. Goodness of fit was assessed using the following indices: Chi-square/degrees of freedom<3.0, goodness of fit index (GFI)<0.9, adjusted goodness of fit index (AGFI)<0.9, and Root Mean Square Error of Approximation (RMSEA) <0.05. The 95% confidence interval (CI) generated from 2000 samples was used to determine the significance of direct and indirect paths. Two tailed significance < 0.05 was considered significant. SEM was performed using AMOS 24.0.0 software (Meadville, PA, USA) (Crowley and Fan 1997).

Receiver operating characteristic (ROC) curves were created to evaluate the identification features of altered indexes between groups using SPSS software. The area under the curve (AUC) of each index was calculated to determine the most valuable index for the diagnosis between any two groups. In addition, a combined factor combining all altered indexes was established. The sensitivity and specificity of each biomarker and combined biomarkers were evaluated.

3. Results

3.1. Characteristics of demographics, neurocognitive assessment, and pathological marker

A total of 114 subjects were enrolled in this study, including 50 HC subjects, 26 pMCI patients, and 38 sMCI patients. Age, gender, and educational level of the patients in the three groups were not statistically significant ($P>0.05$). The pMCI group showed a significantly lower MOCA, episodic memory, executive function, and higher Aβ deposition compared with both sMCI patients and HC subjects. The sMCI group showed significantly lower episodic memory and executive function compared to the HC group. All post-hoc analyses were adjusted by Bonferroni, and $p<0.05$ was considered statistically significant. Clinical characteristics of sMCI patients, pMCI patients, and HC subjects are presented in Table 1.

3.2. Comparisons of VMHC values in HC, sMCI, and pMCI groups

One-way ANOVA was performed to detect the differences in VMHC among the three groups. The results showed significantly altered FC across the three groups, including superior parietal gyrus (SPG), middle frontal gyrus, insular, and middle temporal gyrus (TFCE-FWE, cluster size >100 voxels, $p < 0.05$). Furthermore, compared to HC subjects, sMCI patients showed increased VMHC values in the parahippocampa gyrus, insular, SPG, superior temporal gyrus (STG), and cerebellum (TFCE-FWE corrected, cluster size >30 voxels, $p < 0.05$). In addition, compared to HC subjects, pMCI patients showed increased VMHC values in the superior frontal gyrus (SFG) and the lower part of SPG, while decreased VMHC values were observed in the precentral gyrus and the upper part of the SPG (TFCE-FWE corrected, cluster size >30 voxels, $p < 0.05$). Finally, compared to sMCI patients, pMCI patients demonstrated decreased VMHC values in the insular and thalamus (TFCE-FWE corrected, cluster size >30 voxels, $p < 0.05$). All results controlled gender, age, education level, and gray matter volume as covariates (see Table 2 and Fig. 1).

3.3. Comparisons of corpus callosum volume in HC, sMCI, and pMCI groups

One-way ANOVA showed a significantly altered corpus callosum volume among the three groups (TFCE-FWE, cluster size >100 voxels, $p < 0.05$, Fig. 2). Compared to HC subjects and sMCI patients, pMCI patients exhibited decreased a corpus callosum volume (Bonferroni corrected, $p<0.05$). When comparing sMCI patients and HC subjects, no significant differences were observed in the corpus callosum volume. All results controlled gender, age, education level, and total intracranial volume as covariates (Fig. 2).

Table 1
Demographics and neuropsychological assessment of HC, sMCI, and pMCI.

	HC ($n=50$)	sMCI ($n=38$)	pMCI ($n=26$)	F values (χ^2)	P values
Age (years)	72.73 ±6.94	72.24 ±7.30	72.92±6.48	0.087	0.917
Gender (male/female)	20/30	21/17	13/13	2.111	0.348
Education level (years)	16.90 ±2.03	15.66 ±2.72	16.00±2.56	3.114	0.051
MOCA	27.90 ±1.66	23.82 ±2.90**	21.85 ±3.46***/*	19.004	<0.001 a, b,c
Episodic memory	1.04 ±0.51	0.40 ±0.51***	−0.20 ±0.46***/***	54.456	<0.001 a, b,c
Executive function	0.89 ±0.79	0.54±0.83	−0.04 ±0.79***/*	11.489	<0.001 a, c
AV45	1.15 ±0.21	1.18±0.17	1.45 ±0.19***/***	20.506	<0.001 a, c

Numbers are given as means (standard deviation, SD) unless stated otherwise. Values for age derived from ANOVA; gender from χ-square test; [a] Post hoc analyses showed a significantly group difference between pMCI and HC. [b] Post hoc analyses showed a significantly group difference between sMCI and HC. [c] Post hoc analyses showed a significantly group difference between sMCI and pMCI. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; HC, healthy control; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

Table 2
VMHC differences in brain regions in HC, sMCI, and pMCI.

Region (aal)	peak MNI coordinate			F/t	Cluster Number
	x	y	z		
ANOVA					
B superior parietal gyrus /middle frontal gyrus/insular	±27	−54	72	15.21	7760
B middle temporal gyrus	±60	−42	−6	6.88	114
sMCI > pMCI					
B insular	±30	−15	−3	5.21	583
B thalamus	±9	−24	21	3.55	80
sMCI > HC					
B Parahippocampa gyrus	±3	0	21	−4.16	305
B insular	±48	6	−12	−5.00	160
B superior parietal gyrus	±27	−54	72	−5.28	35
B superior temporal gyrus	±36	18	−27	−3.75	38
B cerebellum posterior lobe	±9	−36	−48	−4.84	71
B cerebellum posterior lobe	±27	−84	−51	−4.83	73
pMCI < HC					
B precentral gyrus/postcentral gyrus	±21	18	18	4.66	718
B superior parietal gyrus	±18	−60	60	4.74	134
pMCI > HC					
B superior frontal gyrus	±6	66	30	−4.83	136
B superior parietal gyrus	±24	−63	69	−5.18	182

The x, y, z coordinates are the primary peak locations in the MNI space. Cluster size >100 voxels in ANOVA analysis, $p < 0.05$; Cluster size >30 voxels in post hoc test, $p < 0.05$, TFCE-FWE corrected; Age, gender, education level, and gray matter volume were used as covariates; L, left; R, right; B bilaterally; HC, healthy control; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

3.4. Behavioral significance of the altered VMHC values and corpus callosum volume

To explore the behavioral significance of the FC change of VMHC, the correlation among the Z-scores of VMHC value, cognitive function, and Aβ deposition was analyzed. The results showed a significant positive and negative correlation among these indicators in sMCI and pMCI patients, respectively (Fig. 3). Partial correlation analysis indicated that the altered VMHC values in the insular and the thalamus positively associated with episodic memory ($r = 0.437$, $p = 0.013$; $r = 0.351$, $p = 0.039$). Moreover, altered VMHC values in the insular positively associated with executive function in pMCI patients ($r = 0.474$, $p = 0.007$). Partial correlation analysis indicated that the altered VMHC values in the insular and the thalamus positively associated with episodic memory function in sMCI patients ($r = 0.283$, $p = 0.043$; $r = 0.307$, $p = 0.30$), and that altered VMHC values in the thalamus positively associated with executive function in sMCI patients ($r = 0.315$, $p = 0.027$). FDR correction was used for multiple comparisons ($p < 0.05$). A negative correlation was observed between Aβ deposition and corpus callosum volume ($r = -0.279$, $p = 0.031$) in both pMCI and sMCI patients. When correlation analysis was conducted separately for pMCI and sMCI patients, no significant correlation was observed between Aβ and corpus callosum volume. Partial correlation analysis indicated that altered VMHC values in the insular and the thalamus negatively correlated with Aβ deposition ($r = -0.299$, $p = 0.020$; $r = -0.338$, $p = 0.008$) in sMCI and pMCI patients. When correlation analysis was conducted separately for pMCI and sMCI patients, no significant correlation was observed between Aβ and VMHC values in the insular and the thalamus. All the

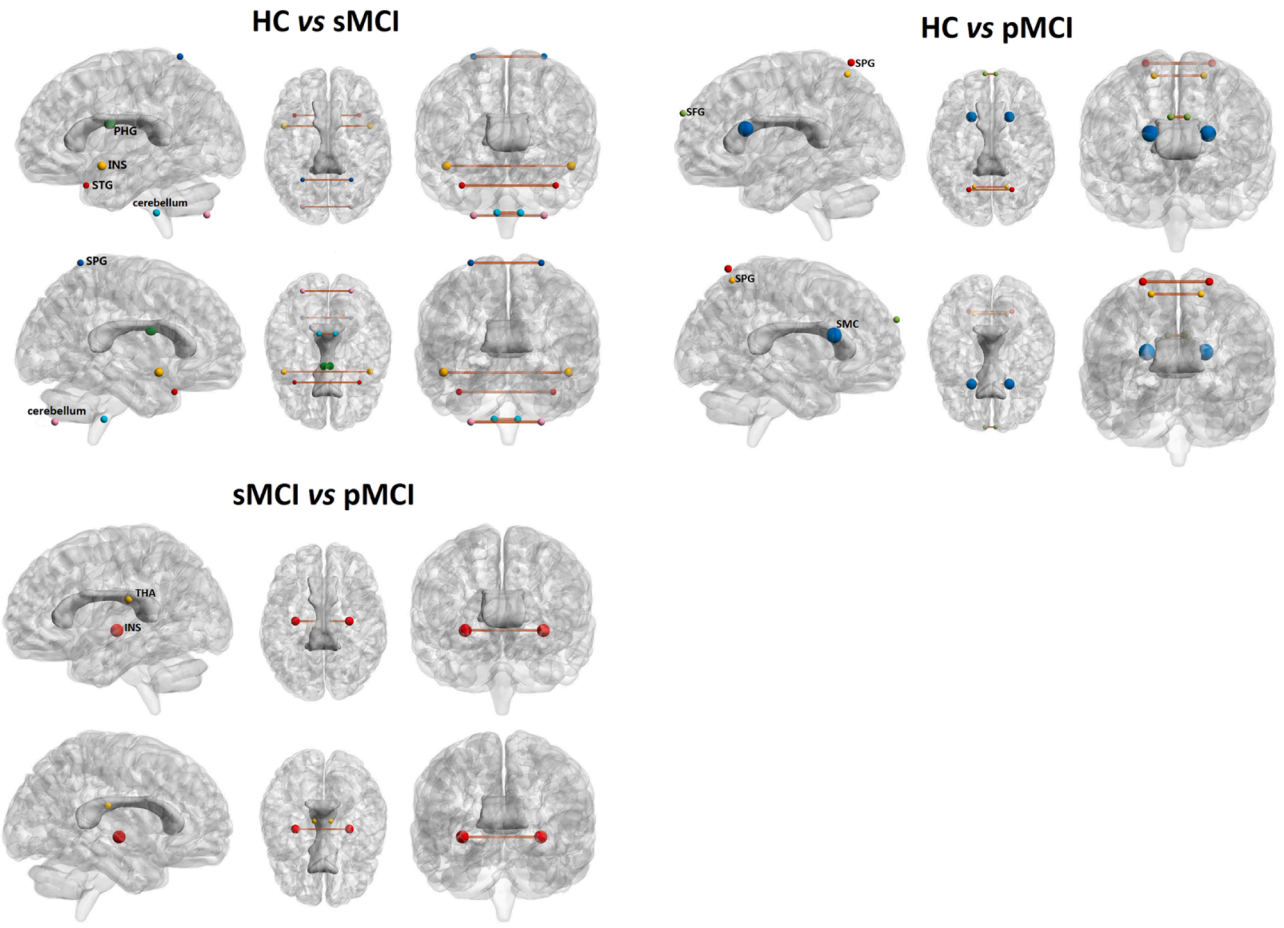

Fig. 1. Pairwise comparison of VMHC values in HC, sMCI and pMCI groups. Compared to HC, sMCI showed increased VMHC values in Parahippocampa gyrus, insular, SPG, STG, and cerebellum. Compared to HC, pMCI showed increased VMHC values in SFG and the lower part of SPG, while decreased VMHC values in precentral gyrus and the upper part of SPG. Compared to sMCI patients, pMCI patients demonstrated decreased VMHC values in insular and thalamus. The results were corrected by TFCE-FWE, and $p<0.05$ was considered significant (cluster size >30 voxels). All results control gender, age, education level, and gray matter volume as covariates. THA, thalamus; INS, insula; PHG, parahippocampa gyrus; SMC: sensorimotor cortex; SPG, superior parietal gyrus; STG, superior temporal gyrus; SFG, superior frontal gyrus; HC, healthy control; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

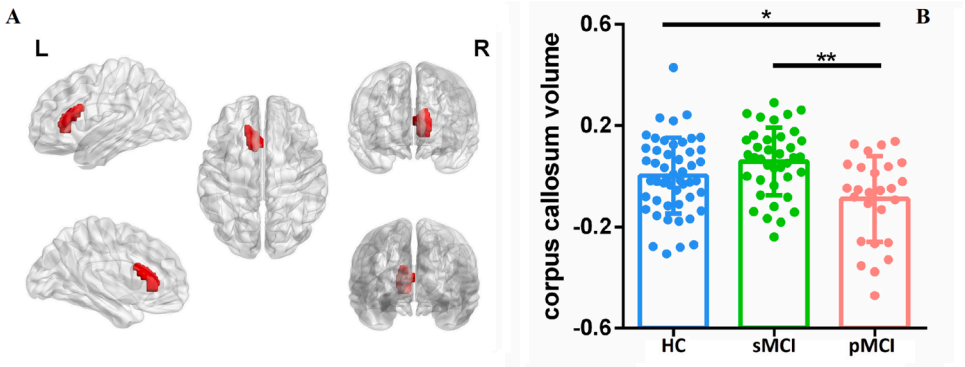

Fig. 2. The comparisons of corpus callosum volume in HC, sMCI, and pMCI groups. A. a map of corpus callosum volume differences obtained by ANOVA for the three groups (CN, sMCI and pMCI). B. Compared to HC and sMCI groups, pMCI group exhibited corpus callosum atrophy (Bonferroni corrected, $p<0.05$). In the comparison between the sMCI and HC groups, there was no significant difference in the volume of the corpus callosum. All results control gender, age, education level, and total intracranial volume as covariates. HC, healthy control; sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

above correlation analyses removed age, gender, and education level as covariates. FDR correction was used for multiple comparisons ($p <$ 0.05).

3.5. Hypothetical model verification using SEM

In this study, SEM was used to separately explore the relationship between structural changes and functional changes, as well as their impact on cognition in pMCI and sMCI patients. The results showed that the episodic memory model had a good fit and significant result in pMCI, but no significant results were observed in sMCI patients. The final SEM is shown in Fig. 4. The square represents the observed variable and the ellipse represents the latent variable. Episodic memory was an endogenous latent variable. The corpus callosum volume, and VMHC values of insular and thalamus were exogenous latent variables. Results of the episodic memory model analysis suggested that GFI=1.000>0.9,

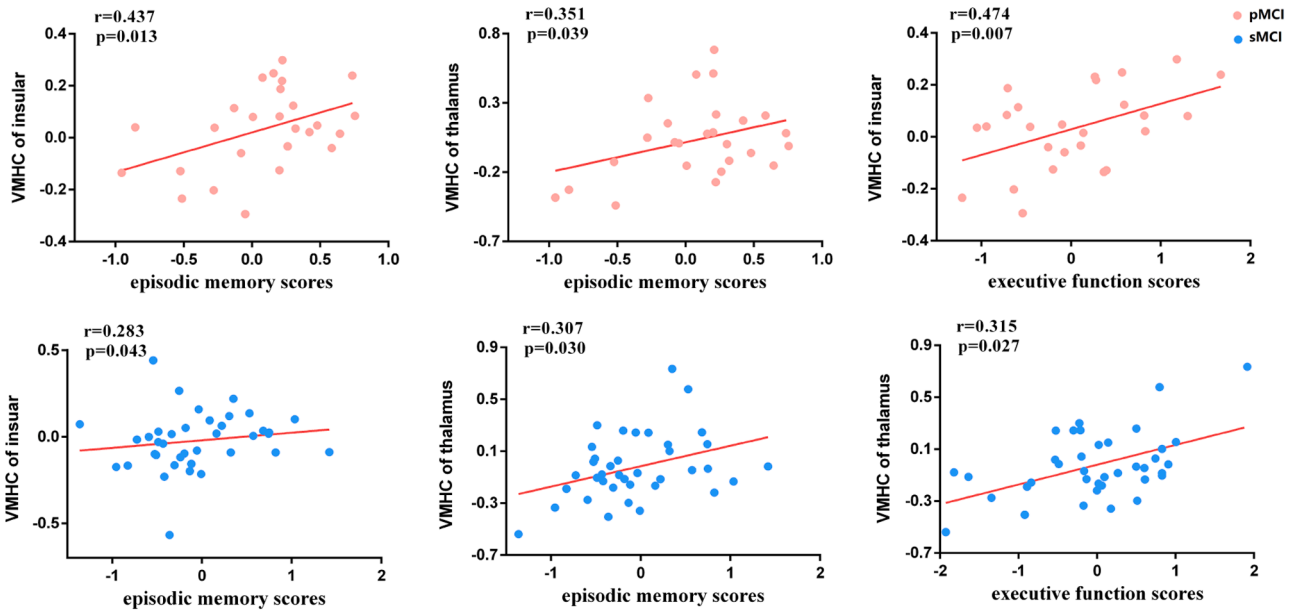

Fig. 3. Significant associations between altered homotopic connectivity and cognitive function in sMCI and pMCI patients. sMCI, stable mild cognitive impairment; pMCI, progressive mild cognitive impairment.

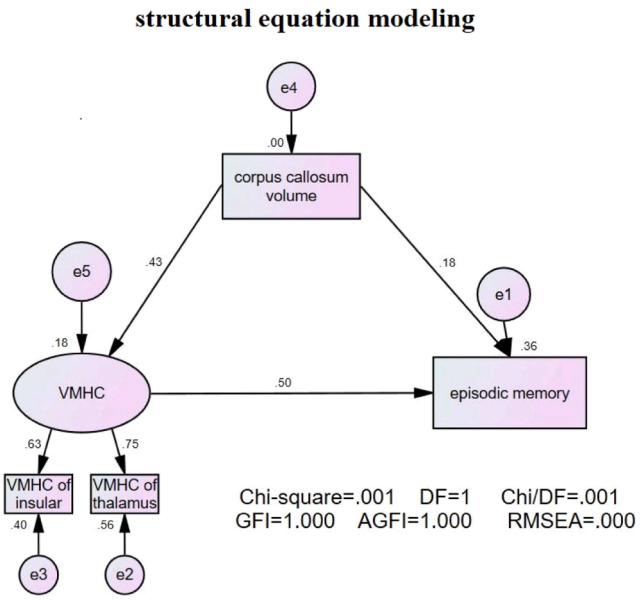

Fig. 4. Structural equation model verification hypothetical model in pMCI. The square represents the observed variable and the ellipse represents the latent variable.

AGFI=1.000>0.9, RMSEA=0.000<0.05, and $\chi 2$ / df =0.01<3. Moreover, results of the executive function model analysis showed no significant significance (p<0.05). The direct effect of corpus callosum atrophy on episodic memory was not significant (p = 0.181), however, the indirect effect was significant (p<0.05).

3.6. Classification of sMCI and pMCI patients using ROC analysis

To calculate the value of the change index to classify sMCI and pMCI, ROC analysis was performed (Fig. 5). In the groups containing sMCI and pMCI patients, the AUC values of VMHC of the insular and the thalamus were 0.872 with $p < 0.001$ and 0.793 with $p < 0.001$. The AUC values of FDG and AV45 were 0.843 with $p < 0.001$ and 0.862 with $p < 0.001$. In the groups containing pMCI patients and HC subjects, the AUC values of VMHC of precentral gyrus and SPG were 0.652 with $p = 0.030$ and 0.842 with $p < 0.001$. The AUC values of VMHC of SFG and SPG were 0.842 with $p < 0.001$ and 0.884 with $p < 0.001$. In the groups containing sMCI patients and HC subjects, the AUC values of VMHC of the PHG, insular, SPG, STG, cerebellum posterior lobe (voxel 71), and cerebellum posterior lobe (voxel 73) were 0.824 with $p < 0.001$, 0.811 with $p < 0.001$, 0.797 with $p < 0.001$, 0.831 with $p < 0.001$, 0.825 with $p < 0.001$, and 0.826 with $p < 0.001$.

As shown in Fig. 5, the optimal classification model was a combination of multiple indicators. The AUC value of the above indicators combined in the group of sMCI and pMCI was 0.970, $p < 0.001$ with the sensitivity = 88.5%, specificity = 94.7%. The AUC value of the above indicators combined in the group of pMCI patients and HC subjects was 0.964, $p < 0.001$ with the sensitivity = 100%, specificity = 88%. The AUC value of the above indicators combined in the group of sMCI patients and HC subjects was 0.946, $p < 0.001$ with the sensitivity = 86.8%, specificity = 92%.

4. Discussion

The aim of this study was to systematically investigate the inter-hemispheric connectivity changes pattern and its relationship with the corpus callosum volume as well as cognitive function in sMCI and pMCI patients. The significance of single and combined functional connectivity between hemispheres as predictors of MCI conversion was also analyzed. First, the destruction of the FC changes between hemispheres and the corpus callosum volume in sMCI and pMCI patients was confirmed. Second, altered FC of insular and thalamus have been found to be closely associated with episodic memory, executive function in sMCI and pMCI patients. Then, the well-fitted SEM results showed that the volume of the corpus callosum mediated altered inter-hemispheric connectivity, which resulted in impaired cognition in pMCI patients. In addition, multiple indicators of the combination of VMHC values may be identified as important biomarkers due to their high accuracy in the diagnosis and identification of sMCI and pMCI patients.

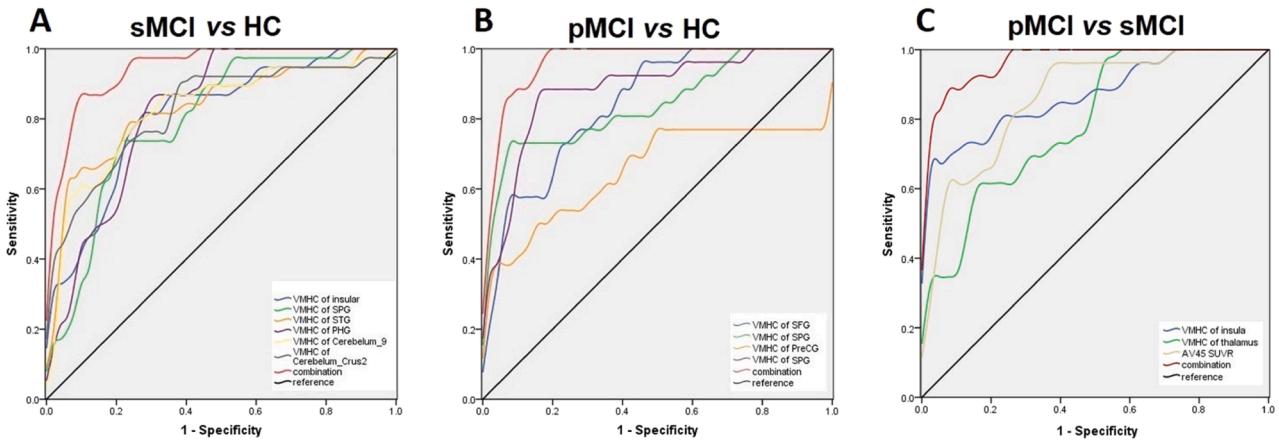

Fig. 5. Diagnosis and differentiation of sMCI and pMCI based on ROC analysis. (A) ROC curve showing the classification of sMCI and HC; (B) ROC curve showing the classification of pMCI and HC; (C) ROC curve showing the classification of pMCI and sMCI.

4.1. Altered functional patterns of inter-hemispheric connectivity in sMCI, pMCI, and HC groups

Previous studies have yielded consistent results regarding the attenuated inter-hemispheric connectivity in AD patients compared to HC groups. However, the changes in homotopic functional connection between cerebral hemispheres in MCI patients have not reached a consensus. In view of the high heterogeneity of clinical outcomes in the MCI population, the inter-hemispheric FC changes in pMCI and sMCI patients were studied and it was explored whether this could be used as imaging markers of AD conversion.

The results showed that sMCI and pMCI patients did have significant changes in homotopic functional connection. Compared with the sMCI group, decreased VMHC of insula and thalamus was indicated in the pMCI group. Insula, which is an important part of the salience network, plays an extremely important role in various cognitive functions of the human brain (Namkung et al., 2017). It functions as a "hub" that can integrate external sensory information with internal emotional and physical state signals into the prefrontal lobe, parietal lobe, cingulate gyrus, hippocampus, and amygdala for further processing and participation in cognitive control, emotional processing, and various sensorimotor processing (Namkung et al., 2017). Previous studies on VMHC have shown that the homotopic functional connection of insula is impaired in AD but not in MCI patients, thereby suggesting that pMCI patients have previously shown some characteristics of AD brain network damage before the conversion (Qiu et al., 2016a). In addition, in a previous study, it was also reported that the insula can coordinate dynamics of the brain network and initiate the switch between the default mode network (DMN) and the central execution network (CEN) (Menon and Uddin 2010). Based on this theory, it was speculated that the early insular connection disorder in pMCI patients may cause an abnormal function conversion between networks, and may even cause subsequent dysfunction within the DMN and CEN networks. However, this hypothesis is based on the results of this study and needs to be confirmed by further longitudinal follow-up studies. The findings of this study are also supported by the data presented in a previous study, which showed insular atrophy in pMCI compared to sMCI (Spulber et al., 2012). The insula module losing symmetrical functional connectivity using graph theory's modular analysis method in the AD group compared to the HC group was in line with our results (Chen et al., 2013).

The thalamus is well known as the advanced sensory center and the most important sensory transfer station. In addition to accepting a variety of sensations inside and outside the body, the thalamus also complexly integrates various sensations, combined with past sensory experiences to play an important role in executive, language, and memory consolidation (De Leon Reyes et al. 2020; Hwang et al., 2021; Kawabata et al., 2021). The thalamus participates in various and advanced activities and information processing by connecting vital cognitive-related regions, such as the medial prefrontal cortex and hippocampus (Cassel et al., 2021; Sweeney-Reed et al., 2021). The results of this study revealed that the decreased connection between the hemispheres of the thalamus in pMCI patients may contribute to failure of the integration and consolidation of memory-related information between the medial prefrontal cortex and the hippocampus (Eichenbaum 2017; Fabiani 2012). The inter-hemispheric connectivity of the insula and the thalamus positively correlated with the episodic memory and executive function, which indicated that attenuated inter-hemispheric connectivity of the two regions contributed to the worsened cognitive performance. In addition, deposition of amyloid beta in the insula (Villemagne et al., 2013) and subcortical areas (thalamus) (Shinohara et al., 2014) were found in the early stages of AD, thereby indicating that these areas were preferentially vulnerable in the early stages of disease. Furthermore, the results of this study revealed that the inter-hemispheric connectivity of the insula and thalamus negatively correlated with Aβ deposition in sMCI and pMCI patients, which was consistent with these earlier studies. Combining the research results of the above-mentioned study, our findings expand the previous study results and provide novel evidence that the attenuated VMHC of the insula and thalamus may be a sensitive indicator for predicting the progression of MCI, and has potential hints for early targeted intervention in the future.

Compared with HC subjects, our data showed that patients with sMCI have inter-hemispheric hyperconnectivity in multiple brain regions, including the parahippocampa gyrus, insula, SPG, STG, and cerebellum. The parahippocampal gyrus is the main cortical input of the hippocampus. It forms a hippocampal loop with the hippocampus, papillary body, prethalamic nucleus, and cingulate gyrus, and plays a role in high-level cognitive functions, such as emotion, learning, and memory (van Strien et al. 2009). Hyperconnectivity in the parahippocampal gyrus may be a compensation phenomenon in sMCI subjects, and recruits more inter-hemispheric neurons to collaboratively combat cognitive decline. Numerous fMRI studies have shown that hyperconnectivity changes in the parahippocampal gyrus in MCI patients in comparison with HC subjects and supported our results (Browndyke et al., 2013; Jacobs et al., 2015; Wierenga et al., 2012). Neuronal plasticity refers to the brain's ability to adapt to environmental changes through recruitment compensation methods, which enables the brain to compensate for the decline in cognitive function, and may help maintain the symptoms of MCI for a longer period time without disease progression (Ashraf et al., 2015; Delli Pizzi et al. 2019). From the perspective of neuroimaging, the plasticity of the brain is mainly manifested as compensatory

hyperconnectivity, that is, an attempt to recruit more neurons to maintain normal network functions. This explains why in this study, sMCI patients could maintain stability for a longer period of time without deterioration. Interestingly, previous studies reported that MCI patients with low amyloid deposition rather than high amyloid deposition tended to exhibit compensatory hypermetabolism (Ashraf et al., 2015). This was consistent with our results showing that the amyloid deposition of sMCI patients was not significantly different from that of HC subjects, and was lower than that of pMCI patients. In addition to the parahippocampal gyrus, previous studies have also reported that other brain regions have been implicated in cognitive compensation, including the insula (Mao et al., 2021), SPG (Behfar et al., 2020), STG (Krajcovicova et al., 2017), and cerebellum (Qi et al., 2019). These findings support our results and strengthen the basis for the theory of the compensation mechanism of the inter-hemispheric connection in sMCI patients (Wang et al., 2015; Zuo et al., 2010).

Compared with HC patients, pMCI patients have hypoconnectivity and compensatory hyperconnectivity coexisting between the hemispheres, which is characterized by decreased functional connectivity in the sensorimotor cortex (SMC) and the upper part of the SPG, and increased connectivity in the SFG and the lower part of the SPG. Previous studies have reported that the functional coordination between the hemispheres in the SMC area gradually strengthens with age (Stark et al., 2008; Zuo et al., 2010). In the disease state, Wang et al. showed that the VMHC connectivity of the SMC region was increased in MCI patients but reduced in AD patients, thereby indicating that the decreased cooperation of inter-hemispheric SMC region may have hints for the conversion from the MCI stage to the AD stage (Wang et al., 2015). The coexistence of hyperconnectivity and hypoconnectivity in the SPG area reflects the exhausted compensation effect in pMCI patients, that is, there are still some neurons that are fully resistant to cognitive decline, but this compensation effect is not sufficient (Delli Pizzi et al. 2019). In a previous study, it was revealed that the weakened inter-hemispheric FC of the parietal lobe was present in AD patients but not in MCI patients, which partially supports our results (Qiu et al., 2016b). The SFG is an important area involving multiple functions, such as motor function, working memory, and advanced cognition (Mountjoy et al., 2005) The decreased inter-hemispheric connectivity in the SFG in the pMCI group compared to the HC group, indicates that pMCI patients do have a further functional coordination disorder between the hemispheres that cannot be compensated. Our findings suggested that patients with pMCI have disordered functional connections between hemispheres. Compensatory hyperconnectivity between hemispheres in some brain regions are no longer sufficient to compensate for the decline in cognitive function and will continue to be exhausted in the future.

4.2. *Corpus callosum degeneration and its relationship with VMHC values and cognitive performance in sMCI and pMCI patients*

Our findings demonstrated that pMCI patients showed significant corpus callosum atrophy compared with sMCI patients and HC subjects, while sMCI patients had no significant atrophy compared with HC subjects. The corpus callosum is the largest commissural fiber connecting the two cerebral hemispheres. The normal function of the corpus callosum supports a wide range of cognitive, behavioral, and neurological consequences in the human brain (Bogen and Bogen 1988; Paul et al., 2007). Previous studies have reported significant corpus callosum atrophy in AD patients (Gootjes et al., 2006; Pantel et al., 1999; Tomimoto et al., 2004). In our study, patients with pMCI have obvious corpus callosum atrophy, which suggests that atrophy of the corpus callosum may be an indicator of disease severity. This hypothesis was supported by a previous study that showed a correlation between corpus callosum atrophy and the severity of dementia in AD patients (Pantel et al., 1999). Numerous MEG and fMRI studies showed that the reduced FC between the hemispheres is closely related to the corpus callosum atrophy in AD patients, which was consistent with our results (Pantel et al., 1999; Pogarell et al., 2005; Teipel et al., 2009; Tomimoto et al., 2004; Yuan et al., 2020).

However, the above-mentioned study only concluded a non-directional correlation relationship between the damaged corpus callosum and the inter-hemispheric functional connection, and the causal relationship between the two is still unclear. Therefore, in our study, the SEM method was used to study direct and indirect effects of inter-hemisphere connectivity, corpus callosum volume, and cognitive performance in pMCI and sMCI patients. The good fit of the SEM model indicated that the path model is a good fit for real data. The results showed that the homotopic connectivity has a direct positive effect on episodic memory in pMCI patients, that is, the lower inter-hemispheric connectivity, the worse the cognitive performance. The data also showed that the structural atrophy of the corpus callosum has no direct effect on episodic memory, but can have an indirect effect on episodic memory by mediating changes in inter-hemispheric connectivity. The positive effect of the VMHC value on episodic memory was realized through its direct effect on episodic memory and the mediating effect of corpus callosum degeneration on the VMHC value. Therefore, our results showed that pMCI patients do have corpus callosum atrophy compared to sMCI patients and HC subjects, and that the causal correlation between corpus callosum atrophy and cognitive performance was caused by mediating effects rather than direct effects. Thus, these findings have great clinical significance for the neuroimaging mechanism of the relationship between the inter-hemispheric connectivity and the corpus callosum volume in pMCI patients.

4.3. *Precise classification of sMCI and pMCI patients through a combined model of inter-hemisphere connectivity*

In this study, ROC analysis was used to calculate the potential of the VMHC index to classify sMCI and pMCI patients and detect the value of homotopic connectivity indicators for predicting MCI conversion. The results showed that both of VMHC values of a single brain region and the combination of multiple brain regions have high specificity and sensitivity in distinguishing between sMCI and pMCI patients. It is worth noting that the distinction between pMCI and sMCI patients based on the combination of multiple indicators was the optimal classification model. The combination of VMHC indicators and Aβ deposition can distinguish pMCI and sMCI patients with a diagnostic accuracy of 0.970, which was almost a perfect model classifier. The combination of VMHC indicators in multiple brain regions had a diagnostic accuracy of 0.946/0.964 in distinguishing sMCI/pMCI patients and HC subjects. In addition, the sensitivity of multiple indicators to distinguish pMCI patients and HC subjects was as high as 100%, which indicated that the homotopic functional connection had great potential to predict the conversion of MCI. In short, our findings indicated that the features of homotopic connectivity between hemispheres have important clinical significance and provide new prospects for the diagnosis and predictive conversion of the clinical AD spectrum.

4.4. *Limitations*

Our study has some limitations. Subjects were divided into sMCI and pMCI patients based on the clinical results of four years of longitudinal follow-up. Therefore, the number of subjects in this study was small. Subjects will continue to be followed up in the ADNI database and in the future, studies with a larger sample size will be conducted. Moreover, SEM analysis was only a possible theoretical explanation for the relationship between selected variables. There may be some confounding factors in the SEM model, such as white matter lesions, Aβ deposition, and iron deposition. In addition, although significant results were obtained in the structural model of pMCI, this result should be interpreted with caution because of the small sample size of pMCI. In the future, detailed group classification and a larger sample size are expected to reduce confounding factors. Because of the small number of subjects, the

ROC curve was not cross-validated, and independent sample validation with a larger sample size in the future is expected.

5. Conclusion

In summary, the current study revealed an alteration of homotopic connectivity and the corpus callosum volume in pMCI and sMCI patients, which was associated with cognitive decline. The exploration of the structure-functional association provided further evidence that the structural integrity of the corpus callosum mediated the alteration of functional activity between hemispheres, and accelerated cognitive decline. Importantly, the combination of multiple brain regions of VMHC can be used as a potential biomarker to predict the progression of MCI.

Ethics statement

The institutional review boards of each participating institution approved the ADNI study. All participants recruited from ADNI study signed written consent.

NOTES

The authors declare that they have no conflict of interest.

Data availability statement

The data that support the findings of this study are openly available in ADNI database at adni.loni.usc.edu.

Author statement

I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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