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Impaired Parahippocampus Connectivity in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract.
Background: The parahippocampal gyrus (PHG) is an important region of the limbic system that plays an important role in episodic memory. Elucidation of the PHG connectivity pattern will aid in the understanding of memory deficits in neurodegenerative diseases.
Objective: To investigate if disease severity associated altered PHG connectivity in Alzheimer's disease (AD) exists.
Methods: We evaluated resting-state functional magnetic resonance imaging data from 18 patients with amnestic mild cognitive impairment (MCI), 35 patients with AD, and 21 controls. The PHG connectivity pattern was examined by calculating Pearson's correlation coefficients between the bilateral PHG and whole brain. Group comparisons were performed after controlling for the effects of age and gender. The functional connectivity strength in each identified region was correlated with the MMSE score to evaluate the relationship between connectivity and cognitive ability.
Results: Several brain regions of the default mode network showed reduced PHG connectivity in the AD patients, and PHG connectivity was associated with disease severity in the MCI and AD subjects. More importantly, correlation analyses showed that there were positive correlations between the connectivity strengths of the left PHG-PCC/Pcu and left PHG-left MTG and the Mini-Mental State Examination, indicating that with disease progression from MCI to severe AD, damage to the functional connectivity of the PHG becomes increasingly severe.

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Conclusions: These results indicate that disease severity is associated with altered PHG connectivity, contributing to knowledge about the reduction in cognitive ability and impaired brain activity that occur in AD/MCI. These early changes in the functional connectivity of the PHG might provide some potential clues for identification of imaging markers for the early detection of MCI and AD.

Keywords: Alzheimer's disease, functional connectivity, mild cognitive impairment, parahippocampus

INTRODUCTION

Alzheimer's disease (AD) is a common progressive neurodegenerative disease that seriously affects human health. Mild cognitive impairment (MCI) is considered to be a transitional stage between normal cognition and dementia; amnestic MCI (aMCI) is considered to be an early stage of AD as confirmed by the similar pathology of the prodromal form of AD observed at autopsy with that of aMCI in most cases [1–3]. Converging evidence suggests that structural/functional alterations emerge more than 10 years before the onset of cognitive impairment in the medial temporal lobe, a region that undergoes the earliest neuropathologic changes associated with AD [4–8].

Quantitative functional connectivity based on resting-state functional magnetic resonance imaging (fMRI) represents a noninvasive tool for investigating large-scale connectivity *in vivo* [9]. Such changes in brain function can be used as measures of underlying AD/MCI. For example, using this technique, disrupted hippocampus connectivity [10–14], impaired default mode connectivity [15–17], and altered whole brain connectivity [18–20] have been identified and thoroughly studied in AD/MCI. These results are not surprising and support the hypothesis that AD/MCI is a disconnection syndrome [21–23].

The parahippocampal gyrus (PHG) covers most of the perirhinal, entorhinal, and posterior parahippocampal cortices [24]. It is an important region of the limbic system and a key region in the episodic memory network [25–31]. Neurofibrillary tangles, one of the hallmark pathologic characteristics of AD, are initially present in the perirhinal cortex, and they subsequently extend to the entorhinal and hippocampus cortices and finally, to the neocortices [6]. Imaging findings have consistently identified abnormal changes in the parahippocampus, such as grey matter atrophy [32], reduced cortical thickness [33], and decreased white matter volume [34–37], which are related to cognitive degradation in AD/MCI patients. Previous studies have also suggested that the parahippocampus plays a key role in modulating the anatomical/functional connectivity of the episodic memory system [26, 38, 39], and episodic memory dysfunction is one of the earliest hallmarks of AD [40, 41]. Therefore, evaluating the functional connectivity pattern of the parahippocampus is crucial to understanding the mechanism of disconnection in AD/MCI, making it worthwhile to search for sensitive imaging biomarkers for AD risk among older individuals with normal cognition (NC).

We hypothesized that there is disease-related alteration in PHG connectivity in individuals with AD/MCI. We also expected that PHG connectivity is highly affected in patients with severe AD and that it is affected to a lesser degree in those with mild AD and MCI; therefore, the strength of PHG connectivity maybe correlated with clinical ability (for example, cognitive variables measured by the Mini-Mental State Examination, MMSE). To test these hypotheses, we investigated bilateral PHG connectivity based on resting-state fMRI data acquired from 18 patients with moderate and severe AD (msAD), 17 with mild AD (mAD), 18 with MCI, and 21 age/gender-matched subjects with NC. Second, an analysis of variance (ANOVA), with age and gender as covariates, was performed to identify the regions with significantly altered PHG connectivity in MCI, mAD, and msAD. Next, posthoc analysis was conducted to elucidate the pattern of altered PHG connectivity among the MCI, mAD, and msAD subjects. Finally, to investigate how PHG connectivity changes as high-risk subjects develop AD, correlation analysis was performed to examine the relationship between the functional connectivity strengths of the identified regions and related clinical variables in the patient groups (Fig. 1).

MATERIALS AND METHODS

The same dataset in the present study has been reported in our previous studies of impaired distance-related network [20], salience network [42], and intra- and inter-network connectivities [43] in MCI and AD. Briefly, the study of the impaired distance-related network has found that AD patients have weaker functional connectivity between regions that are separated by a greater physical distance, especially in the default mode network; the more severe the impairment, the

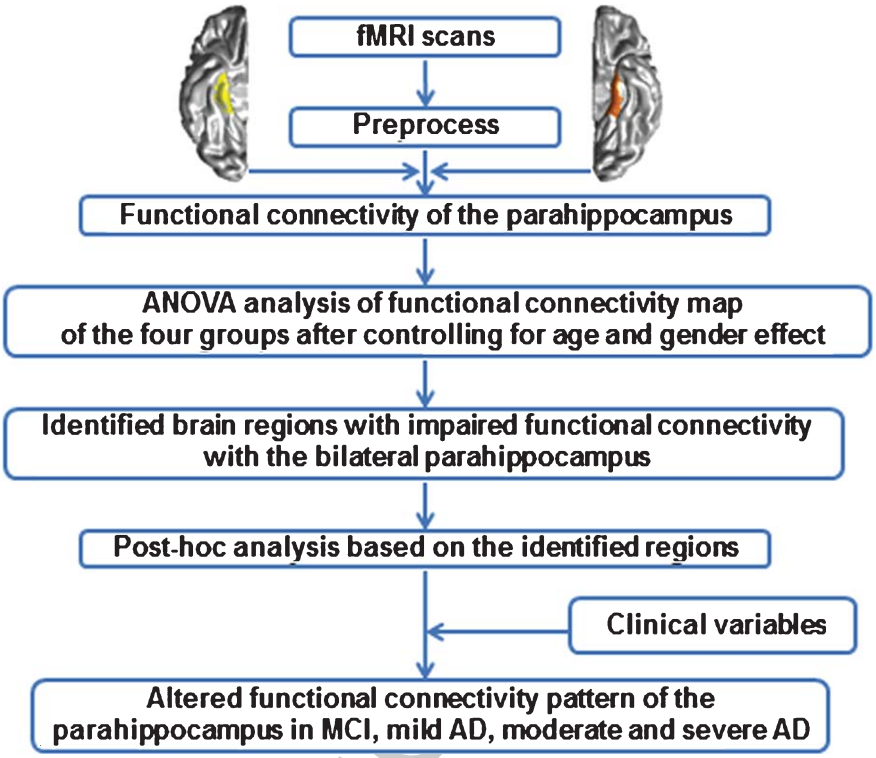

Fig. 1. Schematic of the data analysis pipeline. Regional mean fMRI time series of the bilateral parahippocampus (maps with colored regions are presented at the top) was estimated by averaging the time series within each hemisphere after data preprocessing. Functional connectivity of the bilateral PHG was then determined between the representative time series and the other brain voxels. Next, one-way analysis of variance (ANOVA) was performed to identify the regions with significantly altered PHG connectivity in the MCI, mAD, and msAD groups. Subsequently, *post-hoc* analysis was conducted to elucidate alterations in the PHG connectivity pattern among the MCI, mAD, and msAD subjects. Finally, to investigate how PHG connectivities are altered in high-risk subjects develop AD, correlation analysis was performed to examine the relationship between the functional connectivity strengths of the identified regions and the related clinical variables for all patients (including the MCI, AD patients).

greater the attenuation of long-distance functional connectivity [20]. We have also demonstrated that the inter-network disconnection between the salience and control networks and default mode network occurs during normal aging and that it is associated with cognitive decline in AD/MCI [42]. Based on independent component analysis, we have found a decrease in disease severity-related functional connectivity in several cognitive-related brain networks in AD, including the default mode network and frontoparietal network [43].

As stated in the introduction section, elucidation of a clear functional connectivity pattern of the parahippocampus is crucial to understanding the mechanism of disconnection in AD/MCI. For this reason, the main purpose of the present study was to test the hypothesis that that there is a disease-associated impairment in PHG connectivity in AD/MCI. Hence, analyses conducted in this study do not overlap or conflict with those of previous studies, ensuring the independence of the reported effects. To maintain the scientific integrity of the present study, we have provided a brief description of the data collection and data preprocessing steps. Further details regarding participant selection and exclusion for this dataset can be found elsewhere [20, 42, 43].

Subjects

All subjects were recruited through an advertisement and supported throughout the testing procedures at a specialist neuropsychological research facility at Xuanwu Hospital, Beijing, China. Written consent forms were obtained from all subjects or their legal guardians.

The inclusion criteria: (1) no history of an affective disorder within one month prior to assessment; (2) normal vision and audition and ability to cooperate with cognitive testing; (3) between 50 to 90 years of age; (4) no clinical history of stroke or other severe cerebrovascular disease; and (5) no more

than one lacunar infarction, without patchy or diffuse leukoaraiosis.

The exclusion criteria: (1) any medical disorders of the cardiovascular, endocrine, renal, or hepatic system; other neurological disorders potentially associated with cognitive dysfunction; or psychiatric disorders, such as major depression, alcohol or drug abuse; or (2) concomitant use of a large quantity of psychotropic medication; or (3) insufficient cognitive capacity to understand and cooperate with the study procedures.

Imaging quality control

We excluded mixed dementia and other brain disorders based on conventional MR images [43]. Conventional MR images of each subject were assessed by two experienced radiologists and excluded subjects who met any of the following criteria: (1) with any brain lesions except for lacunar infarction and white matter hyperintensity; (2) with more than one lacunar infarction which is defined as a maximal lesion diameter less than 1 cm; and (3) with moderate to severe white matter hyperintensity larger than 2 as assessed by a Fazekas scale (grades from 0 to 6) [43, 44]. As previously reported [20], to minimize the effect of slight head motion noise on the results, an exclusion criterion of head movement during fMRI scanning of less than 3 mm translation in any axis and of less than 3° angular rotation in any axis was also applied (see data preprocessing for details). Five participants were excluded from further analyses due to excessive head motion during scanning. Additionally, one MCI patient was excluded for incomplete MRI data because of technical problems that occurred during scanning.

Grouping criteria

All subjects underwent complete physical and neurological examinations and standard laboratory tests at Xuanwu Hospital. A senior neurologist (Professor Xinqing Zhang) clinically interviewed the patients and informants (usually a family member). All AD subjects were diagnosed using standard operational criteria (DSM-IVR [American Psychiatric Association, 1994] and NINCDS-ADRDA [45]]). The severity of dementia was assessed using the Clinical Dementia Rating (CDR) scale [46]. Patients were classified as mild AD (mAD) (CDR = 1) or moderate and severe AD (msAD) (CDR = 2 or 3) (This is because the sample size is relative small for moderate or severe AD, separately). MCI subjects met the Petersen's criteria, which is based on cognitive impairments that predominantly affect memory in the absence of dementia or significant functional loss [47], and a CDR score of 0.5 [46].The NC subjects underwent a detailed clinical interview and MMSE test to confirm that they satisfied the exclusion criteria for cognitive deficits. The NC volunteers had a CDR score of 0, no positive signs detected by neurology and medical examinations, normal cranial MRI, and no memory deficits or mental retardation detected by neuropsychological examination [20, 42, 43].

Apolipoprotein E (ApoE) genotypes

Venous blood samples from all subjects were collected after fMRI data acquisition. ApoE genotypes were determined using standard methods and divided into ApoE $\varepsilon 4$ carrier and noncarrier.

Eighty-seven older subjects were recruited to attend the examination. Based on the above criteria, a sample of 21 healthy volunteers (7 males, age: 65.0 ± 8.1 years), 18 patients with MCI (10 males, age: 70.2 ± 7.9 years), and 35 patients with AD [17 with mAD (8 males, age: 66.1 ± 8.3 years), and 18 with msAD (9 males, age: 65.4 ± 8.6 years)] were included in the present study. The demographic and neuropsychological data for the 74 subjects are summarized in Table 1. Additionally, details regarding the participants' demographic and neuropsychological characteristics can be found elsewhere [20, 42, 43].

Resting-state functional MRI data acquisition

As description in our previous studies [20, 42, 43], MR images were acquired with a 3.0 Tesla MR scanner (Magnetom Trio, Siemens, Germany). Functional MRI data were acquired using the same MR system and an echo planar imaging sequence sensitive to blood oxygenation level-dependent (BOLD) contrast with the following parameters: repetition time = 2000 ms; echo time = 30 ms; flip angle = 90°; matrix = 64×64; field of view = 220 mm × 220 mm; and slice thickness = 3 mm with inter-slice gap = 1 mm. Each brain volume consisted of 32 axial slices, and each scanning session lasted for 360 s. T1-weighted MR images were obtained using a magnetization-prepared rapid gradient echo sequence with the following parameters: repetition time = 2000 ms; echo time = 2.6 ms; flip angle = 9°; matrix = 256×224; and field of view = 256 mm × 224 mm for 176 sagittal slices of 1 mm thickness.

Table 1
Demographic, clinical, neuropsychological data and head motion in normal controls (NC), mild cognitive impairment (MCI), mild Alzheimer's disease (mAD), moderate and severe AD (msAD)

	NC ($n=21$)	MCI ($n=18$)	mAD ($n=17$)	msAD ($n=18$)	p value
Gender (M/F)	7/14	10/8	8/9	9/9	0.543
Age (year)	65.0 ± 8.1	70.2 ± 7.9	66.1 ± 8.3	65.4 ± 8.6	0.219
Education (year)	11.0 ± 4.4	9.4 ± 4.8	10.4 ± 4.2	10.9 ± 4.3	0.690
HDRS	1.7 ± 2.0	2.0 ± 3.3	0.6 ± 2.0	0.4 ± 1.0	0.08
ApoE $\varepsilon 4$ carrier/noncarrier	2/19	6/12	5/12	8/10	–
MMSE	28.5 ± 1.4	21.9 ± 5.0^{a}	$14.3 \pm 5.8^{a,b}$	$6.2 \pm 4.9^{a,b,c}$	<0.001
CDR	0	0.5	1.0	2.2 ± 0.4	–
FOM ($n=51$)	17.8 ± 1.5	12.3 ± 5.5^{a}	$5.1 \pm 4.8^{a,b}$	$1.6 \pm 3.3^{a,b,c}$	<0.001
CDT ($n=59$)	2.8 ± 0.4	2.4 ± 0.8^{a}	$1.2 \pm 0.9^{a,b}$	$0.5 \pm 0.6^{a,b,c}$	<0.001
Mean Head Motion	0.08 ± 0.04	0.10 ± 0.06	0.14 ± 0.13	0.11 ± 0.05	0.079

Chi-squared test was used for gender comparisons; One-way ANOVAs with Bonferroni-corrected *post-hoc t* tests were used for age, education, MMSE, FOM, and CDT comparisons. [a]Significant compared to NC. [b]Significant compared to MCI. [c]Significant compared to mild AD. HDRS, Hamilton depression rating scale score; MMSE, Mini Mental State Examination; CDR, Clinical Dementia Rating; FOM, Fuld Object Memory evaluation; CDT, Clock Drawing Test.

Functional MRI pre-processing

The data were pre-processed following the steps described in our previously published papers with in-house Brainnetome fMRI Toolkit (Brat, http://www.brainnetome.org/brat) based on statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). These steps included the following: (1) slice timing correction; (2) realignment for rigid-body motion correction to the first volume; (3) normalization to the standard EPI template and resampling to $2\times2\times2$ mm cubic voxels; (4) the use of a general linear model to regress out several confounding factors (i.e., the six motion parameters and their first derivatives, linear drift and the mean time series of all voxels within the white matter and cerebrospinal fluid); (5) temporal band-pass filtering (0.01–0.08 Hz); and (6) spatial smoothing with full width at half maximum and a 6 mm kernel.

Definition of the bilateral parahippocampus region

As described in our previous studies [48–50], WFU_PickAtlas toolkit (http://www.ansir.wfubmc.edu) was used to identify the bilateral PHG as the region of interest (ROI). To guarantee that the selected voxels were located in the PHG, we intersected the bilateral PHG using an automated anatomical labeling (AAL) template and the SPM Brain template of WFU_PickAtlas toolkit; thus, only the voxels of the overlapping region between the AAL and SPM brain template were selected. The volume of the left PHG was 325 voxels and that of the right PHG was 255 voxels, with a voxel size of 8 mm^3.

Functional connectivity and statistical analysis of the bilateral PHG

A voxel-wise functional connectivity analysis of each ROI was separately performed for each seed region. For each side of the PHG, the mean time series were calculated by averaging the fMRI time series of all of the voxels within the ROI. Then, we computed Pearson's correlation coefficients between the representative time series and those from each voxel in the brain. The Pearson's correlation coefficients were transformed to z-scores using Fisher r-to-z transformation to improve the normality of the correlation coefficients [51]. This step included generation of a map that presented the functional connectivity strength between the PHG and the left voxels in each brain.

Statistical analysis

Analysis of variance

For each side of the PHG, analysis of variance (ANOVA) was performed to evaluate differences among the four groups, with age and gender as covariates, to create an abnormality map (NC, MCI, mAD and msAD) using statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm). The threshold for the resulting F-value map was determined using a $p<0.01$ [$F=4.084$, $df=(3, 68)$] for each voxel and a minimum cluster size of 120 voxels within each identified cluster, which resulted in a corrected threshold of $p_{alpha}<0.01$, as determined by Monte Carlo simulation (the parameters were FWHM = 6 mm, with an AAL template in MRIcro as a mask).

Post hoc analysis based on the cluster level

Subsequently, the regions with significant differences were identified as the ROIs, and the mean PHG connectivity values of the four groups were extracted to evaluate alterations in functional connectivity strength indifferent stages of disease severity (Fig. 1). Statistical comparisons of the mean functional connectivity strengths were performed using the two-sample, two-tailed *t*-test between each pair of groups. To provide more detailed information for group comparisons, different levels of significance were used (e.g., $p < 0.05$, $p < 0.01$, $p < 0.001$).

Relationships between functional connectivity and clinical variables

To determine whether PHG connectivity was altered with increasing disease severity in the MCI and AD subjects, correlation analyses were performed to assess mean PHG connectivity strength and clinical variables (e.g., MMSE) in the MCI, mAD, msAD, AD (mAD+msAD), and MCI&AD groups separately. Because these analyses were conducted for exploratory purposes, we used a relatively loose statistical significance threshold ($p < 0.05$, uncorrected).

RESULTS

Functional connectivity and statistical analysis of the bilateral parahippocampus

Several regions, including the posterior cingulate cortex and precuneus (Pcc/Pcu) and the left middle temporal gyrus (MTG.L), showed significantly different functional connectivities compared with the left PHG in the MCI and AD subjects (Table 2 and Fig. 2A). For the right PHG, several regions, including the joint region of the posterior cingulate cortex, precuneus, and cuneus (Pcc/Pcu/Cun), left MTG, medial prefrontal cortex (MPFC), joint region of the angular and superior temporal gyrus (ANG/STG.L), middle frontal gyrus (MFG), and joint region of the superior parietal lobe and angular gyrus (SPL/ANG.R), showed altered connectivity in the MCI and AD subjects (Table 2 and Fig. 2B).

Post hoc analysis: group comparisons at the identified clusters

As Fig. 3 shows, left PHG-Pcc/Pcu connectivity was significantly altered between the NC and severe AD, NC and MCI, MCI and severe AD, and mAD and msAD groups (Fig. 3A). Only the NC group showed significant connectivity between the left PHG and left MTG compared with the severe AD and MCI groups (Fig. 3A).

The severe AD and MCI groups exhibited significantly decreased connectivities with the right PHG in all of the identified brain regions (Fig. 3B). In the identified brain regions, the PCC/Pcu/Cun, MPFC, and anterior MTG showed significantly stronger connectivities in the NC subjects compared with those in the mAD subjects (Fig. 3B). Only the posterior MTG showed weaker connectivity in the severe AD subjects compared with the MCI subjects; in addition, the posterior/anterior MTG and ANG/STG exhibited weaker connectivities in the subjects with severe AD compared with those with mAD (Fig. 3B).

Altered inter-regional connectivity: association with the MMSE score

As Fig. 4 shows, a positive correlation was detected between left PHG-PCC/Pcu connectivity and the MMSE score for the MCI&AD group ($R = 0.364$, $p = 0.007$) (Fig. 4A-a) and AD group ($R = 0.357$, $p = 0.036$) (Fig. 4A-b). There was also a positive correlation between left PHG–MTG.L connectivity and the MMSE score for the MCI&AD group ($R = 0.302$, $p = 0.028$) (Fig. 4B-a) as well as for the AD ($R = 0.412$, $p = 0.014$) (Fig. 4B-b) and mAD groups ($R = 0.493$, $p = 0.044$) (Fig. 4B-c). There was no correlation between right PHG connectivity strength and the MMSE score.

DISCUSSION

In the present study, resting-state fMRI signals were evaluated for 18 subjects with MCI, 35 with AD (17 with mAD and 18 with msAD), and 21 with NC. Then, seed-based functional correlation analyses were performed to determine the functional correlations between the bilateral PHG and whole brain. The main innovation of this study is that we have explored the functional connectivity pattern of the bilateral PHG in a large and clinically graded sample of MCI, mAD, and msAD patients. Two main findings were obtained as follows: first, several brain regions of the default mode network showed reduced PHG connectivity in the AD patients (Fig. 2, Table 2); and second, PHG connectivity was found to be correlated with disease severity, which is related to the level of impairment in MCI, mAD, and msAD (Fig. 3); moreover, correlation analyses showed that there were positive correlations between the MMSE score and the functional

Table 2
Altered functional connectivity using the parahippocampus as the ROI in the four groups ($p < 0.01$, cluster size > 120 voxels)

Brain Area	Brodmann Area	Cluster Size	F-value	Z-value	MNI Coordinates (x, y, z)
Altered functional connectivity of the left parahippocampus					
Pcc/Pcu	23/31	203	10.90	4.37	10 –42 30
			8.32	3.76	8 –48 22
			5.27	2.81	2 –40 20
MTG.L	21	190	7.77	3.61	–64 –32 –12
			7.02	3.39	–68 –40 –10
			6.50	3.23	–68 –44 –18
Altered functional connectivity of the right parahippocampus					
Pcc/Pcu/Cun	7/23/31	1991	12.22	4.64	–20 –34 0
			10.13	4.20	–6 –46 32
			9.89	4.14	6 –52 14
Posterior MTG.L	20/21	537	12.09	4.62	–66 –40 –12
			11.04	4.40	–54 –32 –4
			6.72	3.30	–64 –24 –16
MPFC	9/10	328	10.52	4.29	–6 62 24
			6.98	3.38	–2 52 26
			6.56	3.25	2 42 12
ANG/STG.L	39/40	733	10.20	4.21	–56 –60 16
			8.22	3.73	–48 –64 44
			8.13	3.71	–42 –64 38
MFG	8/9	387	7.85	3.63	–44 22 42
			7.29	3.47	–34 30 42
			5.54	2.91	–42 12 34
SPL/ANG.R	7	270	7.20	3.44	34 –70 38
			6.65	3.28	30 –72 46
			6.12	3.11	34 –64 46
Anterior MTG.L	21	145	6.67	3.28	–50 10 –42
			6.35	3.18	–48 6 –34
			5.71	2.96	–50 14 –30

L, left; R, right; PHG, parahippocampus; MTG, medial temporal gyrus; ANG, angular gyrus; MFG, middle frontal gyrus; MPFC, medical prefrontal cortex; Pcc, posterior cingulate cortex; Pcu, precuneus; Cun, cuneus; SPL, superior parietal lobe; STG, superior temporal gyrus.

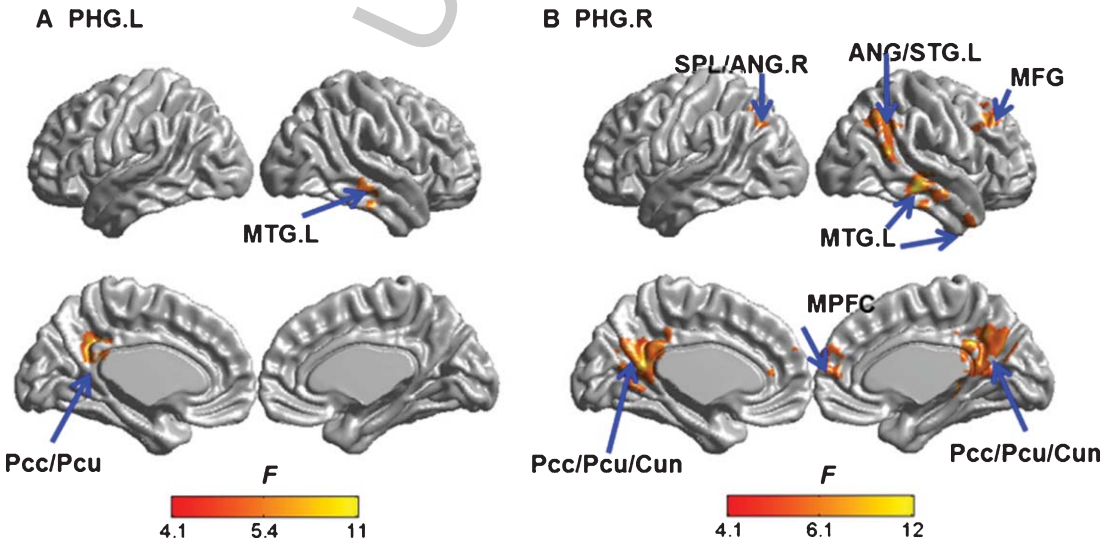

Fig. 2. Altered PHG connectivity in patients with Alzheimer's disease and mild cognitive impairment. Brat viewer software (http://www.brainnetome.org/brat) was used to visualize the anatomical distribution of abnormal functional activity. PHG, parahippocampus; MTG, medial temporal gyrus; ANG, angular gyrus; MFG, middle frontal gyrus; MPFC, medical prefrontal cortex; Pcc, posterior cingulate cortex; Pcu, precuneus; Cun, cuneus; SPL, superior parietal lobe; STG, superior temporal gyrus. Colored bar depicts the altered F values among the NC, MCI, mAD, and msAD groups.

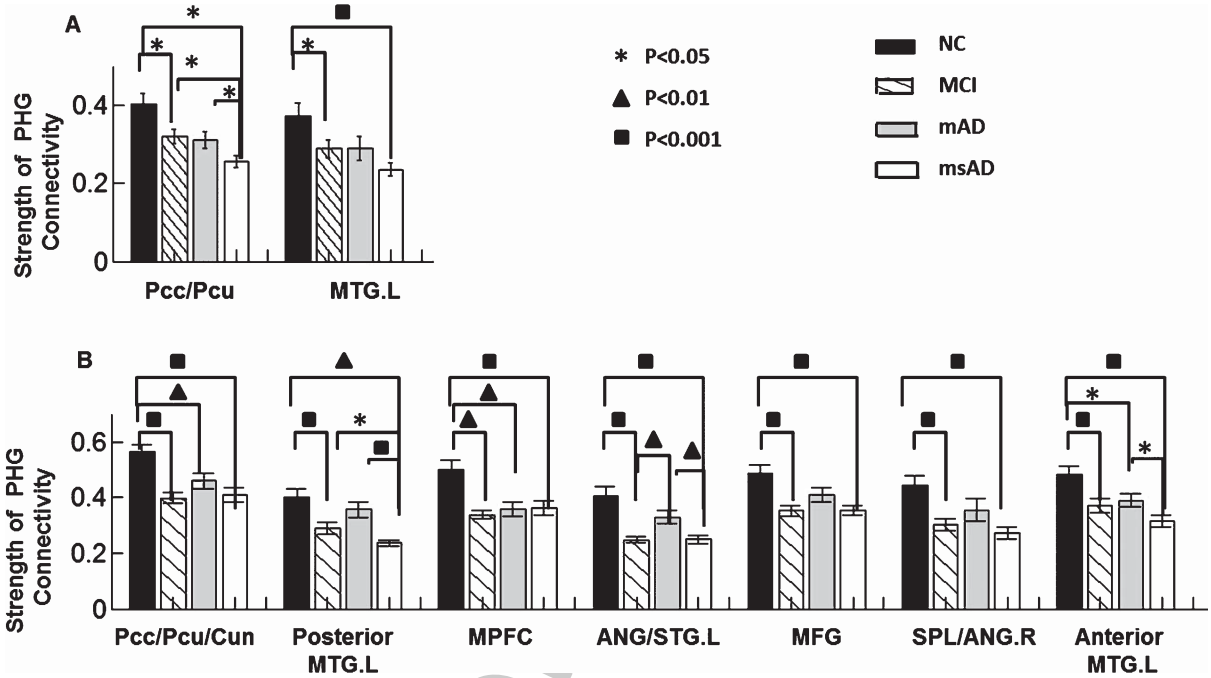

Fig. 3. *Post hoc* analysis with group comparisons at the cluster level of the functional connectivity of the left parahippocampus (A) and right parahippocampus (B). The black bar represents the normal controls, the slashed bar indicates the MCI patients, the gray bar represents the mAD patients, and the white bar indicates the msAD patients. The error bar represents the standard error for each group. $^{*}p<0.05$, $^{\blacktriangle}p<0.01$, and $^{\blacksquare}p<0.001$ for each pair of groups. PHG, parahippocampus; MTG, medial temporal gyrus; ANG, angular gyrus; MFG, middle frontal gyrus; MPFC, medical prefrontal cortex; Pcc, posterior cingulate cortex; Pcu, precuneus; Cun, cuneus; SPL, superior parietal lobe; STG, superior temporal gyrus.

connectivity strengths of the left PHG -PCC/Pcu and left PHG-left MTG, indicating that with disease from MCI to severe AD, functional connectivity damage in the PHG increases in severity (Fig. 4).

The parahippocampal gyrus links the default mode network with the episodic memory system

Clinically, AD patients first show functional impairments in memory (especially episodic memory) and dysfunction in executive control, and they cannot even perform the simplest daily tasks in their final days. Across the AD disease spectrum, episodic memory impairment is typically the earliest and core clinical symptom of AD and MCI [40, 41]. The earliest neuropathological changes, which are among the hallmarks of AD, occur in the medial temporal lobe, which mainly consists of the hippocampus, perirhinal and entorhinal cortices, and the parahippocampus cortex and plays a key role in episodic memory [28, 39, 52, 53]. The brain regions in which PHG connectivity is the most affected in AD include regions that have been previously described as hub regions of the so-called default mode network, such as the posterior cingulate cortex/precuneus/cuneus (Pcc/Pcu/Cun), middle temporal gyrus (MTG), angular gyrus, and medial frontal cortex (MPFC) (Figs. 1, 2) [15, 16]. Among some of these identified brain regions, clinical variability in the MMSE score was significantly correlated with the strength of PHG connectivity (Fig. 4). The default mode network has been suggested to be involved in internally focused tasks, including autobiographical memory retrieval and envisioning of the future [9, 54]. This network is associated with episodic memory and is a sensitive network that becomes damaged in MCI/AD patients [16, 55–58]. The PHG primarily receives direct associational input from the posterior associational brain regions, which are part of the default mode network, and it projects most heavily to the caudal two-thirds of the entorhinal cortex and then to the hippocampus, a hub region in the episodic memory network [24, 59–64], and cortico-parahippocampus-hippocampus connectivity is considered to play key roles in learning and episodic memory [25, 38, 62]. Knowledge of disease severity-related alterations in connectivity between the PHG and the brain regions involved in the default mode network strengthen the understanding of

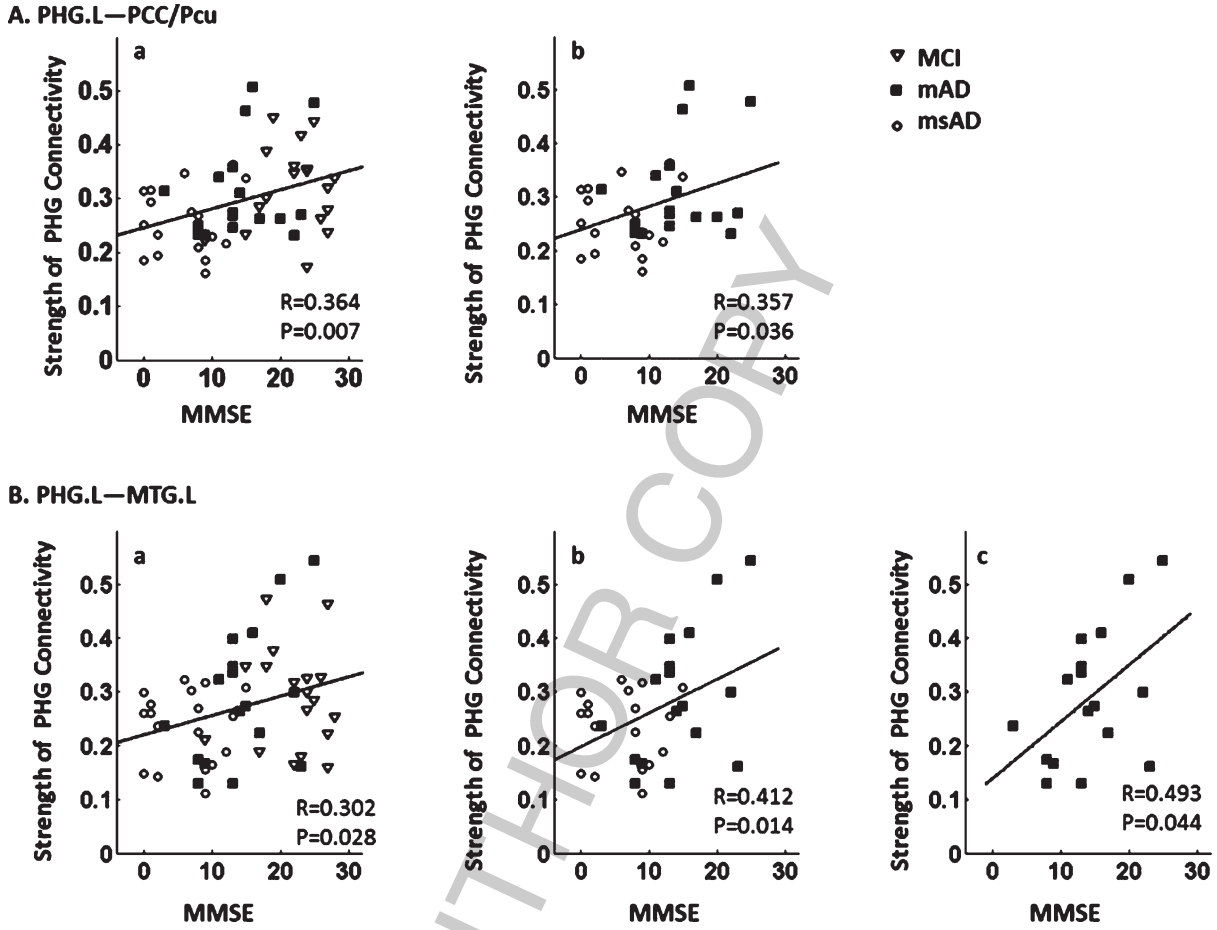

Fig. 4. Relationship between functional connectivity and clinical score. A) Left PHG-PCC/Pcu connectivity is positively correlated with the MMSE score for the MCI&AD group ($R = 0.364$, $p = 0.007$) (A-a) and the AD group ($R = 0.357$, $p = 0.036$) (A-b). B) Left PHG–MTG.L connectivity is positively correlated with the MMSE score for the MCI&AD group ($R = 0.302$, $p = 0.028$) (B-a) and the AD ($R = 0.412$, $p = 0.014$) (B-b) and mAD groups ($R = 0.493$, $p = 0.044$) (B-c). PHG, parahippocampus; MTG, medial temporal gyrus; Pcc, posterior cingulate cortex; Pcu, precuneus; MMSE, Mini-Mental State Examination.

the roles of these areas in impaired episodic memory in AD/MCI.

Parahippocampal gyrus connectivity is associated with disease severity

It should be emphasized that the connection strength between the left PHG and the left Pcc/Pcu and left MTG was positively correlated with between-subject variability, as measured with the MMSE in the MCI and AD groups (Figs. 3 and 4). This finding is in line with previous reports that the connectivity between the hippocampus and posterior cingulate cortex, a major hub of the default mode network, is mediated by PHG connectivity [25, 38] and that the MTG memory system is a brain network that associates with the brain regions of the default mode network through PHG connections [38, 65].

The MMSE is a clinical screening tool that is used to quantitatively assesses the severity of cognitive impairment to aid in diagnosing dementia and to assess its progression and severity [66]. From a clinical perspective, the pathophysiological impairments/alterations of AD are thought to begin many years before the diagnosis of dementia [8, 67]. MCI is a clinical state of cognitive decline that is "greater than expected for an individual's age and education level but does not interfere with activities of daily life" [68]. Of note, individuals with MCI have been suggested to be in the prodromal stage of dementia; in particular, individuals with amnestic MCI have a very high risk of progression to AD [67, 69]. The

significant correlations between the MMSE score and connectivity strength markers might reflect a general relationship between abnormal brain activity and cognitive impairment across clinically categorized patient groups.

No significant correlation has been identified for the right PHG, even when it contains more impaired regions than the left side. This finding suggests that the functional connectivity of the PHG is also affected by asymmetric brain volume-like atrophy and that asymmetry contributes to cognitive deficits [70, 71]. Although the exact underlying mechanism of the change in connectivity of the PHG cannot be evaluated *in vivo* with the currently available tools, the significant correlation found between left PHG connectivity and the MMSE score indicates that the PHG connectivity pattern might be a potential marker for MCI/AD. Assessing this correlation in combination with CSF biomarkers might shed further light on the results of this study, although our results need to be confirmed in future large sample studies.

In the present study, the CDR was used to assign participants to MCI (CDR = 0.5), mAD (CDR = 1), and msAD groups (CDR = 2 or 3). PHG connectivity was found to be significantly impaired in the patient groups. Notably, these correlations could not be identified in all the subgroups. This finding might have been due to the relatively small sample size of each group. It also might have occurred because the MMSE is a brief screening tool for assessing global cognition, and it is not sensitive for assessment of MCI subjects. This reasoning is supported by the lack of significant correlations that were observed between the MMSE score and the connectivity strength of the bilateral PHG in the MCI group in this study.

Caveats and future directions

Post hoc analysis demonstrated that the patient groups (MCI, mAD, and msAD) exhibited reduced connectivity to the bilateral PHG (Fig. 2), demonstrating the presence of disease-related impaired connectivity in the patient groups. Notably, no difference in functional connectivity strength between the MCI and mAD groups was detected for the left PHG, and the mAD group showed stronger connectivity between the ANG/STG and right PHG than that in the MCI group (Fig. 3). This finding might reflect age-related impaired brain activity, which is one of the important factors affecting connectivity strength, even in normal subjects [72–74]. The MCI subjects in this study were the oldest among the patient groups, which might have led to the reduced connectivity observed in this group. Future evaluation of a large sample dataset is needed to validate these findings.

The study has several limitations. First, it was cross-sectional, and the sample size of each subgroup was small; therefore, further studies are needed to evaluate this patient group and to determine whether impaired functional connectivity may serve as a predictor of cognitive decline related to early AD. Second, we analyzed functional connectivity of the bilateral PHG, an integrated region of interest. In fact, the PHG is a complex region that consists of several sub-regions, including most of the parahippocampus and perirhinal and entorhinal cortices [75], and each subregion might play a different functional role in the impaired brain function/connectivity in AD/MCI [59, 76–78]. Future research should focus more on the altered connectivity patterns of these sub-regions in AD. In addition, we calculated correlation coefficients between the mean time series and the time series of other voxels in the bilateral parahippocampus, and our results showed that the mean correlation coefficient was approximately 0.48, with a p-value of less than 10^{-10} for 170 time points (Supplementary Figure 1). These data demonstrate that it is appropriate to consider the mean time series of the bilateral parahippocampus as a representative signal. However, we would like to devise a new method to divide the parahippocampus and to investigate altered functional connectivity of the subregions in AD/MCI subjects.

Additionally, functional connectivity may be influenced by gray matter atrophy. We evaluated the effect of grey matter atrophy by comparing alterations in bilateral PHG functional connectivity patterns, and our results were similar with or without inclusion of the whole brain grey matter volume in regression analyses (Supplementary Figure 2). These results are in line with many previous functional connectivity studies [79–82]. However, there has been a debate in the literature over whether global brain signals should be considered as noise and regressed out during data preprocessing [83–87]. In addition, a recent study has highlighted the possible neurobiological importance of global/local BOLD signal variance alterations in certain psychiatric disorders (e.g., schizophrenia), which may be related to synaptic coupling disruptions that could be amenable to pharmacological intervention [88]. Hence, we did not regress out the whole brain mean signals.

Conclusions

The present study is the first report of the pattern of functional connectivity between the PHG and whole brain among normal, cognitively healthy older subjects and MCI/AD patients. The finding of a correlation between disease severity and altered PHG connectivity strengthens the hypothesis that AD/MCI is a disconnection syndrome.

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SUPPLEMENTARY MATERIAL

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