Hippocampus-based static functional connectivity mapping within white matter in mild cognitive impairment

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Received: 23 November 2021 / Accepted: 4 June 2022 / Published online: 22 July 2022
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Abstract
Mild cognitive impairment (MCI) is clinically characterized by memory loss and cognitive impairment closely associated with the hippocampal atrophy. Accumulating studies have confirmed the presence of neural signal changes within white matter (WM) in resting-state functional magnetic resonance imaging (fMRI). However, it remains unclear how abnormal hippocampus activity affects the WM regions in MCI. The current study employs 43 MCI, 71 very MCI (VMCI) and 87 age-, gender-, and education-matched healthy controls (HCs) from the public OASIS-3 dataset. Using the left and right hippocampus as seed points, we obtained the whole-brain functional connectivity (FC) maps for each subject. We then perform one-way ANOVA analysis to investigate the abnormal FC regions among HCs, VMCI, and MCI. We further performed probabilistic tracking to estimate whether the abnormal FC correspond to structural connectivity disruptions. Compared to HCs, MCI and VMCI groups exhibited reduced FC in the right middle temporal gyrus within gray matter, and right temporal pole, right inferior frontal gyrus within white matter. Specific dysconnectivity is shown in the cerebellum Crus II, left inferior temporal gyrus within gray matter, and right frontal gyrus within white matter. In addition, the fiber bundles connecting the left hippocampus and right temporal pole within white matter show abnormally increased mean diffusivity in MCI. The current study proposes a new functional imaging direction for exploring the mechanism of memory decline and pathophysiological mechanisms in different stages of Alzheimer’s disease.

Keywords Alzheimer’s disease · Functional connectivity · Hippocampus · Mild cognitive impairment · White matter

Introduction
Alzheimer’s disease (AD) is a progressive neurodegenerative disease which has been clinically characterized by memory loss and cognitive impairment, with slow onset and minor early symptoms (Rosales-Corral et al. 2012). Very mild cognitive impairment (VMCI) and mild cognitive impairment (MCI) are important transition states between normal aging and AD (Lombardi et al. 2020), in which memory and other cognitive skills decline at a faster rate than expected. However, this decline does not always interfere with one person’s ability to perform daily tasks (Neugroschl and Wang 2011). The annual incidence of transition from MCI to AD was estimated to be about 10–15%, while the primary incidence of AD was 1–2% per year (Lombardi et al. 2020). However, the specific pathogenesis of AD has not been fully elucidated so far. Exploring the abnormality of functional connectivity (FC) in white matter (WM) may provide a new method for revealing the neural mechanism of progressive decline of memory and cognitive function in AD.

Fiber bundles within WM areas, closely connecting to different gray matter (GM) regions in the brain structure, accounts for almost half of the human brain which consists of axons that connect different brain regions (Walhovd et al. 2014; Sampaio-Baptista and Johansen-Berg 2017). Recent studies have confirmed that the blood-oxygen-level-dependent (BOLD) signals within WM reflect neural activity of the
human brain (Peer et al. 2017; Wang et al. 2020a, 2021a). Therefore, functional magnetic resonance imaging (fMRI) signals from WM have become a new research direction of study. Several studies on brain disorders have reported abnormal FC between different WM and GM regions, such as in schizophrenia (Jiang et al. 2019a), epilepsy (Jiang et al. 2019b), Parkinson’s disease (Ji et al. 2019), and pontine strokes (Wang et al. 2019). In addition, Zhao and colleagues demonstrated that AD showed significantly lower FC within WM compared to healthy controls (HCs) (Zhao et al. 2019). Wang and colleagues demonstrated that compared with HCs, AD and the amnestic MCI groups exhibited reduced GM volume and decreased FC between the bilateral hippocampus and multiple brain regions distributing in the default mode network and control network (Wang et al. 2020b). In addition, Wang and colleagues found that compared to HCs, participants with MCI and VMCI had significantly lower homotopic FC in the middle occipital gyrus, inferior parietal gyrus within GM, and decreased homotopic FC for bilateral middle occipital and parietal lobe within WM (Wang et al. 2021b). Moreover, Gao et al. demonstrated that compared to HCs, cognitively normal patients with advanced MCI and AD dementia have significantly decreased FC by calculating the functional correlation matrix within WM (Gao et al. 2020). However, potential abnormal connectivity between hippocampus and WM has not yet been characterized in the states of VMCI and MCI.

The hippocampus plays an essential role in supporting encoding, consolidation and retrieval of memory, and episodic and semantic long-term memory (William Beecher Scoville 1957; Endel Tulving 1998; Aggleton 2012). Beyond these cognitive functions related to memory, the hippocampus is involved in regulating emotion, fear, anxiety, and stress (Bartsch and Wulff 2015). Previous studies have reported that the hippocampus is one of the earliest brain regions affected in AD (Maruszak and Thuret 2014). The pattern of brain atrophy is present in MCI (Misra et al. 2009). A significant reduction in hippocampal volume shown in MCI relative to controls (De Santi et al. 2001). By the AD stage, the hippocampus shows severe atrophy (Irena Štepán-Buksakowska et al. 2014). In addition, Štepán-Buksakowska et al. found that the cortical surface of the hippocampus was significantly reduced in MCI and AD subjects (Irena Štepán-Buksakowska et al. 2014). Studies of fMRI have demonstrated that compared to HCs, AD subjects have discernable increases in the low-frequency fluctuations of the hippocampus (Liu et al. 2014). These studies show that the hippocampus plays a vital role in maintaining normal human brain function and is a core area to understand the specific pathogenesis of AD.

We hypothesized that VMCI and MCI subjects will show abnormal functional and structural connectivity between bilateral hippocampus and WM regions. To address this hypothesis, we first identified the hippocampus for each subject and then obtained the group-level hippocampal mask by averaging above hippocampus areas across subjects. Seed point-based FC analysis was performed on whole-brain voxels to obtain the FC maps for each subject. To further explore the differences of hippocampus-based FC maps within WM, we performed statistical analysis on the FC maps using one-way ANOVA. We extracted the fiber bundles connecting the hippocampus and abnormal FC regions within WM using probabilistic tracking, and calculated the averaged mean diffusivity to analyze the differences in above fiber bundles among HCs, VMCI, and MCI groups.

Materials and methods

This study used public data from the OASIS-3 dataset (https://central.xnat.org), including 43 MCI, 71 VMCI, and 87 matched HCs. Briefly, OASIS-3 is a compilation of MRI and PET imaging data collected from several studies conducted by the Knight AD Research Center at the University of Washington over the past 15 years. The clinical dementia rating scale was used to assess the dementia status of the uniform data set (Morris et al. 2006). According to the clinical dementia rating, all subjects were divided into different groups. Clinical dementia ratings of 0, 0.5, and 1 indicated HCs, VMCI, and MCI, respectively. Moreover, since the median Mini-Mental State Examination (MMSE) could comprehensively and simply reflect the subjects’ mental status and degree of cognitive impairment, MMSE scores were collected for each subject (Tombaugh and McIntyre 1992). All subjects had provided informed consent before MRI or neurological assessment. In addition, clinical scale information for all subjects had been obtained. More detailed information is shown in Table 1.

The MRI dataset from all subjects was obtained using the 3-T Siemens’s Trio Tim scanners. All subjects were instructed to lie quietly and close their eyes during the scan. Resting-state functional images were collected using an echo-planner imaging sequence with following parameters: repetition time (TR) = 2200 ms, echo time (TE) = 27 ms, flip angle (FA) = 90°, number of slices = 33, slice thickness = 4 mm, and voxel size = 4 × 4 × 4 mm³. For T1-weighted images, the parameters are described as follows: voxel size = 1 × 1 × 1 mm³, echo time = 316 ms, repetition time = 2400 ms, flip angle = 8°, and slice thickness = 1 mm. The echo plane imaging sequence was used to obtain diffusion tensor images (DTI) covering the entire brain, including 24 volumes with diffusion gradients applied along 24 non-collinear directions. The parameters of DTI are as follows: voxel size = 2 × 2 × 2 mm³, echo time = 0.112 s, repetition time = 14.5 s, flip angle = 90°, and slice thickness = 2 mm.
Data preprocessing

Resting-state functional images and T1-weighted image preprocessing was performed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and Data Processing Assistant for Resting-State fMRI (http://rfmri.org/DPARSF). Briefly, functional imaging preprocessing procedures consisted of the following steps: (1) to remove the unstable signals of the magnetic resonance scanner at the beginning of the scan, the first 5 time points were removed; (2) Head motion correction using rigid body translation and rotation, subjects with maximum motion > 3 mm or 3° were excluded; (3) Anatomical images were co-registered to the mean functional image using a trilinear interpolation with degrees of freedom; (4) DARTEL algorithm was used to segment the T1-weighted image of each subject to obtain GM, WM, and cerebrospinal fluid; (5) Regressing interference signal, including 24 head movement parameters and averaging the cerebrospinal fluid signal. To retain as much signal of interest as possible, we did not perform the regression analysis with global and WM signals. We used scrubbing analysis when observing movement "spikes" (frame displacement (FD) > 1 mm), and performed a separate stopper to reduce head-motion effects; (6) removing the linear trends to correct signal drift; (7) to minimize the impact of non-neuronal signals on BOLD fluctuations, a band-pass filter of 0.01–0.1 Hz was used to extract the low-frequency components of functional images; (8) to avoid the confusion of WM and GM signals, the WM and GM templates were, respectively, used to minimize spatial smoothing of the functional images for each subject (4 mm full-width half-maximum [FWHM], isotropic); (9) the smoothed functional images were normalized from native space to MNI space with voxel size 3 × 3 × 3 mm³.

The current study preprocessed and analyzed the DTI dataset using FSL package (http://www.fmrib.ox.ac.uk/fsl). For each subject, the preprocessing steps mainly include removal of non-brain tissue (fractional intensity threshold was 0.2), correction of eddy current distortion, and local fitting of diffusion tensor (Yamada et al. 2014). Mean diffusivity, which describes the rotationally invariant magnitude of water diffusion within brain tissue, is another measure obtained from DTI data that has been used to examine differences in brain structural integrity in psychiatric disorders (DeLisi et al. 2006; Clark et al. 2011). Then, we performed Bayesian estimation of diffusion parameters obtained using sampling techniques with modeling of crossing fibers and Bayesian estimation of diffusion parameters were obtained using sampling techniques (BEDPOSTX) in FSL. In this step, BEDPOSTX executes Markov Chain Monte Carlo sampling to establish the distribution of dispersion parameters on each voxel and performs Bayesian estimation at the same time. To ensure that the DTI dataset of all subjects were in the same standard space, FMRIB’s linear image registration tool was used to perform the standardization analysis.

Table 1  Demographics and clinical characteristics of subjects

| Characteristics | HCs (N = 100) | VMCI (N = 90) | MCI (N = 53) | p Value |
|-----------------|-------------|--------------|--------------|---------|
| Age             | 74.29 ± 8.098 | 74.42 ± 7.749 | 75.47 ± 9.254 | 0.7098a |
| Gender (M/F)    | 45/42       | 39/32        | 29/14        | 0.2274b |
| Education       | 14.26 ± 1.715 | 14.69 ± 3.050 | 14.95 ± 3.177 | 0.5464a |
| MMSE            | 28.80 ± 1.328 | 25.94 ± 2.932 | 22.16 ± 4.214 | <0.0001a |
| Handedness (L/R)| 0/87        | 0/71         | 0/43         |         |
| LOGIMEM         | 12.73 ± 4.240 | 8.286 ± 4.706 | 5.025 ± 3.984 | <0.0001a |
| WAIS            | 53.51 ± 11.05 | 40.64 ± 14.25 | 33.43 ± 15.96 | <0.0001a |
| MEMUNITS        | 11.67 ± 4.429 | 5.886 ± 5.081 | 3.075 ± 3.805 | <0.0001a |
| MEMTIME         | 14.86 ± 2.117 | 16.66 ± 2.843 | 17.83 ± 3.802 | <0.0001a |

Demographics and clinical characteristics for DTI subjects

| Characteristics | HCs (N = 100) | VMCI (N = 90) | MCI (N = 53) | p Value |
|-----------------|-------------|--------------|--------------|---------|
| Age             | 73.38 ± 7.919 | 76.18 ± 7.451 | 76.95 ± 7.925 | 0.1209a |
| Gender (M/F)    | 26/22       | 22/17        | 18/4         | 0.0719b |
| Education       | 14.21 ± 1.774 | 14.90 ± 2.817 | 15.14 ± 3.028 | <0.0001a |
| MMSE            | 29.06 ± 1.137 | 26.21 ± 2.716 | 21.64 ± 4.816 | <0.0001a |
| Handedness (L/R)| 0/48        | 0/39         | 0/22         |         |

F female, HCs health controls, L left, LOGIMEM logical memory, MCI mild cognitive impairment, M Male, MMSE Mini-Mental State Examination, MEMUNITS total number of story units recalled, ME TIME time elapsed since first recall to delayed recall, R right, VMCI Very mild cognitive impairment, WAIS Wechsler adult intelligence scale

aOne-way ANOVA (using nonparametric test)
bChi-square
The group-level hippocampus mask

To obtain the group-level hippocampus template, we adopted FMRIB’s Integrated Registration and Segmentation Tool on individual structural images and obtained the hippocampus mask for each subject (Patenaude et al. 2011). The group-level hippocampus mask was obtained by averaging the individual hippocampus masks across all subjects. Subsequently, to generate the final binarized group-level hippocampus mask, we selected a strict threshold of 0.9 to limit the hippocampus masks. Geroldi and colleagues used MRI images to demonstrate that the bilateral hippocampus of normal adults was a reliable asymmetric structure, and dementia was related to the change of normal anatomy asymmetry (Geroldi et al. 2000). Therefore, based on the functional anatomy and potential lateralization of the hippocampus (Szabo et al. 2001), we used the left and right hippocampus as regions of interest (ROIs) for subsequent whole-brain FC analysis.

Creation of group-level WM and GM masks

To avoid mixing WM and GM signals, we created group-level WM and GM masks. Specifically, using WM and GM images segmented from the above T1-weighted structure images, each voxel in the brain was identified with the maximum probability as WM or GM, which created binary WM and GM masks for each subject. Then, binarized WM masks were averaged across subjects, and then, a threshold with 60% of subjects was used to create a binary group-level WM mask (Jiang et al. 2019a; Peer et al. 2017; Wang et al. 2020a). The voxels of anatomical mask were then selected and recognized as the group-level WM mask in greater than 80% of the subjects in the functional data. To estimate the effect of threshold on current results, we also used two stricter thresholds with 70% and 80% to perform the same analysis process (Supplementary 1). Adopting the same method, the binarized group-level GM mask was obtained, but using a lenient threshold with 20% of subjects. To further limit group-level WM and GM masks, voxels of the resulting mask were then selected, and the final group-level GM mask was defined using voxels that were present in greater than 80% of the subjects in the functional data. Finally, to exclude the effect from deep brain structures, we identified the thalamus, caudate, nucleus putamen, globus pallidus, and nucleus accumbens based on the Harvard–Oxford template and removed them from the group-level WM mask.

Whole-brain FC maps with hippocampus as ROI

The current study explored the abnormal FC between the hippocampus and whole-brain voxels in VMCI and MCI subjects. To this end, the following steps were performed: (1) the averaged time-series of the left hippocampus were extracted for each subject; (2) FC was computed between the time-series of the left hippocampus and all voxels’ time-series within whole brain; (3) Fisher’s z transformation was performed for all correlation coefficients. Moreover, we also calculated FC between the right hippocampus and all voxels within the whole brain using the same steps outlined above.

Probabilistic tracking analysis

The probabilistic tracking analysis of DTI data was performed using FSL_6.0.3 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). We performed probabilistic fiber bundle imaging using probtrackx2. In this step, the distribution estimated by BEDPOSTX was used for simulation. Before the fiber bundles connecting the hippocampus and abnormal WM regions were tracked, these ROIs were transformed from MNI space to individual diffusion space using FMRIB’s linear image registration tool. Several regions showing abnormal FC within WM in the patients (as shown in the results section of Hippocampus-based FC within WM: right frontal gyrus WM, right temporal pole WM, left insula WM, and right inferior frontal gyrus WM) were selected as ROIs for subsequent DTI analysis and dilation by two voxels. Finally, FSL repeatedly samples from the main dispersion direction, calculates streamlines through these sampling points, and generates a set of probability streamlines, thereby extracting the fibers between the hippocampus and the abnormal ROIs within WM. The prior distribution information was established through multiple sampling, and then, the true fiber distribution could be inferred from the prior information. The default 0.5 voxel step size, 5000 samples, and 2000 step size were used (− step length 0.5 − P 5000 − S 2000). Finally, we calculated the averaged mean diffusivity of fiber bundles connecting the hippocampus and ROIs. Two-sample t test was performed to explore the abnormal structural connectivity between the hippocampus and abnormal WM areas among HCs, VMCI, and MCI groups (p < 0.05/number of ROIs, Bonferroni correction was used).

Statistical analysis

Within-group FC between left/right hippocampus and each voxel within the group-level GM mask was calculated using one-sample t test. The results were displayed with xjView (version 9.7, https://www.alivelearn.net/xjview) with p < 0.05 set. Abnormal FC regions within group-level GM masks among HCs, VMCI, and MCI were identified by using one-way ANOVA, with age, gender, and education as covariates. Gaussian Random Field (GRF) theory was performed to correct for cluster-level multiple comparisons (minimum z scores > 2.3; cluster significance: p < 0.05, GRF corrected). Six abnormal ROIs were obtained for post
hoc analysis, and were compared using two-sample t test with age, gender, and education as covariates (two-tailed, \( p < 0.05 \), Bonferroni-corrected for multiple comparisons \( p < 0.05/6 \)).

Moreover, one-sample t test within the group-level WM mask was calculated across all subjects’ FC maps based on the left and right hippocampus as seed ROIs for each of the HCs, VMCI, and MCI. The abnormal FC regions within group-level WM masks were obtained among HCs, VMCI, and MCI using one-sample t test, as well. The significance level of one-sample t test maps was set at \( p < 0.05 \) (uncorrected). Four ROIs were obtained for post hoc analysis and were compared using two-sample t test with age, gender, and education as covariates (two-tailed, Bonferroni-corrected for multiple comparisons, \( p < 0.05/4 \)). Finally, Pearson correlation analysis was performed to explore the potential relationships between averaged FC values within abnormal areas and clinical measures.

## Results

### Clinical data analysis

Demographic and corresponding clinical information is shown in Table 1. The MCI, VMCI, and HCs groups were found to have no significant differences in age (one-way ANOVA, \( p = 0.7098 \)), gender (Chi-square, \( p = 0.2274 \)), and education level (one-way ANOVA, \( p = 0.5464 \)), but MMSE scores show significant difference with \( p < 0.0001 \). Although a few subjects missed the cognitive and memory measures including logical memory, Wechsler adult intelligence scale (WAIS), total number of story units recalled, and time elapsed since first recall to delayed recall, we still included these metrics in a comprehensive format to enable readers to have a clearer understanding about the study population (Table 1). One-way ANOVA among HCs, VMCI, and MCI showed significant difference with \( p < 0.0001 \) in logical memory, WAIS, the total number of story units recalled, and time elapsed since first recall to delayed recall.

### Hippocampus-based FC within GM

Within-group analysis for hippocampus-based FC within GM showed robust regional differences for each group (Fig. 1a, b). The significance level was set to \( p < 0.05 \) (uncorrected). In addition, to explore the abnormal FC among HCs, VMCI, and MCI groups, we performed one-way ANOVA on the hippocampus-based FC maps among HCs, VMCI, and MCI, and found abnormal FC between right hippocampus and right cerebellum Crus II, left cerebellum VIIb, and between left hippocampus and left inferior temporal gyrus, left cerebellum Crus I, right middle temporal gyrus and right cerebellum Crus II. Subsequently, the post hoc analysis showed that compared to HCs, VMCI and MCI groups showed common features with decreased FC between left hippocampus and right middle temporal gyrus (VMCI: \( p < 0.0001, U = 1792 \); MCI: \( p = 0.0002, U = 1122 \)). In addition, MCI showed specifically abnormal decreased FC between right hippocampus and left cerebellum VIIb \( (p < 0.0001, U = 1055) \), and between left hippocampus and left cerebellum Crus I \( (p = 0.0002, U = 1140) \), right cerebellum Crus II \( (p = 0.0004, U = 1166) \), but no difference between VMCI and HCs (left cerebellum VIIb: \( p = 0.3409 \),

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**Fig. 1** Within-group analysis of hippocampus-based FC within GM. a, b The FC maps within GM based on the left/right hippocampus as ROI, respectively. Color bar represents the \( T \) value. The significant level was set to \( p < 0.05 \) (uncorrected). HIP.L left hippocampus, HIP.R right hippocampus.
Finally, compared to the HCs, MCI subjects showed significant differences between right hippocampus and right cerebellum Crus II ($p = 0.0005$, $U = 1177$), and between left hippocampus and left inferior temporal gyrus ($p < 0.0001$, $U = 1018$). However, no difference between MCI and VMCI (right cerebellum Crus II: $p = 0.0360$, $U = 1168$; left inferior temporal gyrus: $p = 0.0072$, $U = 1069$), and between VMCI and HCs (right cerebellum Crus II: $p = 0.0914$, $U = 2605$; left inferior temporal gyrus: $p = 0.0150$, $U = 2394$) (Fig. 2a, b) was observed.

### Hippocampus-based FC within WM

Several studies have demonstrated that the BOLD signals in the WM contain neural activity information, and could reflect neural activities in the human brain (Ding et al. 2018; Peer et al. 2017; Jiang et al. 2019a, b; Wang et al. 2021c). We further explored the abnormal alterations for FC between the bilateral hippocampus and WM regions. Similar to within-group FC maps within the GM, within-group hippocampus-based FC maps within the WM also showed robust regional differences among HCs, VMCI, and MCI (Fig. 3a, b). And we found that showed the same abnormal connectivity regions within WM masks of different threshold values (60%, 70%, and 80%) (Supplementary 1). Compared to HCs, VMCI and MCI groups showed abnormally decreased FC between the left hippocampus and right temporal pole within the WM (VMCI: $p = 0.0002$, $U = 2035$; MCI: $p < 0.0001$, $U = 883$), as well as the right inferior frontal gyrus within the WM (VMCI: $p = 0.0028$, $U = 2238$; MCI: $p < 0.0001$, $U = 988$). Moreover, MCI showed decreased FC between the right hippocampus and right frontal gyrus within the WM ($p = 0.0003$, $U = 1142$), but no significant differences between VMCI and HCs ($p = 0.6757$, $U = 2968$). Finally, compared to HCs, MCI showed significant reduction in FC between the left hippocampus and left insula WM ($p < 0.0001$, $U = 1094$), but no significant differences between MCI and VMCI ($p = 0.0320$, $U = 1160$), and between VMCI and HCs were observed ($p = 0.0198$, $U = 2423$) (Fig. 4a, b).

### Probabilistic tracking analysis

Since structural information is the foundation of functional activities in the human brain, structural connectivity was shown to be closely related to FC (Fjell et al. 2017; Huang and Ding 2016). Therefore, we further analyzed fiber connections between the hippocampus and regions showing abnormal hippocampus-based FC within WM among HCs, VMCI, and MCI. In detail, fiber bundles connecting the hippocampus and abnormal WM areas were extracted using FSL. Then, the averaged mean diffusivity of the above WM fibers was calculated for each subject. One-way ANOVA was performed to compare the differences between HCs, MCI, and VMCI with age, gender, and education as covariates. We found that the abnormal fiber bundles connecting the left hippocampus and right temporal pole within the WM showed significantly increased mean diffusivity in MCI subjects compared to HCs ($p = 0.0074$, $U = 318$), but...
no significant differences between HCs and VMCI groups ($p = 0.0596, U = 715$) (Fig. 5).

**Relationships between FC and clinical measures**

Pearson correlation analysis was performed to explore the potential relationships between averaged FC values within abnormal regions and clinical measures. The values of average FC in the right middle temporal gyrus with left hippocampus as ROI were positively associated with WAIS scores in VMCI group ($r = 0.34, p = 0.01$). In addition, the average FC values in the right temporal pole WM based on the left hippocampus as ROI were also positively related with WAIS scores in VMCI group ($r = 0.3, p = 0.0292$) (Fig. 6).

**Discussion**

The current study explored abnormal hippocampus-based whole-brain FC in the VMCI and MCI. Within-group analysis showed decrease FC with WM-FC$_{\text{MCI}} < $ WM-FC$_{\text{VMCI}} < $ WM-FC$_{\text{HCS}}$ (Fig. 3), indicating that with the deterioration of the disease, FC strength based on the
hippocampus became weaker. We also found abnormal changes of FC between bilateral hippocampus and WM regions, and abnormal structural connectivity within WM, indicating that memory and cognitive dysfunction of AD were not only related to the GM BOLD signals, but also related to the functional activities of WM which is consistent with previous studies showing lower FC within WM in VMCI and MCI (Zhao et al. 2019; Wang et al. 2021b; Gao et al. 2020). Our study may provide a new direction to explore the pathogenesis and diagnosis of AD using fMRI.

The hippocampus, being an important part of the limbic system in the human brain, is a crucial area responsible for storing and retrieving memories (Callen et al. 2002). For AD patients, the hippocampus has been shown to be one of the first areas to be damaged, and one of the most severely affected areas (Frisoni et al. 2010). The current study found abnormal FC within GM between the right hippocampus and...
Fig. 5 Altered structural connectivity between right hippocampus and right temporal pole WM. Left portion represents the brain map showing the fiber bundle connecting the right hippocampus and right temporal pole WM. Right portion represents the bar charts showing the abnormal MD in MCI subjects compared to HC. **The $p < 0.05$ for numbers of ROIs, Bonferroni correction. HIP.R right hippocampus, TP-WM right temporal pole WM.

Fig. 6 Correlations between FC and clinical measures. a The mean FC values within right middle temporal gyrus were positively correlated with WAIS scores in VMCI group ($p_i = 0.34$, $p = 0.01$). b The mean FC values within right temporal pole WM were positively correlated with WAIS scores in VMCI group ($p_i = 0.3$, $p = 0.0292$). HIP.R right hippocampus, TP-WM right temporal pole WM.

right cerebellum Crus II, left cerebellum VIIb, and between the left hippocampus and left inferior temporal gyrus, left cerebellum Crus I, right middle temporal gyrus, and right cerebellum Crus II. The cerebellum not only contributes to motor function (A form of familial degeneration of the cerebellum Holmes 1908), but also participates in high-level
functions related to memory (Schmahmann 2019). Pathological studies demonstrated that the cerebellum largely effected other brain connections (Tang et al. 2021), and was smaller in volume in AD patients (Jacobs et al. 2018). The current study found abnormal hippocampus-based FC in cerebellar regions in the MCI, further elucidating that cerebellar disruption might be one of the factors resulting in AD patients’ cognitive decline. In addition, compared to HCs, the volume of the temporal lobe was significantly decreased in the MCI (Convit et al. 2000). By examining the correlation between time-series of the hippocampus and other GM regions, disrupted FC was shown between the right hippocampus and temporal lobe in AD (Wang et al. 2005). The temporal lobe facilitates the recovery of spatial position from long-term situational memory (Köhler et al. 1998; Buckner and Wheeler 2001), and damage to the temporal lobe leads to incomplete memory function, which is consistent with abnormal hippocampus-based FC in the temporal lobe.

There has been converging evidence supporting the relevance of BOLD signal fluctuations in the WM that correspond to neural activities (Wang et al. 2021a; Ding et al. 2018). In this study, we further explored the abnormal hippocampus-based FC within WM in the states of VMCI and MCI. We found abnormal FC based on hippocampus as ROI distributed in the left insula WM, right temporal pole WM, and right inferior frontal gyrus WM. In detail, FC strength within WM between left hippocampus and right temporal pole, and right inferior frontal gyrus WM. In VMCI and MCI was significantly weaker than that of HCs (Fig. 4). The connection strength between right hippocampus and right frontal gyrus WM, and between left hippocampus and left insula of MCI was also weaker than that of HCs, indicating that WM disruption is an important factor affecting AD patients’ cognitive function and memory ability. An important function of the inferior frontal gyrus is to regulate attention and cognitive speed (Rektorova 2014). Zhu et al. found that compared to HCs, local FC between the bilateral inferior frontal gyri are significantly reduced in AD patients (Zhu et al. 2017). Altered hippocampus-based FC in left insula WM and right inferior frontal gyrus WM may be relevant memory performance in the stages of VMCI and MCI, as the inferior frontal gyrus and anterior insula region are involved in attention and working memory processing (Tops and Boksem 2011). In addition, the current study found that compared to the number of abnormal regions within GM, fewer WM regions exhibited decreased FC (the numbers of abnormal regions within WM and GM are 4 and 6, respectively). Since the structural and functional information was interacting, the potential cause might be that morphological structure within GM showed more abnormal regions than within WM. To compare the regions with abnormal structure of GM and WM, we performed the voxel-based morphometry analysis on all subjects (Supplementary 2). The abnormal VBM regions within GM are distributed in the temporal lobe, precuneus, parietal lobe, and abnormal VBM regions within WM are distributed in the temporal lobe, cerebellum, and midbrain within WM. Obviously, fewer WM regions exhibited decreased FC compared to GM which is consistent with the result that GM has more abnormal FC regions than WM.

Since the function and structure of the human brain are complementary to each other (Sporns 2013), we further explored the structural connectivity between the bilateral hippocampus and abnormal FC areas within WM. DTI analysis revealed that fiber bundles connecting the left hippocampus and right temporal pole WM exhibited abnormally increased mean diffusivity in MCI subjects than HCs (Fig. 5). However, there was no abnormal structural connectivity between the left hippocampus and right temporal pole WM between VMCI and HCs. Steven and colleagues found that AD patients showed significant temporal pole atrophy (Arnold et al. 1994), which might correspond to abnormal functional and structural connectivity between the left hippocampus and right temporal pole WM.

Numerous studies have investigated the complex relationship between structure and function in the human brain (Van Den Heuvel et al. 2008; Horn et al. 2014; Wang et al. 2021a). The structure–function coupling is region-specific, and depending on the function of GM regions (Bazinet et al. 2021), a similar situation may apply to WM. FC between different brain regions is typically calculated as the correlation between the time-series of their respective fMRI BOLD signals, representing the synchronization of activity between distant regions in the human brain. Furthermore, mean diffusivity represents the degree of free diffusion of molecules per unit time. It represents the sum of the overall diffusion level and reflects the underlying fiber organization in the WM, and an increase of diffusivity can be associated with a disruption of this organization. Averaged FC values of right temporal pole WM were positively correlated with WAIS scores in VMCI, suggesting that abnormally decreased FC in right temporal pole WM was associated with clinical symptoms of the disease. In addition, we found that increased mean diffusivity corresponded to decreased FC between the left hippocampus and right temporal pole WM, which showed correspondence between DTI and resting-state FC. Therefore, we have suggested that increased mean diffusivity of fiber bundles connecting the left hippocampus and right temporal pole WM should be related to the clinical manifestations of the disease due to the correspondence of structure and function. While the coupling of structure and function within WM may to some extent confirm the significance of WM BOLD signals, a more thorough and rigorous approach needs to be done to better address this issue.

In this study, several limitations need to be mentioned. First, the WM BOLD signals were not as strong as the GM BOLD signals. It was more susceptible to physiological sources, such as head movement, respiration, pulsatile blood flow, vasomotor, and heart rate changes. Second, the
current study did not consider the effects of drugs on results due to a lack of information on the medication used. Third, the samples used were cross-sectional, and not longitudinal data. Future research is necessary to explore hippocampus-based FC changes within WM in a longitudinal dataset of AD. Fourth, since some participants used in the resting-state data did not have diffusion-weighted imaging (used to compute tractography and mean diffusivity measures), we used 109 subjects who had the DTI data from a total of 201 subjects to further explore the fiber connections between the bilateral hippocampus and functionally abnormal ROIs. Fifth, the resting-state functional images in the current study have relatively large voxel sizes of $4 \times 4 \times 4$ mm$^3$, resulting in relatively low spatial resolution of functional images. However, as a public dataset, it can be conveniently obtained and widely analyzed by various independent researchers. Finally, the relationship between neuroimaging biomarkers and clinical measures is complex. It can be confounded by many technical and cognitive factors, so more comprehensive analyses with other relevant parameters are required to elucidate this relation.

**Conclusion**

In this study, we explored the abnormal changes of hippocampus-based FC within whole-brain voxels in the states of VMCI and MCI, and further estimated the structural connectivity between the hippocampus and abnormal FC regions within WM. The right temporal pole WM showed abnormal functional and structural connectivity with the left hippocampus in MCI subjects, indicating that the BOLD signals within WM might be a new direction toward the clinical diagnosis of AD.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00429-022-02521-x.

**Funding** This work was supported by the China MOST2030 Brain Project (Grant numbers: 2022ZD0208500) and the National Natural Science Foundation of China (Grant numbers: 61871420, 62171101).

**Data availability** The current study employed the public available dataset from the OASIS-3 dataset (https://central.xnat.org). The OASIS-3 is a compilation of MRI and PET imaging data collected from several studies conducted by the Knight AD Research Center at the University of Washington over the past 15 years. All subjects had provided informed consent before MRI or neurological assessment. In addition, clinical scale information for all patients has been obtained.

**Conflict of interest** The authors declare no conflict of interest.

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