Increased hippocampal-inferior temporal cortex white matter connectivity following donepezil treatment in patients with mild cognitive impairment: A diffusion tensor probabilistic tractography study

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Research Article

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Abstract

The incidence of Alzheimer's disease (AD) has been increasing each year; however, few methods are available to identify the effects of treatment for AD. Defective hippocampus has been associated with mild cognitive impairment (MCI), an early stage of AD. However, the effect of donepezil treatment on hippocampus-related networks is unknown. The purpose of this study was to evaluate the hippocampal white matter (WM) connectivity following donepezil treatment in patients with MCI using probabilistic tractography, and to further determine the WM integrity and changes in brain volume. Magnetic resonance imaging and diffusion tensor imaging (DTI) data of patients with MCI before and after 6-month donepezil treatment were acquired. Volumes and DTI scalars of 11 regions of interest comprising the frontal and temporal cortices and subcortical regions were measured. Seed-based structural connectivity analyses were focused on the hippocampus. Compared with healthy controls, patients with MCI showed significantly decreased hippocampal volume and WM connectivity with the superior frontal gyrus, as well as increased mean diffusivity (MD) and radial diffusivity (RD) in the amygdala ($p < 0.05$, Bonferroni-corrected). After six months of donepezil treatment, patients with MCI showed increased hippocampal-inferior temporal gyrus (ITG) WM connectivity ($p < 0.05$, Bonferroni-corrected), which was normalized to the healthy control. These findings will be useful in developing theories to describe the etiology of MCI and the therapeutic role of anticholinesterases.

Introduction

Alzheimer's disease (AD) is characterized by progressive deterioration in learning and memory ability, which typically progresses slowly in three general stages: preclinical AD, mild cognitive impairment (MCI), and AD-dementia[1]. MCI can be defined as cognitive decline greater than expected for individual age and education, without interfering with activities of daily living[2,3]. Approximately 10–15% of patients with MCI progress to AD each year, whereas only 1–2% of individuals with normal cognitive level develop AD[4,5]. Early detection of MCI and intervention are essential to predict and prevent AD.

Recent advances in neuroimaging reported the effect of structural and functional abnormalities in the brain on MCI, suggesting abnormalities in the medial temporal lobe including hippocampus in patients diagnosed with AD. Hippocampal atrophy has been specifically implicated in MCI and AD. A structural magnetic resonance imaging (MRI) study[6] revealed decreased gray matter (GM) volume in the hippocampus, specifically in the right subiculum and left cornu ammonis (CA3). A similar study[7] suggested that decreased volumes involving the hippocampus and hippocampal-precuneus/posterior cingulate cortical tracts was associated with early signs of AD in patients diagnosed with MCI. Patients with MCI showed significantly decreased direct functional connectivity from the left hippocampus to the right inferior temporal gyrus, right middle temporal gyrus, right parahippocampal gyrus, and part of the medial frontal cortex compared with normal controls[5].

It is important to screen and treat MCI at an early stage before the development of AD. Treatment with acetylcholinesterase inhibitors (AChEIs) in patients with MCI prevents the breakdown of acetylcholine

(ACh) and increases cholinergic transmission, resulting in improved cognitive function[6,8]. Donepezil is the most frequently prescribed drug clinically to inhibit acetylcholinesterase activity in the cerebral cortex and hippocampus of the rat brain, revealing increased ACh activity in the brain areas associated with cognitive function[9–11]. A functional magnetic resonance imaging (fMRI) study[12] reported increased medial temporal lobe activation and improved task-related connectivity of cholinergic networks after approximately 3 months of cholinergic enhancement with donepezil in patients with MCI. A similar study[13] revealed increased activity in the ventrolateral prefrontal cortex during visual memory task after 6-month donepezil treatment of MCI.

Recent studies[14] have shown that complex networks along with diffusion-weighted imaging (DWI) are effective and promising for early detection of changes in structural pathology of patients with AD. White matter (WM) degeneration occurs early in AD and is useful in evaluating pathologic progression before the disease is clinically evident[15,16]. Probabilistic tractography in diffusion tensor imaging (DTI) has recently been used increasingly for the detection of WM integrity of an entire bundle, facilitating evaluation of structural connectivity by estimating the likelihood of connection between two areas of the brain[16,17]. The most prominent structural changes in AD occur initially in hippocampus. A positron emission tomography (PET) study[18] reported that reduced hippocampal connectivity occurs predominantly in the AD connectome, correlating with hippocampal tau in MCI. A structural study investigating the interaction between hippocampus and cortical/subcortical regions using probabilistic tractography following donepezil treatment has yet to be reported. Identifying objective predictors of WM connectivity in MCI can contribute to data-driven approaches aimed at AD prevention.

The purpose of this study was to evaluate the hippocampal white matter connectivity following donepezil treatment in patients diagnosed with MCI using probabilistic tractography, and to further assess the WM integrity and changes in brain volume.

Materials And Methods

Participants

Patients with MCI were inpatients or outpatients of the CNUH. Ten patients diagnosed with MCI (mean age = 72.4 ± 7.9 years) underwent MR examination before (baseline) and after (follow-up) 6 months of donepezil treatment. The control group included nine sex- and age-matched healthy controls (mean age = 70.7 ± 3.5 years), who were recruited via advertisements.

Patients with MCI were recruited based on the following criteria[6,16,19]: (1) Alzheimer-type MCI according to both the DSM-IV and the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria; (2) no history of MCI treatment and other neurological or psychiatric illnesses; (3) a score of 0.5 or 1 on the Clinical Dementia Rating (CDR) scale; (4) a score less than 26 on the Korean version of the Mini-Mental State Examination (K-MMSE); (5) reconfirmation of the typical symptom severity including changes in cognition recognized

by the affected individual or observers, objective impairment in one or more cognitive domains, functional independence, and absence of dementia. After performing the first MR examination, the patients received 5 mg/day of Aricept®(donepezil hydrochloride; Pfizer Inc., New York, NY) for the first 28 days and 10 mg/day thereafter. The treatment duration for the patients was 194.0 ± 29.5 days, without any side effects, such as agitation, gastrointestinal bleeding, and stomach ulcer. Healthy controls were selected based on the following criteria: (1) no AD based on both the DSM-IV and the NINCDS-ADRDA criteria; (2) a score greater than 26 on the K-MMSE; and (3) no history of AChEI treatment and neurological or psychiatric disorders.

Patients with and without donepezil treatment were assessed using the following questionnaires: K-MMSE to determine the severity of cognitive decline; AD assessment scale-cognitive subscale (ADAS-Cog) to establish the severity of cognitive and non-cognitive dysfunction from mild to severe AD; CDR to assess the severity of cognitive impairment; and geriatric depression scale (GDS) to evaluate the severity of depressed mood. The questionnaires were administered to patients with MCI before and after 6-month donepezil treatment. Mann-Whitney *U*-test was used to analyze the differences between healthy controls and patients with MCI as well as healthy controls and donepezil-treated patients. A Wilcoxon's signed-rank test was used to compare the scores on K-MMSE, ADAS-Cog, CDR, and GDS before and after 6-month donepezil treatment.

Image acquisition

All MRI data collected on 3T clinical scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany) using a head coil. Sagittal T1-weighted images were acquired using a 3-dimensional magnetization-prepared rapid acquisition gradient echo pulse sequence with the following parameters: repetition time (TR) = 1,700 ms, echo time (TE) = 2.2 ms, field of view (FOV) = 256 × 256 mm^2, matrix = 512 × 512, slice thickness = 5 mm, and slice gap = 2 mm. Axial DTI were acquired using echo-planar imaging pulse sequence with the following parameters: TR: 5,200 ms, TE = 105 ms, matrix = 128 × 128, and FOV = 220 × 220 mm^2. DTI consists of 24 directions (b factor = 1,000 s/mm^2) and 5 images without diffusion weighting (b factor = 0 s/mm^2). Phase-encoding was conducted in the anterior to posterior direction using a factor of 2 in-plane acceleration.

Data processing and analysis

T1-weighted images were analyzed with FreeSurfer v6.0 software (MGH, U.S.A., http://surfer.nmr.mgh.harvard.edu). DTI images were analyzed using Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) v6.0 software (Oxford, U.K; www.fmrib.ox.ac.uk/fsl). The Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) protocol was used to detect outliers and for visual inspection.

Brain volume analysis

Post-processing of T1 images entailed the following steps using the FreeSurfer segmentation pipeline[6]: correction for head motion and non-uniformity of intensity, Talairach transformation of each subject's brain, removal of non-brain tissue, segmentation of cortical gray matter (GM), subcortical white matter (WM) and deep GM volumetric structures, triangular tessellation of the GM/WM interface and the GM/cerebrospinal fluid (CSF) boundary, and topology correction. Based on previous studies focused on AD, the brain regions of interest (ROIs) were selected as follows: superior/middle/inferior frontal gyrus (SFG/MFG/IFG), superior/middle/inferior temporal gyrus (STG/MTG/ITG), amygdala, caudate nucleus, hippocampus, putamen, and thalamus (Figure 1). These ROIs were extracted for individual T1 imaging via automated parcellation of Freesurfer. Mann-Whitney *U*-test was used to compare brain volume between healthy controls vs. patients with MCI, and a Wilcoxon signed-rank test was used to compare brain volume between patients treated with and without donepezil using SPSS (version 27.0, IBM, Armonk, NY, USA). The significance level was set to 0.05 after Bonferroni correction for the 11 ROIs to adjust for multiple comparisons (the level of significance after Bonferroni correction: $p < 0.0046$).

DTI scalars and WM connectivity analyses

DTI pre-processing entailed skull removal and correction for motion and eddy currents[16]. Multiple DTI scalars (FA; fractional anisotropy, MD; mean diffusivity, RD; radial diffusivity, and AD; axial diffusivity) were generated for individual subject using the DTIFIT program that fits a DT model at each voxel of the diffusion images. The individual T1 images were rigidly registered to their corresponding non-diffusion-weighted (B0) images using FMRIB's Linear Image Registration Tool (FLIRT) combined with mutual information cost function and trilinear interpolation[16]. The 11 ROIs were extracted for each hemisphere in each subject's T1 imaging data via automated parcellation.

One patient showed motion artifact in the T1 images obtained after treatment, and thus 11 ROIs in the patient were extracted in the T1 image obtained before treatment to register their T1 images with the diffusion space. We calculated the average values of FA, MD, RD, and AD in the 11 ROIs of the 3 groups. To evaluate the structural connectivity, diffusion parameters were modeled using Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) with crossing-fiber modeling[16]. The BEDPOSTX model of diffusion signal as ball (isotropic) and stick (anisotropic) components generates a distribution of likely fiber orientations within each voxel as well as an estimate of the uncertainty in these orientations[20]. We used FSL probabilistic tractography (connectivity modeling) to evaluate WM connectivity between seed (hippocampus) and target (10 ROIs) regions as follows: 5000 streamlines per each voxel in the thalamus, 0.2 curvature threshold, 0.5 mm step length, and loop check. The connectivity values were routinely thresholded at 10% to eliminate aberrant connections due to noise and error[16,21]. For the group analysis, a Mann-Whitney *U*-test was used to compare DTI scalars and WM connectivity between healthy controls and patients with MCI. Wilcoxon's signed-rank test was used to compare DTI scalars and WM connectivity between patients treated with and without donepezil using SPSS (version 27.0, IBM, Armonk, NY, USA). The significance level was set to 0.05 after Bonferroni correction for the 10 to 11 ROIs to adjust for multiple comparisons (the levels of significance after Bonferroni correction: $p < 0.0046$ for DTI scalars and $p \leq 0.005$ for WM connectivity).

Results

Changes in symptom severity

The average K-MMSE scores in healthy controls, untreated patients with MCI (baseline), and donepezil-treated patients (follow-up) were 28.6 ± 1.1, 16.5 ± 4.9, and 17.5 ± 2.9, respectively. The average K-MMSE score of patients with MCI was improved by 7.9% after 6 months of donepezil treatment ($p = 0.031$). Average ADAS-Cog scores in patients with MCI and treated patients were 25.6 ± 6.2 and 24.4 ± 5.9, respectively ($p = 0.506$); average CDR scores were 0.6 ± 0.2 and 0.6 ± 0.2, respectively ($p = 0.317$), and GDS scores were 13.2 ± 5.2 and 12.7 ± 4.9, respectively ($p = 0.372$).

Brain volume changes

Patients with MCI showed significantly decreased hippocampal volume compared with healthy controls ($p < 0.05$, Bonferroni corrected) (Figures 2-3, Table 1). However, no significant differences were detected in the 11 ROIs between patients with MCI and treated patients (Figure 3, Table 1).

Changes in DTI scalars

Compared with healthy controls, patients with MCI had higher MD ($p = 0.003$) and RD ($p = 0.002$) in the amygdala ($p < 0.05$, Bonferroni corrected) (Figure 4). Patients with MCI showed decreased FA in the hippocampus and amygdala ($p \leq 0.05$, not corrected for multiple comparison) (Figure 2). None of the other ROIs showed significant differences in MD and RD between healthy controls and patients with MCI (Supplemental Tables 1-4). In addition, no significant differences were found in the DTI scalars of the 11 ROIs between patients with MCI and treated patients (Supplemental Tables 1-4).

Hippocampal white matter connectivity

Patients with MCI showed a significant decrease in hippocampal-SFG WM connectivity compared with healthy controls ($p < 0.05$, Bonferroni corrected) (Figure 2, Table 2). Following 6-month donepezil treatment, the patients with MCI showed increased hippocampal-ITG WM connectivity ($p < 0.05$, Bonferroni corrected) (Figure 5, Table 2).

Discussion

4.1. Summary of main findings

Compared with healthy controls, patients with MCI showed decreased hippocampal volume and WM connectivity with the SFG, as well as increased MD and RD in the amygdala ($p < 0.05$, Bonferroni-corrected). Given that the hippocampal volume loss is consistent with evidence supporting AD diagnosis and tracking[22,23]. Further, patients with MCI showed enhanced MMSE scores and increased hippocampal-ITG connectivity ($p < 0.05$, Bonferroni-corrected) after 6-month donepezil treatment. These results suggest that increased hippocampal-ITG WM connectivity may be attributed to donepezil treatment.

4.2. Brain volume and DTI scalars in MCI

It is well known that hippocampus atrophy is at the core of AD pathophysiology. Patients with MCI showed a significant decrease in hippocampal volume compared with healthy controls. These results support the notion that hippocampal abnormalities are associated with early detection of AD[7,24-27]. However, no volumetric increase across all the brain areas was detected after donepezil treatment.

Compared with healthy controls, patients with MCI showed higher MD and RD in the amygdala ($p < 0.05$, Bonferroni-corrected). Patients with MCI showed decreased FA in the hippocampus and amygdala ($p < 0.05$, not corrected for multiple comparison), but the level of significance via multiple comparison correction was not high enough to validate this finding. A DTI study[28] reported a decreased FA and a three-fold increase in trace value compared with MD in the hippocampus and amygdala of patients with AD compared with healthy controls. A similar study[29] also found a significantly elevated MD in the hippocampus and amygdala of AD patients. MD measures the average diffusivity in the non-colinear directions of free diffusion and RD quantifies the diffusion of water molecules in a direction perpendicular to the axon fibers[30-32]. The increased MD in the amygdala of patients with MCI was associated with an increase in free water diffusion and the increased RD was related to greater myelin damage. However, no change in DTI scalars in the all brain areas of patients was detected after donepezil treatment. Thus, alterations of hippocampal volume and DTI scalars in patients with MCI may be associated with early prediction of progression to AD.

4.3. Structural connectivity in MCI

Structural connectivity is potentially important for the early diagnosis of AD. We found a decreased hippocampal-SFG WM connectivity in patients with MCI compared with healthy controls. This result, which has not been reported in previous structural connectivity studies, was consistent with that of a functional connectivity study[33] suggesting that AD patients manifested decreased hippocampal-SFG connectivity compared with healthy controls. Another recent study[34] showed decreased hippocampal-SFG connectivity in MCI patients. The STG occupies the medial part of PFC (mPFC), which plays a critical role in multi-tasking, social cognition, attention, and emotion[35]. A 7T fMRI study[36] revealed decreased hippocampal-SFG connectivity in AD, suggesting that lower MMSE scores were associated with reduced connectivity between the hippocampus and SFG. Thus, the decreased hippocampal-SFG WM connectivity is a potentially important biomarker for the early clinical diagnosis of AD.

4.4. Structural connectivity after donepezil treatment in MCI

To our knowledge, this is the first study evaluating hippocampus-related structural connectivity in patients with MCI following donepezil treatment. In the current study, the MMSE scores of patients with MCI improved after donepezil treatment by 7.9%. Additionally, patients with MCI showed increased hippocampal-ITG WM connectivity after 6 months of treatment. The ITG plays an important role in verbal fluency, a cognitive function affected early in the onset of AD[37]. A study[38] investigating the cognitive

function of ITG in patients with MCI reported that MMSE scores are significant positively correlated with hippocampal-ITG connectivity. AD patients with a decline in the MMSE score following nine months of donepezil treatment showed decreased volume in the inferior temporal gyrus compared with increased MMSE[39]. Improved K-MMSE scores concomitant with increased hippocampal-ITG WM connectivity are potentially attributed to donepezil treatment.

Donepezil activates central cholinergic transmission and enhances the survival of newborn neurons in the hippocampal dentate gyrus[40]. Dong et al.[41] suggested that donepezil treatment reduced beta-amyloid plaques and increased synaptic density. Beta-amyloid deposition has been linked to AD pathology and induces multiple biochemical changes in cells including an increase in cytosolic calcium, which contributes to down-regulation of the expression of glutamate receptors in postsynaptic membrane[42]. Patients with early AD showed an increase in serum concentration of brain-derived neurotrophic factor (BDNF) during donepezil treatment. BDNF belongs to the family of nerve growth factors and plays an important role in neuronal survival and synaptic plasticity in the central nervous system[43]. These findings provide evidence suggesting that hippocampal atrophy and decreased hippocampal-SFG WM connectivity may be closely related to AD pathogenesis and the increased hippocampal-ITG WM connectivity in donepezil-treated patients can be attributed to the treatment.

4.5. Limitations and future directions

This study has some limitations that should be mentioned. The small sample size does not ensure sufficiently high statistical power. To address this limitation, a statistical threshold of P value less than 0.05 using Bonferroni correction was used. Another limitation is the short follow-up duration after donepezil treatment. Therefore, a placebo-controlled study of a large population of MCI patients and a long-term follow-up are needed to evaluate the time course of treatment change. In addition, such studies should investigate the changes in structural connectivity between mild and moderate AD and between moderate and severe AD in light of the effects of donepezil treatment.

Conclusion

This study demonstrates variations in WM connectivity after donepezil treatment in patients with MCI. Increased K-MMSE scores and hippocampal-ITG WM connectivity in donepezil-treated patients can be attributed to treatment, suggesting that the hippocampal-ITG WM connectivity are a potentially important biomarker for donepezil treatment. These findings can be used to develop theories explaining the etiology of MCI and the mode of treatment using anticholinesterases.

Declarations

Compliance with ethical standards

This study approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (CNUH). The experimental procedures and methods were performed in accordance with the relevant guidelines and regulations approved by IRB-CNUH. Informed consent form was obtained from each participant.

Conflict of interest

The authors declare that they have no conflicts of interest.

Data Availability

The data that support the findings of this study are available from the corresponding author, Gwang-Woo Jeong, upon reasonable request.

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Author contributions: G.W.K., K.S.P., and G.W.J. designed the study; G.W.K. and G.W.J performed the majority of experiments; G.W.K., K.S.P., and G.W.J contributed to the analysis and interpretation of results; G.W.K., K.S.P., and G.W.J wrote the first draft of the manuscript; G.W.J. has approved the final manuscript and completed manuscript; also, all authors agree with the content of the manuscript.

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Tables

Due to technical limitations,Tables 1 and 2 are only available as a download in the Supplemental Files section.

Figures

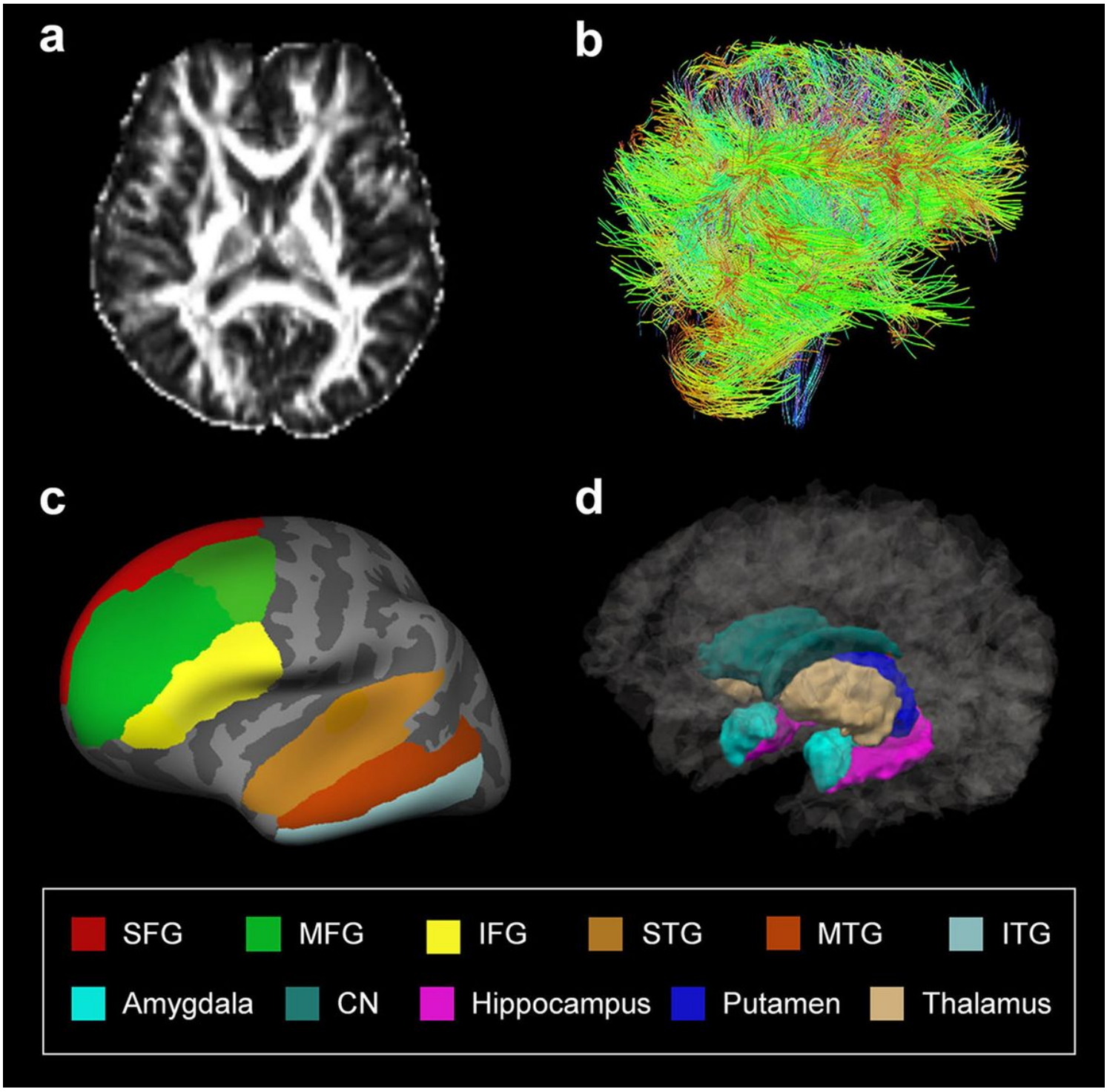

Figure 1

Illustration of diffusion-weighted imaging (a), fiber tracts (b), cortical regions of interest (ROIs) (c), and subcortical ROIs (seed regions) (d). This figure was created using Freesurfer (version 6.0

https://surfer.nmr.mgh.harvard.edu) and Microsoft Powerpoint (version 16 https://www.microsoft.com). SFG; superior frontal gyrus, MFG; middle frontal gyrus, IFG; inferior frontal gyrus, STG; superior temporal gyrus, MTG; middle temporal gyrus, ITG; inferior temporal gyrus, CN; caudate nucleus.

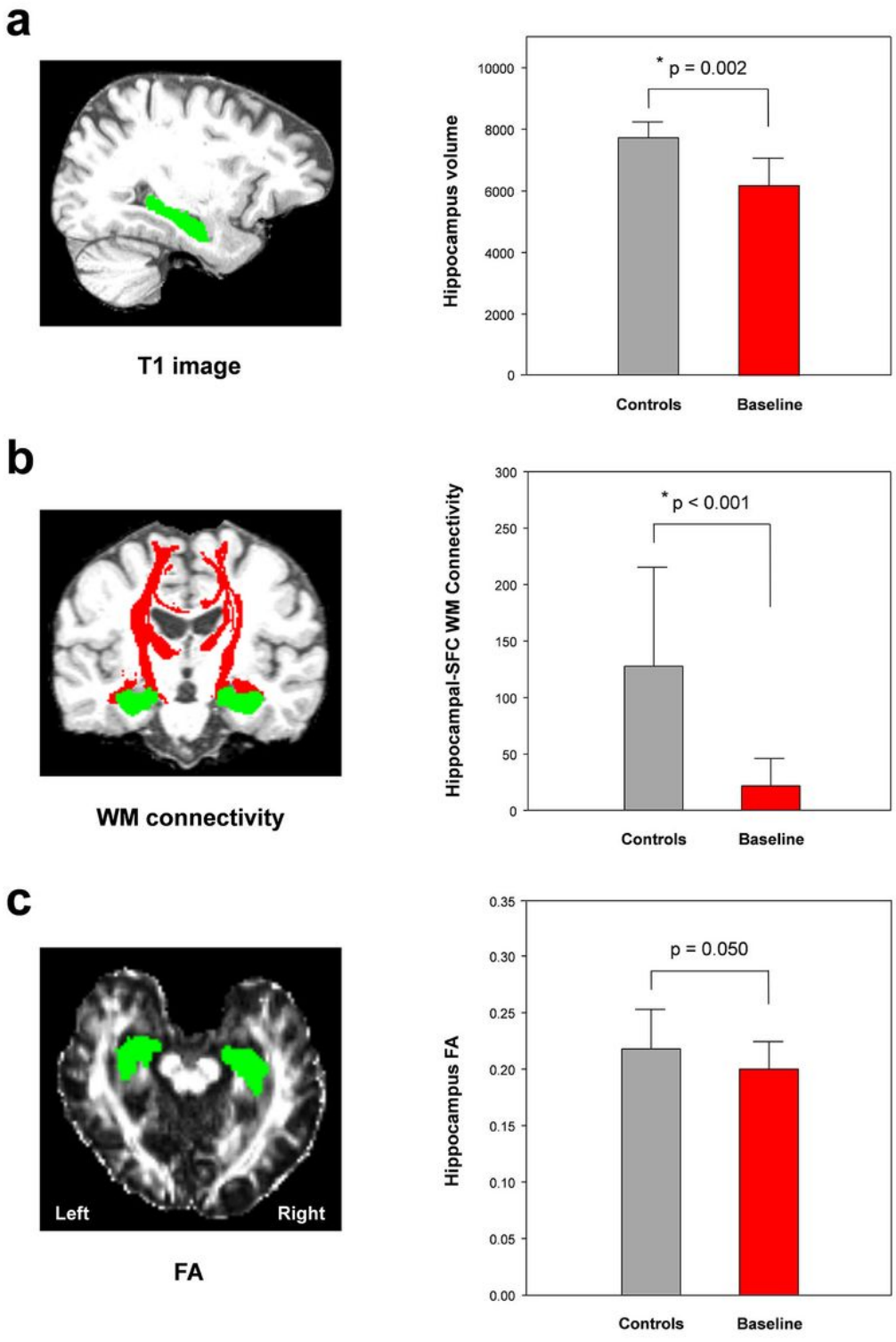

Figure 2

The decreased hippocampal volume (a) and hippocampal-superior frontal cortex (SFG) white matter (WM) connectivity (b) in the patients with MCI (baseline) compared with healthy controls ($p < 0.05$,

Bonferroni-corrected). Patients with MCI showed decreased fractional anisotropy (FA) in the hippocampus (p = 0.05, not corrected for multiple comparison) (c). Green in the left figure; hippocampal seed ROI, Red in left figure; WM connectivity. This figure was created using Freesurfer (version 6.0 https://surfer.nmr.mgh.harvard.edu), MRIcron (version 6 https://www.nitrc.org/projects/mricron), and Microsoft Powerpoint (version 16 https://www.microsoft.com). * significant difference (Bonferroni corrected, p < 0.05).

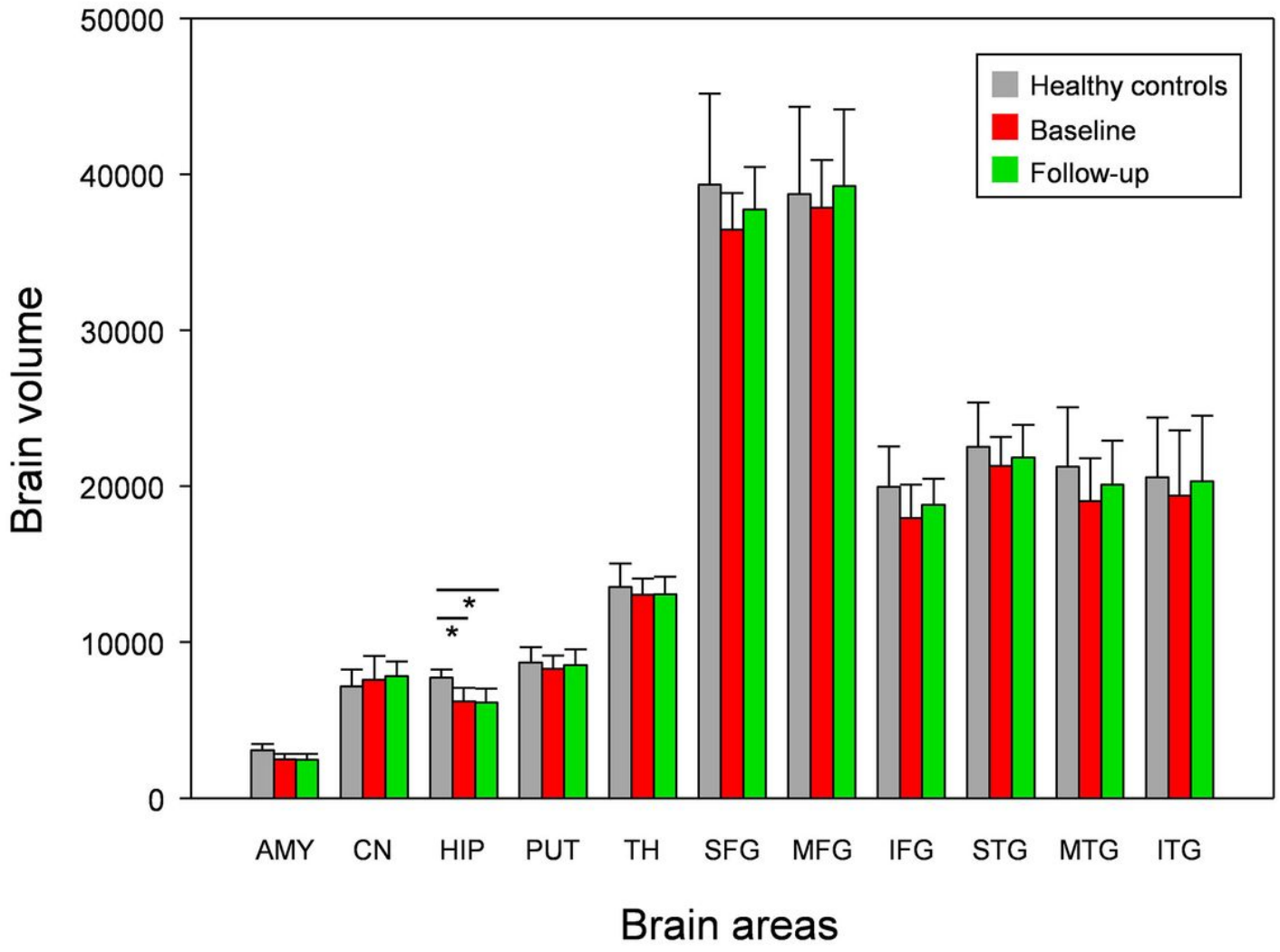

Figure 3

Mean brain volume in the 11 ROIs in patients with MCI (baseline), donepezil-treated patients (follow-up), and healthy controls. However, no significant differences were detected in the 11 ROIs between patients with MCI and treated patients. AMY; amygdala, CN; caudate nucleus, HIP; hippocampus, PUT; putamen, SFG; superior frontal gyrus, MFG; middle frontal gyrus, IFG; inferior frontal gyrus, STG; superior temporal gyrus, MTG; middle temporal gyrus, ITG; inferior temporal gyrus. This figure was created using SigmaPlot (version 13 https://systatsoftware.com/products/sigmaplot) and Microsoft Powerpoint (version 16 https://www.microsoft.com). * significant difference (Bonferroni corrected, p < 0.05).

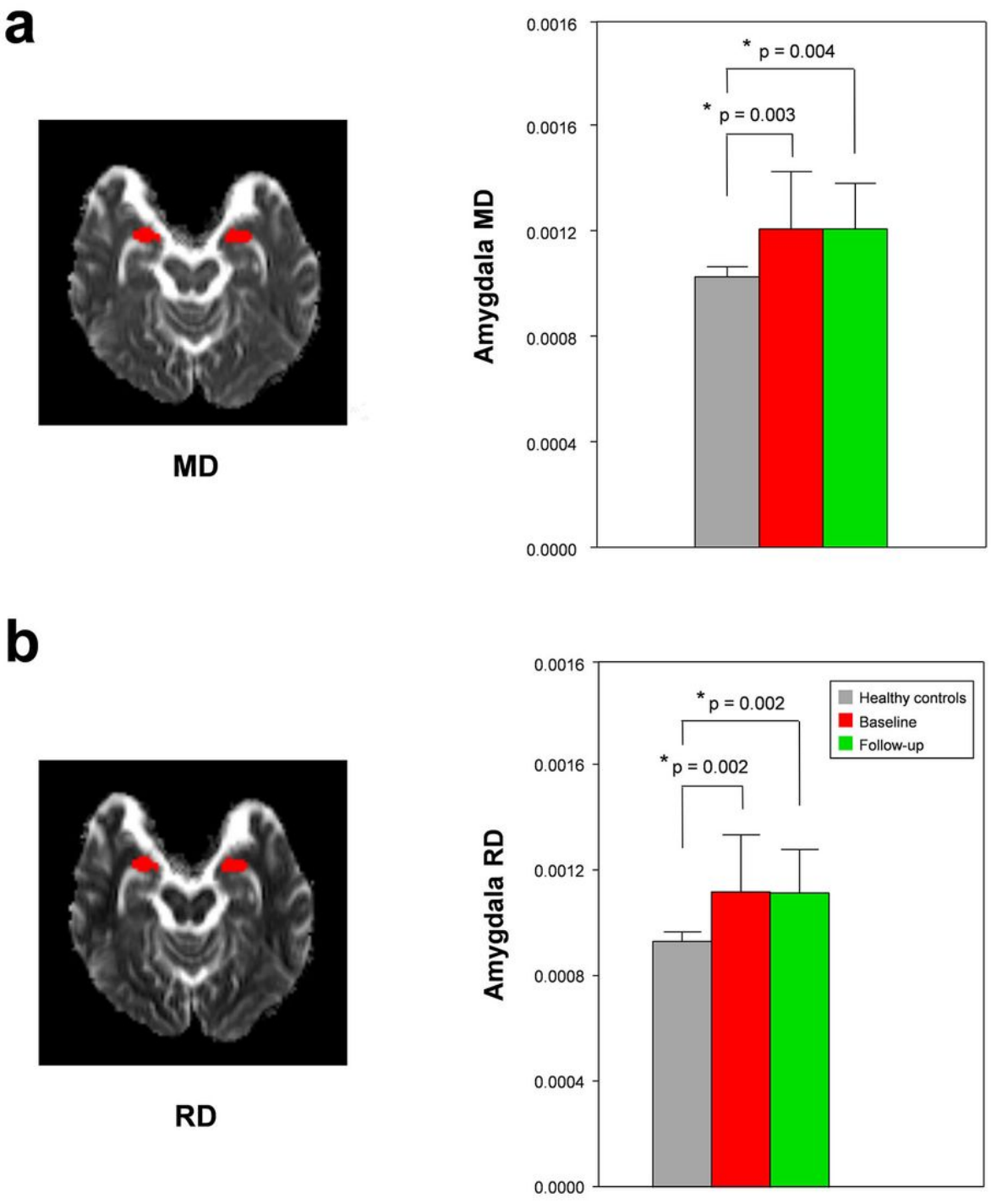

Figure 4

Increased mean diffusivity (MD) (a) and radial diffusivity (RD) (b) in the amygdala in the patients with MCI compared with healthy controls ($p < 0.05$, Bonferroni corrected). None of the other 10 ROIs showed significant differences in the DTI scalars between healthy controls and patients with MCI. In addition, no significant differences were found in the 11 ROIs between patients with MCI and treated patients. Red in the left figure; the amygdala ROI. This figure was created using SigmaPlot (version 13

https://systatsoftware.com/products/sigmaplot) and Microsoft Powerpoint (version 16 https://www.microsoft.com). * significant difference (Bonferroni corrected, $p < 0.05$).

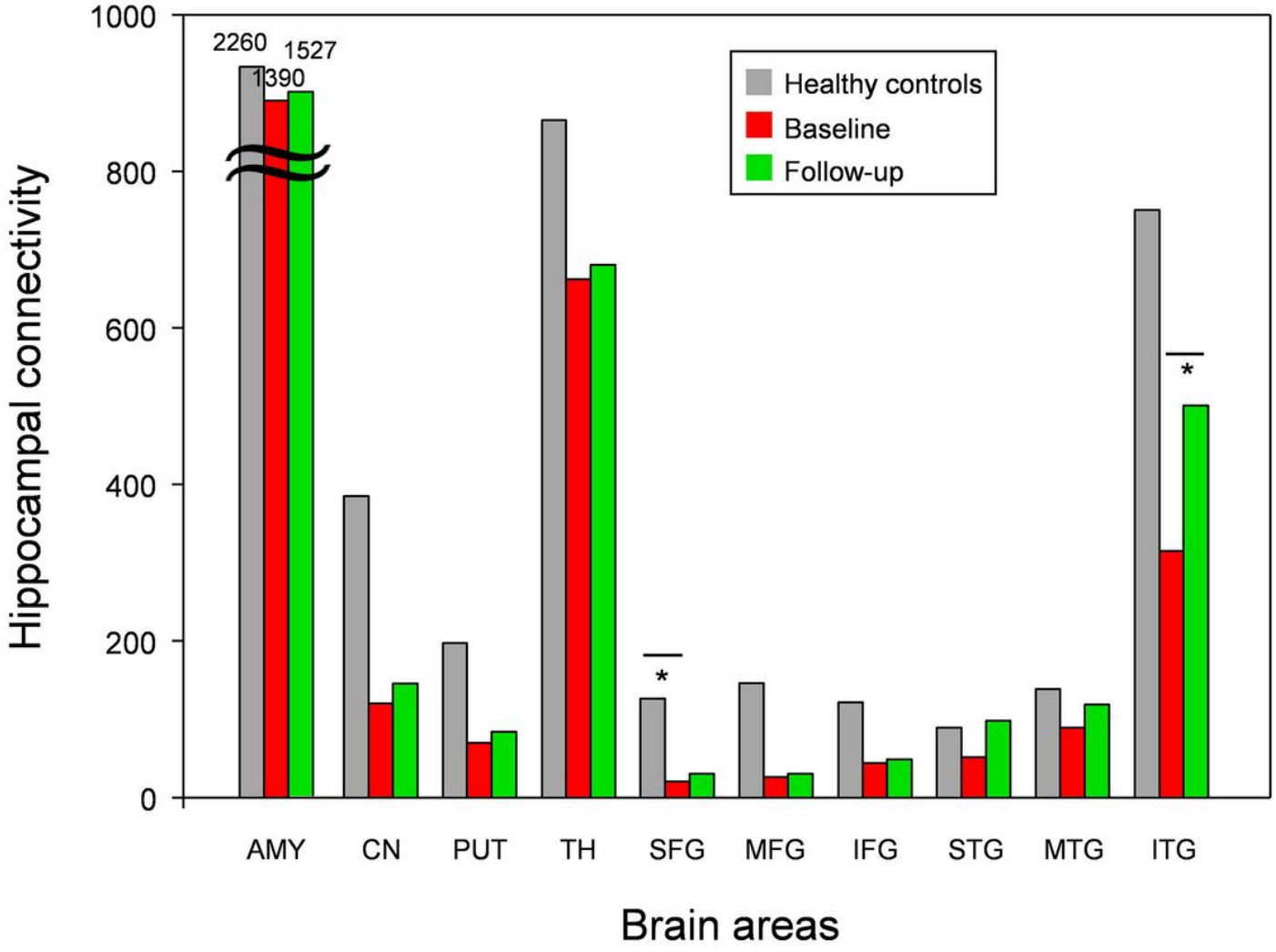

Figure 5

Mean white matter connectivity (WM) between the hippocampus (seed region) and the 10 ROIs in patients with MCI (baseline), donepezil-treated patients (follow-up), and healthy controls. Patients with MCI showed a significant decrease in the hippocampal-SFG WM connectivity compared with healthy controls ($p < 0.05$, Bonferroni corrected). Following 6-month donepezil treatment, the patients with MCI showed increased hippocampal-ITG WM connectivity ($p < 0.05$, Bonferroni corrected). AMY; amygdala, CN; caudate nucleus, HIP; hippocampus, PUT; putamen, SFG; superior frontal gyrus, MFG; middle frontal gyrus, IFG; inferior frontal gyrus, STG; superior temporal gyrus, MTG; middle temporal gyrus, ITG; inferior temporal gyrus. This figure was created using SigmaPlot (version 13 https://systatsoftware.com/products/sigmaplot) and Microsoft Powerpoint (version 16 https://www.microsoft.com). * significant difference (Bonferroni corrected, $p < 0.05$).

Supplementary Files

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