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Gray and White Matter Degenerations in Subjective Memory Impairment: Comparisons with Normal Controls and Mild Cognitive Impairment

Yun Jeong Hong,[1] Bora Yoon,[2] Yong S. Shim,[3] Kook Jin Ahn,[4] Dong Won Yang,[3] and Jae-Hong Lee[1]

[1]Department of Neurology, University of Ulsan College of Medicine, Asan Medical Center, Seoul; [2]Department of Neurology, Konyang University College of Medicine, Daejeon; [3]Department of Neurology, Catholic University of Korea, Seoul; [4]Department of Radiology, Catholic University of Korea, Seoul, Korea

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Address for Correspondence:
Dong Won Yang, MD
Department of Neurology, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82.2-2258-6077, Fax: +82.2-599-9686
E-mail: neuroman@catholic.ac.kr

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Subjective memory impairment (SMI) is now increasingly recognized as a risk factor of progression to dementia. This study investigated gray and white matter changes in the brains of SMI patients compared with normal controls and mild cognitive impairment (MCI) patients. We recruited 28 normal controls, 28 subjects with SMI, and 29 patients with MCI aged 60 or older. We analyzed gray and white matter changes using a voxel-based morphometry (VBM), hippocampal volumetry and regions of interest in diffusion tensor imaging (DTI). DTI parameters of corpus callosum and cingulum in SMI showed more white matter changes compared with those in normal controls, they were similar to those in MCI except in the hippocampus, which showed more degenerations in MCI. In VBM, SMI showed atrophy in the frontal, temporal, and parietal lobes compared with normal controls although it was not as extensive as that in MCI. Patients with SMI showed gray and white matter degenerations, the changes were distinct in white matter structures. SMI might be the first presenting symptom within the Alzheimer's disease continuum when combined with additional risk factors and neurodegenerative changes.

Keywords: Subjective Memory Impairment; Diffusion Tensor Imaging; Voxel-based Morphometry; Mild Cognitive Impairment

INTRODUCTION

Subjects with subjective memory impairment (SMI) complain of memory impairment although they perform within the normal range on neuropsychological tests. However, considerable evidence has shown that subjects with SMI are not typical in their cognitive functioning (1,2). Recently, a few studies using brain imaging have reported degenerations compatible with Alzheimer's disease (AD) in subjects with SMI (2-4). SMI in elderly is now increasingly recognized as a risk factor for progression to mild cognitive impairment (MCI) and AD.

Voxel-based morphometry (VBM) detects gray matter atrophy using three-dimensional magnetic resonance imaging (3D-MRI). VBM has been widely used to detect structural changes related to AD. On the other hand, diffusion tensor imaging (DTI) can be used to quantify microscopic white matter integrity not detectable on conventional MRI (5). Recently, white matter structures such as cingulum or hippocampus have been shown to be damaged early in AD (6,7). However, the few studies that have examined microstructural or macrostructural degeneration in subjects with SMI have reported conflicting results (4,8,9). A few reported that SMI showed gray matter atrophy comparable with AD (9), whereas others showed intermediate microstructural degenerations between normal controls and MCI (8) or conflicting results between cortical thickness and white matter changes (4). These might be due to the lack of a general inclusion criteria and existence of several terms that complicates the comparability of results (9). Hence, we planned a cross-sectional study which adopted various approaches to clarify the degree of neurodegeneration. We investigated whether brain MRI shows any gray and white matter changes in elderly SMI subjects compared with normal controls and amnestic MCI.

MATERIAL S AND METHODS

Subjects and evaluations

All participants except normal controls were referrals to the memory clinic of St. Mary's Hospital for a diagnostic work-up due to memory complaints. All participants underwent neurological examinations, detailed neuropsychological tests and

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blood tests. Geriatric depression scale (GDS) was done using the Korean version of GDS including 30-item questions based on the original version by Yesavage et al. (10). Furthermore, all participants underwent brain MRI scans, including DTI and 3D T1-weighted imaging (spoiled gradient recalled echo, SPGR). The MRIs were carefully examined and we excluded subjects with severe white matter hyperintensities (Fazekas scale 3), multiple (more than five) lacunes, hemorrhages, or tumors because these may cause cognitive disorders unrelated to AD pathology. Subjects were excluded if they were younger than 60 yr of age or had a disease that may cause a cognitive disorder or a major psychiatric disease except major depression. Patients with abnormal lab findings (e.g., abnormal thyroid function, low vitamin B_{12}/folate, positive syphilis serology) were excluded.

The detailed neuropsychological battery, named Seoul Neuropsychological Screening Battery (SNSB) (11), contains tests for attention, confrontational naming, visuospatial function, verbal and visual memory function. Scores below the 16th percentile compared with age-, gender-, and education-specific norms, which are comparable to -1 standard deviation (SD), were defined as abnormal. Subjects with SMI and the normal controls showed no cognitive impairment on all domains of SNSB and scores on the Korean version of the Mini-Mental State Examination (K-MMSE) (12) were at least -1.0 SD compared with age- and education-matched norms. Normal controls (n = 28) without memory complaints were recruited from the general population by advertisement. Their clinical dementia rating scale (CDR) score was zero and they were also assessed using a questionnaire of the 28 illnesses proposed by Christensen (13) that may be associated with cognitive impairment. Inclusion criteria for SMI included the followings: elderly subjects who complained of memory declines but performed within the normal ranges on all domains of SNSB (n = 28). Finally, we enrolled 29 patients with amnestic MCI who fulfilled the clinical diagnostic criteria of Petersen et al. (14).

DTI imaging acquisition and processing

DTIs were acquired using a 1.5-Tesla MRI (Signa Excite 11.0, GE Medical Systems, Milwaukee, WI, USA) with a single-shot, spin-echo, echo-planar, diffusion-weighted sequence. A series of axial diffusion-weighted images with a diffusion-sensitizing gradient (b value = 1,000 s/mm^2) along 25 directions was obtained, as well as axial images without diffusion weighting (b value = 0). Other diffusion parameters were as follows: TR = 10,000 ms, TE = 83.3 ms, matrix = 128 × 128 mm, field of view = 260 mm × 260 mm, number of excitations = 1, 33 axial slices, and slice thickness = 4 mm, with no inter-slice gap.

The raw DTI data (DICOM files) were processed using the programs Volume-One and dTVII (www.volume-one.org, www.utradiology.umin.jp/people/masutani/dTV.htm). The fractional anisotropy (FA) and mean diffusivity (MD) values were measured using the region-of-interest (ROI) method in the bilateral hippocampal body, anterior and posterior cingulum, and anterior and posterior corpus callosum. Each ROI was a 3D based voxels of interest (VOI), with a size of 19 μL; All ROIs were manually drawn on a coronal-section image by the same rater blinded to the diagnosis (Fig. 1). The FA and MD values were obtained three times, and the mean value was measured. The intraclass correlation coefficients for each measurement varied from 0.763 to 0.927 for this rater.

Anatomical landmarks according to Bernasconi (15) were used for hippocampal ROIs. ROIs for the cingulum and corpus callosum were placed according to the landmarks of Atmaca and colleagues (16). We coregistered the various DTI images of the subjects using the "Add computational channels" tool in the dTV.II program and found landmarks by comparing the various images in various planes to avoid the effect of any CSF contamination or any evaluator bias by misplacement of ROIs.

Voxel based morphometry

SPGRs were performed using a 1.5-Tesla MRI (Signa Excite 11.0, GE Medical Systems) with 1.2-mm slice thickness, field of view (FOV) = 260 × 260 mm, number of excitation (NEX) = 1, no interslice gap, TR = 22 ms, TE = 6 ms, and flip angle = 30°. The images were saved in DICOM format and changed to an appropriate format for VBM using MRIcro. VBMs were performed using the SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). The procedures were as follows: Spatial normalization, modulation to compensate for voxel differences, tissue segmentation into gray matter, white matter and CSF, and final-

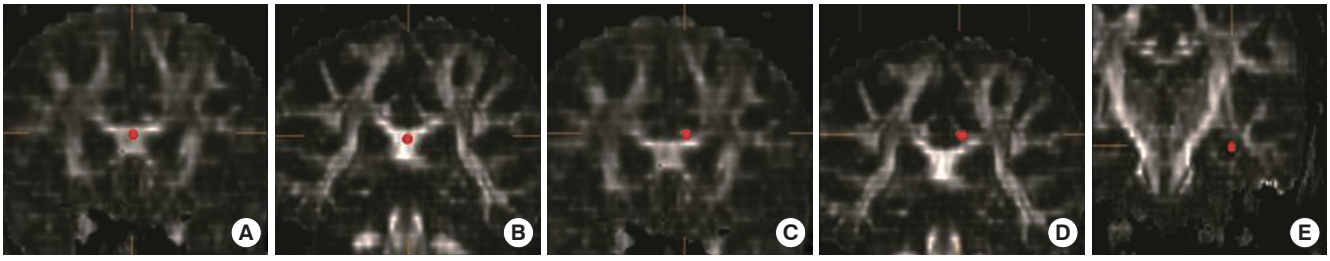

Fig. 1. Region-of-interest in each area. (**A**) Anterior corpus callosum. (**B**) Posterior corpus callosum. (**C**) Left anterior cingulum. (**D**) Left posterior cingulum. (**E**) Left hippocampal body.

ly smoothing with a 12-μL full-width at half-maximum Gaussian kernel for preprocessing. After image processing, voxel-based comparisons among the groups were made using two-sample *t*-tests between groups. Because mean age, gender, and educational levels were similar among the groups, only total intracranial volume (TIV), obtained automatically using SPM5, was used as a covariate. Only areas with voxel levels of $P = 0.005$, uncorrected, were regarded as significant.

Volumetry of the hippocampus

We measured the volume of the bilateral hippocampus in all participants. The software package Analyze (ver. 10.0; Mayo Clinic Foundation, Rochester, MN, USA) was used for manual measurements for the volumes of the hippocampus on each side. The DICOM files of the MRI were converted to Analyze files, which were reformatted to cubic volume (3D) with resliced 0.97-mm image thickness. To calculate the volume of each part, we multiplied areas by the section thickness, and these values were summed. Hippocampal volumes were divided into TIV to compensate for individual differences in brain size among subjects. We used the anatomical boundaries of the hippocampus proposed by Pruessner (17). The test and retest intraclass correlation coefficients of the hippocampal volumes for the rater were 0. 931 (right hippocampus) and 0.945 (left hippocampus).

Statistical analysis

We compared the mean FA and MD values among the three groups using ANOVA and post hoc analyses using the SPSS software (ver. 12.0). The Bonferroni method was used if equal variance was assumed, and Dunnett's T3 method was used if equal variance was not assumed in post hoc analyses. Comparisons of age, education, mean neuropsychological tests results, FA values, MD values, and hippocampal volume ratios were made among groups. For comparisons of gender distribution, chi-square tests were used. All statistical tests were performed at the 5% level of significance.

Ethics statement

This study was approved by the institutional review board of St. Mary's Hospital of the Catholic University (IRB No. KC11RASI0132). Written informed consent was obtained after providing a complete description of the study to the subjects and their caregivers.

RESULTS

The basic demographic data and neuropsychological test results are shown in Table 1. We found no difference in demographics among the groups. All domains in SNSB except the verbal delayed recall test were similar between normal controls and SMI. The mean scores of verbal delayed recall test were different in each group although scores in both normal controls and SMI group were very high (88.0 ± 7.49 percentile in normal control and 61.2 ± 23.44 percentile in SMI).

FA values in patients with SMI were lower, and their MD values were higher than those of normal controls in all measured ROIs. Mean FA and MD values in subjects with SMI were similar to those in patients with MCI, with the exception of the hippocampal body. FA values in the hippocampal body were highest in normal controls, followed by SMI and MCI, in that order. MD values in the hippocampal body were lowest in normal controls, and they were higher in SMI and MCI, in that order (Table 2).

In the VBM, patients with MCI showed gray matter atrophy

Table 1. Basic demographic and neuropsychological test results

Parameters	NC (n = 28)	SMI (n = 28)	MCI (n = 29)	*P* value	Post hoc
Mean age (yr)	70.6 ± 6.48	70.9 ± 6.23	70.5 ± 5.17	0.969	NC = SMI = MCI
Female, n (%)	19/28 (67.9%)	19/26 (73.1%)	19/28 (67.9%)	0.828	NC = SMI = MCI
Education (yr)	8.8 ± 6.16	9.2 ± 5.70	8.6 ± 4.36	0.914	NC = SMI = MCI
GDS*	12.3 ± 4.68	13.0 ± 7.55	11.5 ± 7.25	0.763	NC = SMI = MCI
K-MMSE	28.7 ± 1.36	27.4 ± 2.67	25.5 ± 2.81	< 0.001	NC > SMI > MCI
CDR	0	0.3 ± 0.24	0.5 ± 0.13	< 0.001	MCI > SMI > NC
CDR-SB	0	0.7 ± 0.53	1.5 ± 1.07	< 0.001	MCI > SMI > NC
Backward digit span†	48.6 ± 31.05	67.1 ± 26.46	55.3 ± 29.71	0.204	NC = SMI = MCI
Boston naming test†	69.3 ± 27.41	80.1 ± 23.27	36.2 ± 37.12	< 0.001	NC = SMI > MCI
RCFT copy†	68.0 ± 18.37	61.5 ± 24.87	50.0 ± 31.36	0.212	NC = SMI = MCI
COWAT (phonemic)†	53.3 ± 26.96	54.7 ± 30.30	50.5 ± 27.84	0.891	NC = SMI = MCI
Stroop test†	58.7 ± 20.25	49.8 ± 34.16	34.4 ± 30.65	0.142	NC = SMI = MCI
Verbal delayed recall†	88.0 ± 7.49	61.2 ± 23.44	20.2 ± 29.60	< 0.001	NC > SMI > MCI
Verbal recognition†	77.3 ± 22.69	63.1 ± 19.41	31.6 ± 29.02	< 0.001	NC = SMI > MCI
Visual delayed recall†	66.6 ± 31.81	60.7 ± 26.63	20.1 ± 23.73	< 0.001	NC = SMI > MCI
Visual recognition†	81.8 ± 16.37	72.2 ± 27.66	41.5 ± 32.88	0.001	NC = SMI > MCI

Values are means ± SD. *GDS involves 30-item questions; †Scores of neuropsychological tests are shown in percentile scores. NC, normal controls; SMI, subjective memory impairment; MCI, mild cognitive impairment; GDS, geriatric depression scale; K-MMSE, Korean version of the Mini-Mental State Examination; CDR, clinical dementia rating; CDR-SB, CDR-sum of boxes; RCFT, Rey complex figure test; COWAT, controlled oral word association test.

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Table 2. Fractional anisotropy (FA) and mean diffusivity (MD) results

	NC (n = 28)	SMI (n = 28)	MCI (n = 29)	*P* value	Post hoc
FA					
HB	0.15 ± 0.013	0.12 ± 0.015	0.10 ± 0.012	< 0.001	NC > SMI > MCI
AC	0.53 ± 0.040	0.47 ± 0.055	0.47 ± 0.055	< 0.001	NC > SMI = MCI
PC	0.54 ± 0.040	0.50 ± 0.056	0.49 ± 0.035	< 0.001	NC > SMI = MCI
Ant. CC	0.59 ± 0.051	0.53 ± 0.050	0.56 ± 0.052	< 0.001	NC > SMI = MCI
Post. CC	0.65 ± 0.051	0.58 ± 0.068	0.60 ± 0.043	< 0.001	NC > SMI = MCI
MD					
HB	0.86 ± 0.057	0.93 ± 0.062	0.99 ± 0.064	< 0.001	MCI > SMI > NC
AC	0.77 ± 0.049	0.84 ± 0.040	0.82 ± 0.041	< 0.001	SMI = MCI > NC
PC	0.72 ± 0.050	0.80 ± 0.033	0.77 ± 0.049	< 0.001	SMI = MCI > NC
Ant.CC	0.90 ± 0.108	1.05 ± 0.093	1.05 ± 0.115	< 0.001	SMI = MCI > NC
Post.CC	0.92 ± 0.115	1.07 ± 0.139	1.07 ± 0.100	< 0.001	SMI = MCI > NC

Values are means ± SD. NC, normal controls; SMI, subjective memory impairment; MCI, mild cognitive impairment; FA, fractional anisotropy; MD, mean diffusivity; HB, hippocampal body; AC, anterior cingulum; PC, posterior cingulum; Ant. CC, anterior corpus callosum; Post. CC, posterior corpus callosum.

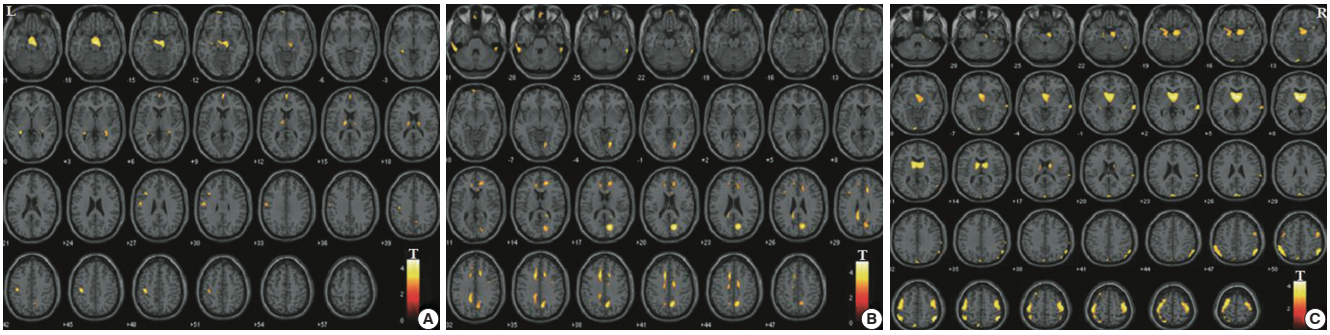

Fig. 2. Voxel wise comparisons of gray matter atrophy among groups. (**A**) Gray matter atrophy in mild cognitive impairment (MCI) compared with normal controls. (**B**) Gray matter atrophy in subjective memory impairment (SMI) compared with normal controls. (**C**) Gray matter atrophy in MCI compared with SMI. Results were considered statistically significant at $P < 0.005$, cluster level, uncorrected. The regions represent reduced gray matter density.

in the left hippocampus, posterior central gyrus, inferior frontal gyrus, mid cingulate gyrus, right medial frontal gyrus, and bilateral precuneus compared with normal controls. On the other hand, subjects with SMI showed gray matter atrophy in the left orbito-frontal gyrus, inferior frontal gyrus, right calcarine gyrus, precuneus, lingual gyrus, inferior temporal gyrus, and both mid cingulate areas, compared with normal controls ($P < 0.001$, uncorrected, Fig. 2, Table 3). Compared with that of SMI, patients with MCI showed significant atrophy in multiple fronto–parieto–temporal regions, particularly in the left posterior area ($P < 0.001$, uncorrected, Fig. 2, Table 3). We also compared hippocampal volume and found no difference between normal controls and subjects with SMI, whereas the mean hippocampal volume in patients with MCI was smaller than that of subjects with SMI and normal controls, particularly in the left hippocampus (Table 4).

DISCUSSION

We found significant microstructural changes and macrostructural gray matter loss in the brains of subjects with SMI compared with normal controls; thus, confirming that subjects with SMI are neuroanatomically different from normal controls although hippocampal volumetric changes are not yet apparent. DTI revealed similar neurodegenerative changes in white matter regions vulnerable to AD in subjects with SMI and MCI. The hippocampus is critical for memory and learning and is involved early in AD (18). The corpus callosum connects neocortical areas and is important for cognitive functioning. The cingulum is part of the Papez circuit and plays an important role in memory (19). However, the results of the VBM between subjects with SMI and MCI were somewhat different from those identified using DTI. VBM analysis revealed slightly different pattern and more extensive gray matter atrophy in patients with MCI than in those with SMI. Subjects with SMI showed cortical atrophy in several fronto–temporo–parietal areas compared with normal controls, however, the findings disappeared after comparing SMI with MCI. Cortical atrophy develops in SMI as shown in this study, but this might be somewhat different with those in MCI, a more clinically symptomatic state. These seemingly inconsistent findings between the DTI and VBM may be the result of dissociative pathological changes in the white matter and gray matter. Recently, it has been shown that alteration of DTI measures in early stage of AD is independent of gray matter degeneration such as hippocampal volume or cortical thickness (4,8,20). Wallerian degeneration is not sufficient to explain

the preceding changes in DTI parameters. The etiology of these early independent changes is not established, it may be due to vascular pathology, direct effect of β-amyloid peptide or tau pathology on white matter microstructure (21,22).

Additionally, we analyzed the volume of the hippocampus using manual volumetry. Subjects with SMI showed no difference compared with normal controls. Only patients with MCI showed significant hippocampal atrophy, particularly on the left, suggesting that the volume loss had not yet occurred in patients with SMI. Interestingly, DTI analysis in hippocampus also showed more neurodegeneration in MCI compared with that in SMI although other regions showed similar degree of degeneration between the two groups. According to our results, smaller hippocampus in MCI also showed more microstructural degenerations measured by DTI probably because it is one of the most vulnerable and stage-sensitive structures of AD process (23).

An unexpected atrophic changes around brainstem and basal ganglia shown in Fig. 2 can be explained as incomplete registration to conventional template, individual difference of brainstem and basal ganglia, small vessel disease such as lacune that cause regional atrophy and heterogeneity of aMCI and SMI that include both AD and non-AD related pathology. Larger sample size and subject-specific template might improve the accuracy in the future study.

Our study has some limitations. First, pathological confirmation was lacking. Thus, subjects with pure depression or anxiety or other pathology unrelated with AD may have been included in the SMI group. The heterogeneity of SMI might be another explanation about the different results between patients with SMI and patients with MCI in the gray matter VBM. Hence, the results of our study should be interpreted with caution and further biomarker evaluations are needed. Second, we manually drew ROIs for the DTI analysis only in selected white matter structures specific to the AD process. Manual ROIs are useful for quantitative comparisons and are sensitive to changes in small structures, such as the hippocampus; however, this method is a labor-intensive process, which makes it difficult to measure multiple structures. However, whole-brain methods using standardized templates such as tract-based spatial statistics (TBSS) may not be suitable for quantitative analyses of small structures such as the hippocampus. An automated whole-brain ROI analysis might be a good option in future studies. Lack of information about other risk factors such as APOE4 carrier status and family history of dementia might be another limitation. Future DTI studies should continue to address the association between genetic information and white matter changes in SMI.

Despite these limitations, our study has strengths in that we carefully diagnosed candidates using detailed neuropsychological tests battery, enrolled relatively homogeneous subjects who were age-, gender- and education-matched, and adopted various neuroimaging techniques to compare different degrees of neurodegenerations among groups. Subjects with SMI in our study revealed significant white matter and gray matter changes compared with those in normal controls, although the gray matter atrophy was not comparable to those in MCI. We also report an interesting result that microstructural degeneration might be distinct than gray matter atrophy also in elderly with SMI. Additionally, detecting microstructural degeneration, par-

Table 3. Voxel based morphometric analysis results

Cerebral gray matter	Hemisphere	T score	MNI (mm)		
			x	*y*	*z*
NC > MCI					
Posterior central gyrus	L	3.79	-38	-22	46
Hippocampus	L	3.61	-30	-36	0
Inferior frontal gyrus	L	3.42	-36	18	28
Medial frontal gyrus	R	3.31	2	60	12
Precuneus	R	2.77	10	-56	40
Precuneus	L	2.76	0	-54	-62
NC > SMI					
Calcarine cortex	R	4.89	14	-74	20
Precuneus	R	4.06	10	-58	42
Mid cingulate gyrus	L	3.37	-14	-14	44
Lingual gyrus	R	3.93	16	-70	-2
Inferior temporal gyrus	R	3.79	64	-42	-26
Mid cingulate gyrus	R	3.77	14	18	36
Orbito frontal gyrus	L	3.61	-2	68	-14
Inferior frontal gyrus	L	3.18	-36	18	28
SMI > MCI					
Inferior parietal gyrus	R	4.47	48	-56	56
Superior frontal gyrus	L	4.18	-28	-8	70
Posterior central gyrus	L	3.86	-48	-18	60
Precentral gyrus	R	3.82	48	-18	64
Superior frontal gyrus	R	3.31	30	-8	70
Precuneus	L	3.31	-8	-78	56
Cuneus	L	2.95	-2	-84	40
Calcarine cortex	L	3.36	-4	-98	-12
Superior parietal gyrus	L	3.35	-24	-66	66
Hippocampus	L	3.06	-20	-10	-16
Superior temporal gyrus	L	3.03	-30	6	-18
Parahippocampal gyrus	L	2.85	-16	-20	-20
Inferior temporal gyrus	R	2.85	48	-56	-20

Regions of more atrophic gray matter ($P < 0.005$, cluster level, uncorrected) were presented. NC, normal controls; SMI, subjective memory impairment; MCI, mild cognitive impairment.

Table 4. Comparisons of hippocampal volume among the groups

Regions	NC (n = 28)	SMI (n = 28)	MCI (n = 29)	*P* value	Post hoc
Rt.hippocampus/TIV	1.563 ± 0.2031	1.556 ± 0.1669	1.400 ± 0.2537	0.013	NC = SMI > MCI
Lt.hippocampus/TIV	1.528 ± 0.1801	1.498 ± 0.1853	1.314 ± 0.2637	0.001	NC = SMI > MCI

Values are means ± SD. NC, normal controls; SMI, subjective memory impairment; MCI, mild cognitive impairment; TIV, total intracranial volume.

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ticularly in the hippocampus, may be complimentary to other MRI techniques because it can quantify the degree of white matter neurodegeneration sensitively. In conclusion, subjects with SMI showed gray and white matter degenerations, the changes were distinct in white matter structures. Considering that AD pathology develops for decades before the diagnosis of dementia, SMI might be the first presenting symptom within AD continuum when combined with additional risk factors and neurodegenerative changes suggesting preclinical AD (24). Due to the heterogeneity of SMI, differentiating SMI of preclinical AD from SMI without pathologic changes or other pathologies unrelated with AD might need further studies.

DISCLOSURE

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTION

Study design and manuscript preparation: Hong YJ, Yang DW. Data acquisition and statistical analysis: Yoon B, Shim YS, Ahn KJ. Discussion and manuscript revision: Yang DW, Lee JH.

ORCID

Yun Jeong Hong *http://orcid.org/0000-0002-4996-4981*
Dong Won Yang *http://orcid.org/0000-0002-4733-7298*

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