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[^{18}F]THK5351 PET Imaging in Patients with Mild Cognitive Impairment

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Background and Purpose Mild cognitive impairment (MCI) is a condition with diverse clinical outcomes and subgroups. Here we investigated the topographic distribution of tau in vivo using the positron emission tomography (PET) tracer [^{18}F]THK5351 in MCI subgroups.

Methods This study included 96 participants comprising 38 with amnestic MCI (aMCI), 21 with nonamnestic MCI (naMCI), and 37 with normal cognition (NC) who underwent 3.0-T MRI, [^{18}F]THK5351 PET, and detailed neuropsychological tests. [^{18}F]flutemetamol PET was also performed in 62 participants. The aMCI patients were further divided into three groups: 1) verbal-aMCI, only verbal memory impairment; 2) visual-aMCI, only visual memory impairment; and 3) both-aMCI, both visual and verbal memory impairment. Voxel-wise statistical analysis and region-of-interest -based analyses were performed to evaluate the retention of [^{18}F]THK5351 in the MCI subgroups. Subgroup analysis of amyloid-positive and -negative MCI patients was also performed. Correlations between [^{18}F]THK5351 retention and different neuropsychological tests were evaluated using statistical parametric mapping analyses.

Results [^{18}F]THK5351 retention in the lateral temporal, mesial temporal, parietal, frontal, posterior cingulate cortices and precuneus was significantly greater in aMCI patients than in NC subjects, whereas it did not differ significantly between naMCI and NC participants. [^{18}F]THK5351 retention was greater in the both-aMCI group than in the verbal-aMCI and visual-aMCI groups, and greater in amyloid-positive than amyloid-negative MCI patients. The cognitive function scores were significantly correlated with cortical [^{18}F]THK5351 retention.

Conclusions [^{18}F]THK5351 PET might be useful for identifying distinct topographic patterns of [^{18}F]THK5351 retention in subgroups of MCI patients who are at greater risk of the progression to Alzheimer's dementia.

Key Words mild cognitive impairment, neurofibrillary tangles, positron emission tomography.

INTRODUCTION

Mild cognitive impairment (MCI) affects a clinically and pathologically heterogeneous group of patients with cognitive dysfunction who are thought to be in a transitional state between normal cognition (NC) and dementia.[1,2] Previous studies have shown that certain subgroups of MCI patients have an increased likelihood of converting to Alzheimer's dementia (AD), and so great efforts have been made to characterize different subgroups of MCI in order to better predict their clinical outcomes for both research purposes and enrollment in potentially disease-modifying clinical trials.[3] MCI can be broadly divided into two types: 1) amnestic MCI (aMCI), in which memory decline is the defining feature, and 2) nonamnestic MCI (naMCI), in which there are predominant deficits in attention, executive function, visuospatial skills, and/or language.[4] It has been shown that patients

diagnosed with aMCI are at greater risk of progressing to AD,[5,6] whereas the disease endpoints of naMCI are more diverse, including dementia with Lewy bodies (DLB), cerebral small-vessel disease, frontotemporal dementia (FTD), and depression, as well as AD.[7-9] Further differentiation of aMCI according to the presence of verbal and visual memory impairments has revealed that conversion rates to AD are higher in patients with dysfunction of either verbal or both verbal and visual memory, but not visual memory alone.[10-12] aMCI patients with cognitive impairment in multiple domains on neuropsychological tests were also found to progress more frequently to dementia compared to single-domain aMCI.[13-15]

Histologically, neurofibrillary tangles (NFTs) along with amyloid plaques are characteristic features of AD. NFTs arise from the aggregates of aberrantly folded, hyperphosphorylated tau proteins that typically spread from the medial temporal lobe to the primary neocortex as the disease progresses.[16] The brains of aMCI patients have an increased propensity for NFTs compared to NC subjects.[7,17] Longitudinal studies have identified increasing cerebrospinal fluid (CSF) tau levels as a strong predictor of cognitive decline from MCI to AD.[18-20] In contrast, pathological findings corresponding to AD such as NFTs are less frequent in naMCI patients.[8] Lower levels of β-amyloid in the CSF[18,19] or the presence of amyloid in MCI patients based on amyloid positron emission tomography (PET) findings also increases the probability of conversion to AD,[21] while aMCI patients with negative amyloid pathology based on PET are less likely to develop AD.[22] Although both tau and β-amyloid are associated with neuron loss and disease progression, the accumulation of tau pathology is more strongly correlated with the severity of cognitive decline than is β-amyloid deposition.[23-28]

The development of radiotracers for tau imaging[29-31] means that NFT pathology can now be visualized in vivo. Tau PET images are strongly correlated with cerebral atrophy, cognitive impairment, and postmortem histopathological findings.[31,32] However, concerns about off-target binding to monoamine oxidase-B (MAO-B) for the [^{18}F]THK5351 radiotracer have emerged recently.[33] Nonetheless, PET studies using tau-targeted tracers may provide important insight into the pathomechanism underlying patients according to the clinical presentation.

We hypothesized that analyzing [^{18}F]THK5351 deposition in MCI subgroups will help identify distinct topographic patterns of [^{18}F]THK5351 retention in subgroups of MCI patients who are at greater risk of AD progression. Previous tau PET studies involving specific MCI subpopulations have investigated prodromal AD such as aMCI[32,34,35] and amyloid-positive MCI.[36,37] However, to our knowledge only a few studies have investigated differences in tau distribution between various MCI subgroups. In this study we therefore analyzed the differences between the topographic distributions of NFTs in aMCI with verbal and/or visual memory impairment, naMCI, and control NC groups using the tau PET tracer [^{18}F]THK5351.

METHODS

Participants

The 97 initially enrolled participants had been clinically diagnosed with aMCI (*n*=38) or naMCI (*n*=21), or had NC (*n*=38). All subjects underwent [^{18}F]THK5351 PET and 3.0-T MRI at Gachon University Gil Medical Center between March 2015 and August 2017. [^{18}F]flutemetamol (FLUTE) PET was also performed in 63 participants (25 with MCI and 38 with NC). Amyloid positivity was present in 12 (63.2%) of the 19 scanned aMCI patients (12/19), 2 (33%) of the 6 scanned naMCI patients, and 1 NC subject. We excluded the single amyloid-positive participant in the NC group, resulting in 37 NC study subjects.

MCI participants were diagnosed according to a modified criteria proposed by Petersen[4,38] for MCI that have been used in previous studies.[12,39] aMCI patients were defined as those with a performance below -1.0 SD of the norm in at least one of the following memory tests: Seoul Verbal Learning Test (SVLT), delayed recall; and Rey Complex Figure Test (RCFT), delayed recall. naMCI patients had task scores worse than -1.0 SD below the norm in at least one of the following tests: neuropsychological tests of language and related functions, visuospatial function, and frontal/executive function. aMCI patients were further categorized into three subgroups based on the modality of memory impairment: 1) verbal-aMCI patients had abnormal verbal memory scores but normal visual memory function, 2) visual-aMCI patients had abnormal visual memory task scores but normal verbal memory function, and 3) both-aMCI patients had abnormalities in both visual and verbal memory tasks. Twelve, 10, and 16 participants met the criteria for verbal-aMCI, visual-aMCI, and both-aMCI, respectively. Details of the neuropsychological tests are presented in the supplementary data section under Supplementary Material 1 (in the online-only Data Supplement).

Participants with structural lesions on brain MRI such as territorial infarctions, intracranial hemorrhage, traumatic brain injury, hydrocephalus, severe white-matter hyperintensity (WMH) or WMH associated with radiation, multiple sclerosis, or vasculitis were excluded. Secondary causes of cognitive decline were also ruled out through laboratory tests assessing complete blood counts, vitamin B_{12} and folate levels, thyroid function, metabolic profile, and syphilis serology. *APOE* genotyping was performed in all participants. The 37 NC sub-

jects had no history of neurological or psychiatric illness or abnormalities detected in a neurological examination, a Clinical Dementia Rating (CDR) score of 0, normal cognitive function determined by neuropsychological tests results (defined as above -1.0 SD of the age- and education-corrected normative mean), no structural lesions on brain MRI such as cerebral infarctions, intracranial hemorrhage, traumatic brain injury, hydrocephalus, or severe WMH, and amyloid-negative [^{18}F]FLUTE PET results. The NC subjects were either the spouses of the patients or volunteers from the community.

This study was approved by the Institutional Review Board of Gachon University Gil Medical Center, and written informed consent was obtained from each participant (IRB No. GDIRB2015-272).

Image acquisition and preprocessing

MRI image acquisition and parcellation

All participants underwent a 3D T1-weighted magnetization-prepared rapid acquisition with gradient echo (MPRAGE) scan using a 3.0-T MRI scanner (Verio, Siemens, Erlangen, Germany) with a Siemens matrix coil. The detailed MRI parameters are presented in Supplementary Material 2 (in the online-only Data Supplement). Images were analyzed using FreeSurfer (version 6.0, www.surfer.nmr.mgh.harvard.edu), and MRI parcellation was performed as described previously.[34]

PET image acquisition

All PET scans were acquired with a Siemens Biograph 6 Truepoint PET/CT scanner (Siemens) with a list-mode emission acquisition. All participants underwent a 20-minute emission scan starting 50 minutes after injecting 185 MBq of [^{18}F]THK5351 intravenously. [^{18}F]THK5351 was synthesized and radiolabeled at the Gachon University Neuroscience Research Institute. Among 96 participants, 62 underwent a 20-minute emission scan at 90 minutes after the intravenous injection of 185 MBq of [^{18}F]FLUTE . Low-dose CT was performed for attenuation correction prior to all scans. The images were reconstructed onto a 256×256× 109 matrix with a voxel size of 1.3×1.3×1.5 mm^3 using a 2D ordered subset expectation maximization (OSEM) algorithm (8 iterations and 16 subsets), with corrections for physical effects. In participants who underwent [^{18}F]THK5351 and [^{18}F]FLUTE PET, the mean interval between these scans was 10 days.

PET quantification

Individual [^{18}F]THK5351 and [^{18}F]FLUTE PET images were coregistered onto individual T1-weighted images using FreeSurfer software. Region-based partial volume correction (PVC) was performed on the PET images using the PETSurfer tool in FreeSurfer.[40,41] In order to compare [^{18}F]THK5351 retention in each group quantitatively, we defined 21 regions of interest (ROIs) (details are provided in Supplementary Material 3 in the online-only Data Supplement). Regional standardized uptake value ratios (SUVRs) were calculated with reference to the cerebellar gray matter for [^{18}F]THK5351 images[42,43] and the pons for [^{18}F]FLUTE images.[44] SUVR images were generated from the MRI coregistered PET images with voxel-based PVC.[40,41] An SUVR threshold of 0.62 for amyloid positivity was applied to the [^{18}F]FLUTE PET data.[44]

Statistical analysis

Demographic and clinical data were analyzed using independent *t*-test or one-way analysis of variance (ANOVA) with Bonferroni correction (p<0.05). The chi-square test was used to compare the distributions of the following categorical variables: sex , *APOE* ε4 status, amyloid positivity, hypertension, diabetes mellitus, coronary artery disease, dyslipidemia, and history of stroke. Regional [^{18}F]THK5351 SUVRs were compared between groups using one-way analysis of covariance with adjustment for age and years of education. Region-wise multiple comparisons were corrected in analyses of ROIs using the Benjamini-Hochberg false-discovery rate (FDR) method.[45] Neuropsychological test results are presented as age- and education-adjusted standard scores (z scores). Neuropsychological data were compared between groups using one-way ANOVA with Bonferroni correction (p<0.05). All statistical analyses were performed using SPSS (version 19, IBM Crop., Armonk, NY, USA).

Voxel-wise statistical analyses were performed to compare the regional pattern of [^{18}F]THK5351 retention using statistical parametric mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK). For each diagnostic group, voxel-wise comparisons of SUVR images were performed using the two-sample *t*-test with adjustment of age and years of education. Multiple regression analyses were also performed with SPM12 to determine the correlation between cognitive function and [^{18}F]THK5351 retention. These analyses were combined with raw Mini Mental State Examination (MMSE) scores adjusted for age and years of education. Spearman correlations were used in the analysis between [^{18}F]THK5351 retention and CDR-Sum of Boxes (SOB) or z scores from the neuropsychological tests. The resulting t-score maps (p<0.05, FDR corrections; >50 clusters) for partial correlation were overlaid on an inflated FSaverage brain using MRtools software (http://mrtools.mgh.harvard.edu/).

RESULTS

Demographics and clinical characteristics

The demographics and clinical characteristics of the study population are presented in Table 1. There were significant differences in global cognition (MMSE and CDR-SOB scores), WMHs, mean cortical thickness and hippocampal volumes between MCI patients and NC subjects. The demographics of the aMCI subgroups and MCI patients with amyloid-positive or -negative PET findings are presented in Table 2 and Supplementary Table 1 (in the online-only Data Supplement), respectively. The proportion of *APOE* ε4 carriers was higher among both-aMCI patients (50%) than NC subjects (21.6%) (Table 2).

Compared to the NC group, the aMCI group showed significant impairment in all domains, while patients with naMCI displayed lower scores for attention, language, visuospatial function, and frontal executive function (Supplementary Table 2 in the online-only Data Supplement). The neuropsychological test results of the aMCI subgroups and the amyloid-positive and -negative MCI patients are presented in Table 3 and Supplementary Table 3 (in the online-only Data Supplement), respectively.

[^{18}F]THK5351 PET findings in all MCI patients and the MCI subgroups

MCI, aMCI, and naMCI groups

Voxel-wise analyses revealed that [^{18}F]THK5351 retention was greater in MCI patients than in NC subjects in the lateral temporal, mesial temporal, and parietal cortices, and portions of the frontal cortex and precuneus. Patients with aMCI showed significantly higher [^{18}F]THK5351 retention than NC subjects in more extended regions of the frontal, lateral temporal, mesial temporal, parietal cortices, precuneus, and posterior cingulate cortices. There were no significant differences between naMCI patients and NC subjects. These results are presented at a threshold of $p<0.05$ with FDR-correction adjusted for age and years of education in Fig. 1.

In the ROI-based analyses, the patients with MCI showed significantly higher [^{18}F]THK5351 retention than NC subjects in nearly all ROIs except for the sensorimotor, anterior cingulate cortices and striatum (Supplementary Table 4 in the online-only Data Supplement). [^{18}F]THK5351 retention

Table 1. Demographics and clinical characteristics of the study population

Variable	MCI (*n*=59)	aMCI (*n*=38)	naMCI (*n*=21)	NC (*n*=37)
Age, years	69.6±9.24 *	70.1±8.08	68.5±11.19	64.6±11.68
Age at onset, years	66.8±9.25	67.8±7.88	65.1±11.34	-
Sex, female	40 (67.8)	27 (71.1)	13 (61.9)	20 (54.1)
Education, years	7.66±4.81*	7.81±4.60*	7.40±5.29*	11.95±4.47
Disease duration, months	35.8±16.34	30.7±15.90	39.3±16.04	-
MMSE score	24.5±3.96*	23.9±4.18*	25.6±3.33*	28.4±1.76
CDR-SOB score	1.26±1.19*	1.63±1.32*	0.59±0.43*	0.00±0.00
APOE ε4 carrier	21 (35.6)	14 (36.8)	7 (33.4)	8 (21.6)
Amyloid positivity	14/25 (56.0)	12/19 (63.2)	2/6 (33.3)	0 (0)
Hypertension	29 (49.2)	15 (39.5)	14 (66.7)	12 (32.4)
Diabetes mellitus	10 (16.9)	5 (13.2)	5 (23.8)	3 (8.1)
Coronary artery disease	7 (11.9)	3 (7.9)	4 (19.0)	3 (8.1)
Dyslipidemia	21 (35.6)	9 (23.7)	12 (57.10)	13 (35.1)
History of stroke	6 (10.2)	3 (7.9)	3 (14.3)	0 (0)
Total lacunes	0.85±0.97	0.71±0.80	1.10±1.12	0.62±0.75
Total microbleeds	0.36±2.22	0.55±2.76	0.00±0.00	0.08±0.36
Total WMH volume, mm^3	8,922±13,144*	10,321±15,426*	6,657±8,071	3,122±4,268
PWMH volume, mm^3	7,390±10,043*	8,422±11,561*	5,719±6,859	2,763±3,634
DWMH volume, mm^3	1,532±3,866*	1,898±4,726	938±1702	360±815
Mean cortical thickness, mm	2.42±0.08*	2.41±0.07*	2.44±0.10	2.49±0.07
Hippocampal volume, mm^3	3,565±619*	3,457±616*	3,761±588*	4,160±397
Intracranial volume, mm^3	$1.39\times10^6\pm1.92\times10^5$	$1.40\times10^6\pm1.92\times10^5$	$1.38\times10^6\pm1.98\times10^5$	$1.37\times10^6\pm1.66\times10^5$

Data are mean±SD values for continuous variables and *n* (%) values for categorical variables.
*$p<0.05$ versus NC in independent *t*-test for continuous variables and chi-square test for categorical variables.
aMCI: amnestic MCI, CDR-SOB: Clinical Dementia Rating–Sum of Boxes, DWMH: deep WMH, MCI: mild cognitive impairment, MMSE: Mini Mental State Examination, naMCI: nonamnestic MCI, NC: normal cognition, PWMH: periventricular WMH, WMH: white-matter hyperintensity.

Table 2. Demographics and clinical characteristics of the aMCI and NC subgroups

Variable	Verbal-aMCI (*n*=12)	Visual-aMCI (*n*=10)	Both-aMCI (*n*=16)	NC (*n*=37)
Age, years	71.0±11.42*	71.5±5.02*	68.6±6.78	64.6±11.7
Age at onset, years	70.2±10.19	68.2±5.18	65.7±7.16	64.4±11.41
Sex, female	8 (66.7)	8 (80.0)	11 (68.8)	20 (54.1)
Education, years	6.29±3.36*	8.80±5.15	8.34±5.01*	11.95±4.47
Disease duration, months	28.0±16.24	28.8±19.55	34.0±13.44	-
MMSE score	24.3±3.81*	26.1±2.13*	23.3±4.86*	28.4±1.76
CDR-SOB score	1.25±0.89*	0.80±0.58*	2.43±1.50*	0.00±0.00
APOE ε4 carrier	4 (33.3)	2 (20.0)	8 (50.0)*	8 (21.6)
Amyloid positivity	3/5 (60.0)*	2/3 (66.7)*	7/11 (63.6)*	0 (0)

Data are mean±SD values for continuous variables and *n* (%) values for categorical variables.
*$p<0.05$ versus NC in independent *t*-test for continuous variables and chi-square test for categorical variables.
aMCI: amnestic MCI, Both-aMCI: MCI with both visual and verbal memory impairment, CDR-SOB: Clinical Dementia Rating-Sum of Boxes, MCI: mild cognitive impairment, MMSE: Mini Mental State Examination, NC: normal cognition, Verbal-aMCI: MCI with verbal memory impairment, Visual-aMCI: MCI with visual memory impairment.

Table 3. Neuropsychological test results according to subgroups of memory impairment (*n*=38) and NC (*n*=37)

	Verbal-aMCI (*n*=12)	Visual-aMCI (*n*=10)	Both-aMCI (*n*=16)	NC (*n*=37)
Attention				
Digit Span Test, forward	0.79±1.44	0.44±1.22	0.22±1.14*	1.03±0.79
Digit Span Test, backward	0.45±0.67	-0.20±1.35	-0.44±0.83*	0.47±1.09
Language and related function				
K-BNT score	-0.26±1.07	-0.44±0.77*	-1.92±1.68*	0.18±0.85
Visuospatial function				
RCFT, copying	0.48±0.84	-0.23±1.22	-0.60±2.11	0.50±0.61
Memory				
SVLT, immediate recall	-0.86±0.43*	-0.51±0.89*	-1.35±0.94*	0.30±0.78
SVLT, delayed recall	-1.74±0.44*	-0.37±0.51*	-2.27±0.59*	0.38±0.69
RCFT, immediate recall	0.00±0.72*	-1.04±0.44*	-1.49±0.72*	0.83±0.89
RCFT, delayed recall	-0.23±0.64*	-1.53±0.20*	-1.82±0.56*	0.89±0.83
Frontal executive function				
COWAT, animal names	-0.55±0.82	-1.03±0.54*	-1,78±0.92*	0.05±0.96
COWAT, supermarket items	-0.64±0.89*	-0.18±0.79	-1.28±0.82*	0.36±0.91
COWAT, phonemic fluency	-0.14±0.81*	0.28±1.07	-0.43±1.26*	0.58±0.94
Stroop test, color reading	-0.79±0.65*	-0.02±1.30	-1.33±1.25*	0.39±0.90
TMT-B	-1.15±1.39*	-0.64±1.38*	-4.19±4.57*	0.20±0.82

Data are mean±SD values. All data are z scores.
*$p<0.05$ versus NC in independent *t*-test for continuous variables.
aMCI: amnestic MCI, Both-aMCI: MCI with both visual and verbal memory impairment, COWAT: Controlled Oral Word Association Test, K-BNT: Korean version of the Boston Naming Test, MCI: mild cognitive impairment, MMSE: Mini Mental State Examination, NC: normal cognition, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, TMT-B: Trail-Making Test type B, Verbal-aMCI: MCI with verbal memory impairment, Visual-aMCI: MCI with visual memory impairment.

was also significantly greater in aMCI patients than in NC subjects in the following 19 ROIs: prefrontal, orbitofrontal, sensorimotor, superior parietal, inferior parietal, precuneal, posterior cingulate cortices, occipital, superior temporal, middle temporal, inferior temporal, mesial temporal, entorhinal cortices, parahippocampus, hippocampus, amygdala, fusiform gyrus, lingual gyrus, and global cortex. THK retention did not differ significantly between naMCI patients and NC subjects (Supplementary Table 4 in the online-only Data Supplement). However, at an individual level, five naMCI patients exhibited abundant [^{18}F]THK5351 retention in the association cortices (Supplementary Fig. 1 in the online-only Data Supplement). Two of these patients underwent [^{18}F]FLUTE PET, which revealed amyloid positivity in both of them (#18 and #19).

Verbal-aMCI, visual-aMCI, and both-aMCI groups

Voxel-wise analyses uncorrected for multiple comparisons with adjustments for age and years of education showed that both-aMCI patients displayed greater [^{18}F]THK5351 retention in almost all associated cortices except for the primary sensorimotor and primary visual cortices. Verbal-aMCI pa-

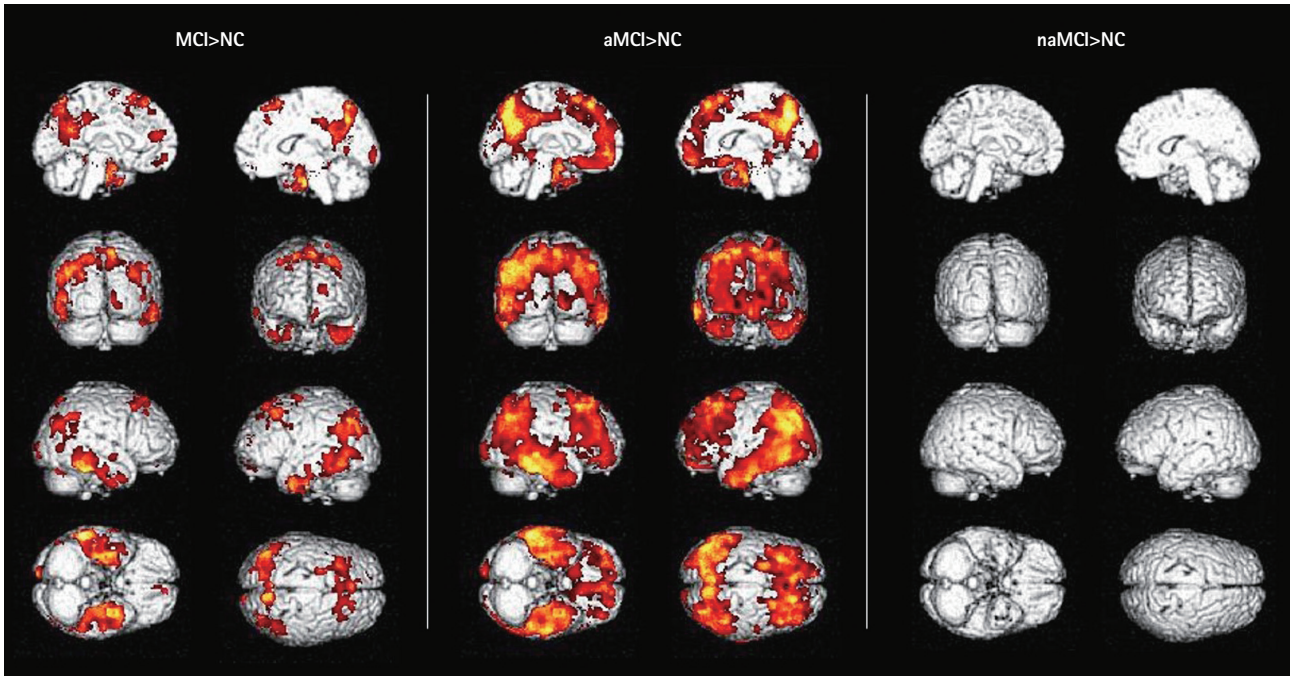

Fig. 1. [^{18}F]THK5351 retention in MCI, aMCI, and naMCI patients. Voxel-wise comparisons of [^{18}F]THK5351 retention between cognitively impaired groups and NC subjects. The results are presented at a threshold of $p<0.05$ with false-discovery rate (FDR)-correction adjusted for age and years of education, and with >50 clusters. aMCI: amnestic MCI, MCI: mild cognitive impairment, naMCI: nonamnestic MCI, NC: normal cognition.

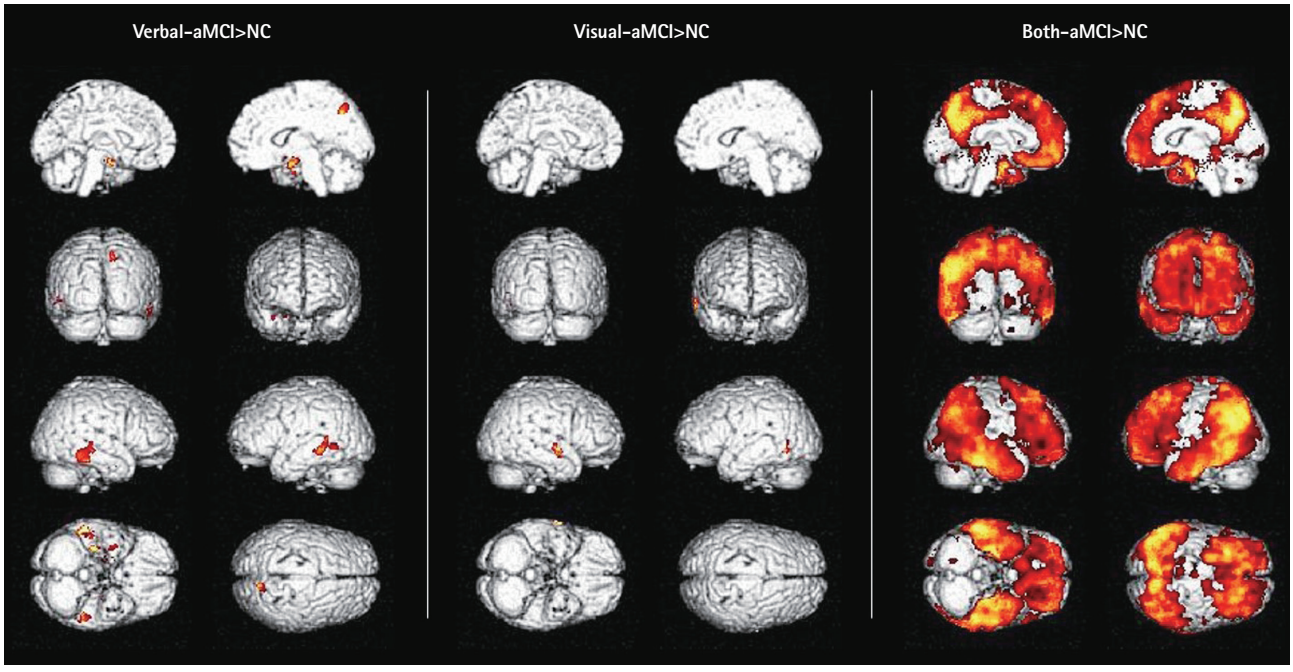

Fig. 2. [^{18}F]THK5351 retention in subgroups of aMCI patients. Voxel-wise comparisons between subgroups of aMCI and NC subjects. The results are presented at a threshold of $p<0.001$, uncorrected for multiple comparisons with adjustments for age and years of education, and with >50 clusters. aMCI: amnestic MCI, Both-aMCI: MCI with both visual and verbal memory impairment, MCI: mild cognitive impairment, NC: normal cognition, Verbal-aMCI: MCI with verbal memory impairment, Visual-aMCI: MCI with visual memory impairment.

tients showed greater [^{18}F]THK5351 retention in the lateral temporal, parietal and mesial temporal areas, while visual-aMCI patients showed greater [^{18}F]THK5351 retention in small regions of the lateral temporal cortex (Fig. 2).

In ROI-based analyses, [^{18}F]THK5351 retention was significantly greater in nearly all ROIs except for the right anterior cingulated cortices, left lingual gyrus, and bilateral striatum in both-aMCI patients than in NC subjects. The regions in which these differences remained significant after multiple comparisons in verbal-aMCI patients were the prefrontal, orbitofrontal, occipital, middle temporal, inferior temporal, mesial temporal, entorhinal cortices, hippocampus, amygdala, and global cortex in the right hemisphere. [^{18}F]THK5351 retention did not differ significantly between visual-MCI patients and NC subjects (Table 4).

Amyloid-positive and -negative MCI patients

Amyloid-positive MCI patients showed greater [^{18}F]THK5351 retention in the frontal, lateral temporal, parietal, occipital, precuneus and mesial temporal cortices compared to amyloid-negative NC subjects, while patients with amyloid-negative MCI showed [^{18}F]THK5351 retention only in small parts of the frontal, anterior cingulate, and mesial temporal regions (Fig. 3). These results were calculated at a threshold of $p<0.001$ and not corrected for multiple comparisons with adjustments for age and years of education.

[^{18}F]THK5351 retention was greater in amyloid-positive MCI patients than in amyloid-negative NC subjects in nearly all ROIs except for striatum. It was also greater in the prefrontal, orbitofrontal, middle temporal, inferior temporal, mesial temporal, entorhinal cortices, parahippocampus, amygdala and fusiform gyrus in amyloid-negative MCI patients than in amyloid-negative NC subjects. (Supplementary Table 5 in the online-only Data Supplement).

Correlation between [^{18}F]THK5351 and neuropsychological test results

Global cognition as measured using tests such as the MMSE or CDR-SOB was correlated with [^{18}F]THK5351 retention in the lateral temporal, inferior parietal, precuneal, and mesial temporal areas. [^{18}F]THK5351 retention was associated with the scores for cognitive function tests that are dependent on

Table 4. Regional standardized uptake value ratio (SUVR) in [^{18}F]THK5351 positron emission tomography of aMCI subgroups and the NC group

Region	Right cerebral hemisphere				Left cerebral hemisphere			
	Verbal-aMCI (n=12)	Visual-aMCI (n=10)	Both-aMCI (n=16)	NC (n=37)	Verbal-aMCI (n=12)	Visual-aMCI (n=10)	Both-aMCI (n=16)	NC (n=37)
Prefrontal	1.81±0.47*	1.65±0.31	1.92±0.32*	1.47±0.25	1.74±0.35	1.65±0.29	1.99±0.47*	1.47±0.23
Orbitofrontal	2.37±0.65*	2.10±0.40	2.41±0.33*	1.93±0.33	2.24±0.53	2.12±0.36	2.50±0.51*	1.90±0.32
Sensorimotor	1.26±0.17	1.22±0.20	1.34±0.23*	1.16±0.20	1.27±0.18	1.27±0.18	1.38±0.24*	1.17±0.20
Anterior cingulate	3.24±0.70	3.03±0.63	3.29±0.38	2.96±0.41	3.21±0.58	2.96±0.64	3.46±0.54*	2.97±0.46
Superior parietal	1.46±0.26	1.49±0.31	1.73±0.41*	1.28±0.22	1.45±0.20	1.43±0.29	1.78±0.43*	1.25±0.19
Inferior parietal	1.68±0.29*,†	1.68±0.35	1.93±0.32*	1.41±0.24	1.67±0.32	1.65±0.32	2.08±0.52*	1.40±0.25
Precuneus	1.79±0.30	1.76±0.39	2.17±0.40*	1.52±0.26	1.80±0.31	1.81±0.35	2.29±0.52*	1.55±0.25
Posterior cingulate	2.25±0.38	1.72±1.17	2.53±0.33*	1.94±0.27	2.25±0.43	2.07±0.45	2.56±0.43*	1.94±0.27
Occipital	1.40±0.20*	1.36±0.41	1.40±0.40*	1.12±0.19	1.31±0.26	1.23±0.25	1.34±0.48*	1.06±0.17
Superior temporal	1.86±0.28	1.92±0.35	2.05±0.29*	1.70±0.26	1.85±0.30	1.94±0.35	2.16±0.46*	1.70±0.31
Middle temporal	2.16±0.50*	2.00±0.40	2.30±0.34*	1.72±0.29	2.06±0.52	1.97±0.43	2.37±0.60*	1.69±0.32
Inferior temporal	2.10±0.52*	1.99±0.51	2.27±0.36*	1.69±0.29	2.03±0.43	1.95±0.44	2.36±0.51*	1.67±0.31
Mesial temporal	3.15±0.93*	2.76±0.51	3.29±0.55*	2.52±0.31	2.95±0.63*,†	2.71±0.38	3.36±0.62*	2.50±0.33
Entorhinal	2.93±1.27*	2.48±0.73	2.90±0.65*	2.18±0.39	2.62±0.57	2.40±0.48	3.08±0.75*	2.23±0.42
Parahippocampus	2.28±0.40	2.15±0.35	2.58±0.41*	1.96±0.35	2.31±0.38	2.21±0.38	2.79±0.67*	2.04±0.42
Hippocampus	3.09±0.84*	2.76±0.50	3.28±0.58*	2.55±0.30	2.93±0.70*,†	2.71±0.35	3.27±0.52*	2.49±0.29
Amygdala	4.72±1.67*	3.77±0.77	4.73±1.40*	3.36±0.52	4.15±1.12*,†	3.66±0.59	4.62±1.01*	3.28±0.44
Fusiform gyrus	1.83±0.30	1.87±0.55	2.05±0.39*	1.56±0.24	1.87±0.32	1.85±0.36	2.26±0.70*	1.61±0.25
Lingual gyrus	1.41±0.23	1.28±0.38	1.44±0.36*	1.20±0.21	1.54±0.27*,†	1.37±0.33	1.45±0.43	1.24±0.24
Striatum	3.60±0.88	3.48±0.51	3.50±0.57	3.15±0.51	3.48±0.87	3.35±0.47	3.52±0.62	3.07±0.51
Global cortex	1.87±0.34*	1.78±0.33	2.03±0.31*	1.57±0.24	1.83±0.31	1.76±0.30	2.11±0.43*	1.56±0.23

Data are mean±SD values. One-way analysis of covariance with adjustment for age and years of education.
*p<0.05 versus NC, †Regions in which statistical significance was lost after region-wise correction for multiple comparisons.
aMCI: amnestic MCI, Both-aMCI: MCI with both visual and verbal memory impairment, MCI: mild cognitive impairment, NC: normal cognition, Verbal-aMCI: MCI with verbal memory impairment, Visual-aMCI: MCI with visual memory impairment.

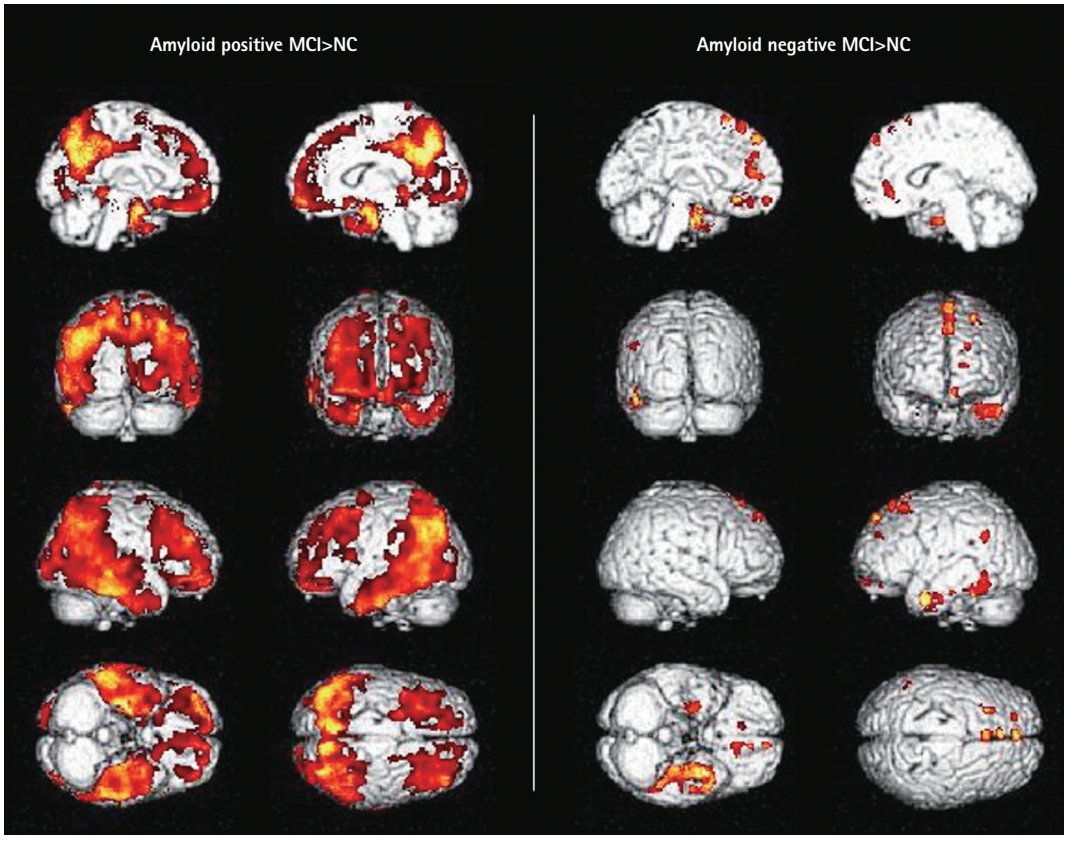

Fig. 3. [^{18}F]THK5351 retention in amyloid-positive and -negative MCI patients. Voxel-wise comparison of participants with [^{18}F]flutemetamol positron emission tomography. The results are presented at a threshold of p<0.001, uncorrected for multiple comparisons with adjustments for age and years of education, and with >50 clusters. MCI: mild cognitive impairment, NC: normal cognition.

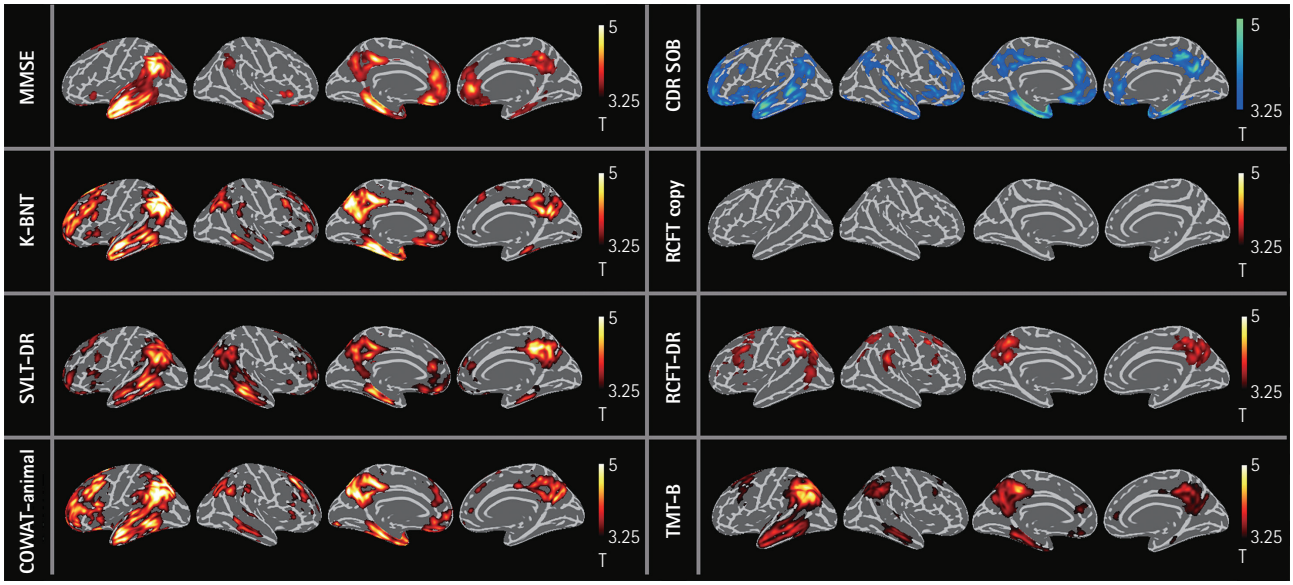

Fig. 4. Multiple regression analyses using statistical parametric mapping of [^{18}F]THK5351 retention in MCI. Brain areas with increased [^{18}F]THK5351 retention versus worsening cognitive function in MCI patients. Red and blue indicate negative and positive correlations, respectively. The results are presented at a threshold of p<0.05 with false-discovery rate corrections and >50 clusters. CDR-SOB: Clinical Dementia Rating-Sum of Boxes; COWAT: Controlled Oral Word Association Test; K-BNT: Korean version of the Boston Naming Test; MMSE: Mini Mental State Examination; RCFT copy: Rey Complex Figure Test, copy; RCFT-DR: Rey Complex Figure Test, delayed recall; SVLT-DR: Seoul Verbal Learning Test, delayed recall; TMT-B: Trail-Making Test type B.

language function, such as the Korean version of the Boston Naming Test (K-BNT); Controlled Oral Word Association Test (COWAT)-animal; and Trail-Making Test type B (TMT-B); and correlated with similar areas of the brain as global cognition tests, but with a stronger left-side predilection. Worse verbal memory scores (SVLT, delayed recall) were correlated with greater [^{18}F]THK5351 retention in the lateral temporal and inferior parietal cortices, precuneus, and part of the dorsolateral prefrontal cortex. In contrast, visual memory impairment was associated with smaller regions in the inferior parietal cortex and precuneus. Visuospatial function (RCFT, copy) was not correlated significantly with [^{18}F]THK5351 retention in the voxel-wise analysis. These results are presented at a threshold of $p<0.05$ with FDR corrections in Fig. 4.

DISCUSSION

This study identified different topographic patterns of [^{18}F]THK5351 retention in MCI patients according to the absence or presence of memory impairment, modality of memory impairment, and amyloid PET results. The retention of [^{18}F]THK5351 in aMCI patients mirrored findings in AD, while that in naMCI patients did not differ significantly from that in the NC group. Both-aMCI patients showed greater [^{18}F]THK5351 retention in nearly all associated cortices, while visual-aMCI patients displayed only small regions of [^{18}F]THK5351 retention. Verbal-aMCI was associated with an intermediate level of tracer binding. Moreover, [^{18}F]THK5351 retention was more pronounced in the subgroup of MCI patients with amyloid positivity in [^{18}F]FLUTE PET.

Overall the MCI patients showed greater [^{18}F]THK5351 retention in the frontal, lateral temporal, mesial temporal, and parietal cortices, and precuneus (Fig. 1) compared to the NC group. The topographic distribution of tau PET uptake was similar to previously reported observations using [^{18}F]THK5351 and other tau targeting tracers in cognitively impaired subjects.[34,36,37,46] Cho et al.[32,34] showed increased tau binding using the ligand [^{18}F]AV-1451 in the entorhinal cortex in patients with MCI, while in one of our previous studies using [^{18}F]THK5351, retention was greater in most association cortices as well as the limbic area than in NC subjects, with the distribution being similar but at lower intensities than in patients with AD.[35] Other studies have produced similar findings in amyloid-positive MCI patients.[36,37] However, broader regions with greater tau retention were observed in the present aMCI group. Clinical studies suggest that the amnestic subtype of MCI is more like to progress to AD,[2,47,48] while neuropathological studies have also shown the existence of more NFTs in aMCI patients than in naMCI patients.[7] Some pathological reports have argued that aMCI is identical to early AD based on the NFT distribution.[49,50] The present study found that the distribution of [^{18}F]THK5351 retention was similar in aMCI and AD patients,[35] which corresponds to later stages of tau deposition according to Braak staging.[16] Our findings support previous suggestions that aMCI is a precursor or early state of AD.

On the other hand, tau retention did not differ significantly between the naMCI patients and NC subjects. Similarly, Cho et al.[32] found that more than 70% of naMCI patients and NC subjects exhibited no significant accumulation of tau using [^{18}F]AV-1451 PET, while this percentage dropped significantly for aMCI and clinically AD patients. This may have been due to the clinically diverse nature of naMCI, which has been suggested to develop into FTD, DLB, or vascular dementia.[4] Autopsy studies have found fewer AD-related pathological findings and a higher frequency of alpha-synucleinopathy in naMCI patients.[7,8] Clinical studies have also shown that the conversion rate to dementia is lower for naMCI than for aMCI,[48] the prevalence of depression and vascular risk factors is higher for naMCI than for non-MCI subjects,[51] and prefrontal executive dysfunction is worse in naMCI patients than in aMCI patients.[8,52] Although overall there were no significant differences between the naMCI and NC groups, individually we found that 24% of naMCI patients exhibited abundant [^{18}F]THK5351 retention in the association cortices, and amyloid positivity was found in all of those who underwent [^{18}F]FLUTE PET. Although these patients who presented clinically as naMCI, follow-up studies would be needed to determine whether these patients who also exhibit abundant [^{18}F]THK5351 retention progress to dementia.

We further analyzed subgroups of aMCI based on the modality of memory impairment. Patients with verbal memory dysfunction exhibited increased [^{18}F]THK5351 retention in the bilateral medial and lateral temporal lobes and the right precuneus. Patients with visual memory impairment showed smaller, focal regions of tracer uptake bilaterally in the lateral temporal cortices. Previous studies found that the risk of progression to dementia was higher in verbal-aMCI and both-aMCI patients than in visual-aMCI patients.[10-12] Our results contrast with cortical thinning studies revealing left medial temporal atrophy in verbal-aMCI patients compared to NC subjects.[39] This difference may have been due to the smallness of the sample in the verbal-aMCI subgroup or nonspecific binding of [^{18}F]THK5351 in the medial temporal regions reducing its resolving power in this area.[34] [^{18}F]THK5351 retention in both-aMCI patients was found throughout the brain except for the primary sensorimotor and occipital cortices (Fig. 2), suggesting more-extensive neuronal degeneration and a more-severe state of disease progression. Impairment of both visual and verbal memory also showed more extensive

cortical thinning, suggesting a more-advanced subgroup on the spectrum from MCI to AD,[39] analogous to the tau PET findings in this study.

The neural substrates of visual memory recall are less well defined in the literature. A study of visual delayed recall in probable AD patients using SPECT showed the involvement of bilateral temporal regions.[53] Another study testing visual memory using the Wechsler Memory Scale showed an association with the right precuneus and right cingulate gyrus.[54] [^{18}F]FDG PET analysis using the figure-recall task in the Benton Visual Retention Test showed that regional cerebral glucose metabolism was predominantly correlated with the left parietal and temporo-occipital regions.[55] However, that study also found that consortium to establish a registry for Alzheimer's disease neurophychological battery (CERAD) constructional praxis recall was correlated with the right prefrontal, parietal, and temporal regions. The left inferior temporo-occipital cortex has been shown to be activated by shape- and object-based memory tasks.[56-58] Moreover, patients with lesions in the left temporal lobe without hippocampal sclerosis showed large decrements in figure and spatial recall using the RCFT compared to right-side lesions.[59] In contrast, cortical thinning studies have found no differences between normal controls and visual-aMCI patients on statistical maps of the cortical thickness.[39] The voxel-wise analysis performed in the present study showed a small area of involvement in both lateral temporal cortices (left predominant) in the visual-aMCI group compared to the NC group, while ROI analysis revealed no significant differences between the two groups. Investigating larger samples and evaluating different methods for visual memory recall may help to elucidate these discrepancies in visual memory localization.

MCI patients who were amyloid positive in [^{18}F]FLUTE PET exhibited greater [^{18}F]THK5351 retention in the frontal, lateral temporal, parietal, occipital, precuneal, and mesial temporal cortices compared to amyloid-negative NC subjects. These findings are consistent with previous findings of increased tau retention in amyloid-positive MCI patients.[36,37] We also found that MCI patients with amyloid-negative [^{18}F]FLUTE PET findings displayed small regions of [^{18}F]THK5351 retention in the frontal, anterior cingulate, and mesial temporal areas (Fig. 3). These observations might reflect the involvement of other neurodegenerative processes without evidence of amyloid deposition such as tauopathies or neuroinflammation. [^{18}F]THK5351 has been shown to bind to not only paired helical filaments but also nonspecifically to MAO-B, which is abundant in astrocytes.[33] MAO-B availability has been found in patients with neuroinflammation as well as in normal aging[60] and AD.[61] It is also possible that some cases are prodromal AD with subthreshold levels of amyloid deposition,[62] or with mainly diffuse plaques or soluble amyloid for which amyloid PET ligands have a low affinity.[63] However, studies have shown that naMCI patients are more likely to have low Pittsburgh Compound B (PiB) retention and higher β-amyloid levels in the CSF.[64,65] It has also been shown that there are no significant differences in the hippocampal volume, cortical thickness, and hippocampal metabolism between amyloid-negative MCI patients and elderly controls, with the CSF levels of p-tau and t-tau being lower and the longitudinal cognitive performance being better in amyloid-negative MCI patients than in amyloid-positive MCI patients.[22,66] The finding of greater [^{18}F]THK5351 retention in the present aMCI group might have been due to a trend for greater amyloid positivity in that group compared to the naMCI group. However, the small number of amyloid PET scans performed in the naMCI group and the lack of further histological evaluation prevented us from drawing more-definite conclusions.

We found that [^{18}F]THK5351 retention in the neocortex—including the lateral temporal, frontal, mesial temporal, and parietal cortices, and the precuneus—was correlated with the performance in tasks for verbal memory, verbal fluency, and confrontational naming. Tests of visual memory were associated with [^{18}F]THK5351 retention to a lesser extent in the parietal cortices and precuneus, with little involvement of the temporal cortex. These findings are similar to a previous report.[36] Longitudinal studies have found that the progression of cognitive decline is predicted more accurately by deficits in verbal memory tasks than in tasks for visual memory.[36] Several studies have also shown that the left hemisphere is involved more frequently during the initial stages of AD.[67-69] Cortical volumetric studies have shown more cortical thinning in the temporal lobes of aMCI patients with verbal memory impairment than in patients with visual memory dysfunction.[39] Our data seem to support the differences observed between verbal and visual memory with regards to AD progression reported in the literature, with greater involvement of the lateral temporal area in MCI patients with verbal memory impairment.

The main limitation of this study is related to a recent report of [^{18}F]THK5351 also binding to MAO-B. Ng et al.[33] showed that the administration of MAO-B inhibitors reduced [^{18}F]THK5351 retention in the striatum by 52% and in the cortex by 36%, with the cerebellar cortex affected to a lesser extent. These data are correlated with human autopsy findings showing MAO-B concentrations are highest in the striatum followed by the cerebral cortex, and lowest in the cerebellum and white matter.[70] The nonspecific binding of [^{18}F]THK5351 to MAO-B was recently confirmed in vitro by Harada et al.,[71] who showed binding of the radiotracer to both paired helical filament-tau and MAO-B but not MAO-A in brain slices. It

has also been recently reported that [^{18}F]AV-1451 (which is another tau tracer) binds with similar affinities to MAO-A and MAO-B as well as tau fibrils.[72] These reports have indicated that about one-third of the [^{18}F]THK5351 cortical signal might not be attributable to tau. Higher levels of MAO-B are found in astrocytes and are also associated with neurodegenerative diseases such as AD.[73,74] Therefore, we cannot conclude that the findings of the present are solely due to tau pathology. Another limitation of this study is the smallness of the sample in each aMCI subgroup. This combined with the small numbers of patients with amyloid PET data meant that voxel-wise comparisons between these groups and NC were presented uncorrected for multiple comparisons. The cross-sectional nature of this study also prevents us from drawing definite conclusions regarding the [^{18}F]THK5351 topographic patterns and the risk of AD progression. Further studies with larger samples are therefore needed to confirm the generalizability of our findings.

In conclusion, [^{18}F]THK5351 retention was greater in MCI patients who were amnestic, who had both verbal and visual memory impairments, and who were amyloid positive in [^{18}F]FLUTE PET. Cognitive functioning in the MCI patients was significantly correlated with cortical [^{18}F]THK5351 retention. To the best of our knowledge, this is the first study to use [^{18}F]THK5351 PET to identified distinct topographic patterns of [^{18}F]THK5351 deposition in MCI subgroups. However, the contribution of NFTs and neuroinflammation to the differences seen in [^{18}F]THK5351 binding could not be differentiated.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2020.16.2.202.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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