Medial temporal tau can be a predictor for amyloid-ß positivity in mild cognitive impairment

Hanna Cho
Yonsei University College of Medicine
Min Seok Baek
Yonsei University College of Medicine
Hye Sun Lee
Yonsei University College of Medicine
Jae Yong Choi
Yonsei University College of Medicine
Jae Hoon Lee
Yonsei University College of Medicine
Young Hoon Ryu
Yonsei University College of Medicine
Myung Sik Lee
Yonsei University College of Medicine
Chul Hyoung Lyoo (lyoochel@yuhs.ac)
Gangnam Severance Hospital https://orcid.org/0000-0003-2231-672X

Research

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Abstract

Introduction Although both amyloid-ß (Aß) and tau positron emission tomography (PET) are important for the assessment of Alzheimer's disease pathology, obtaining two PET scans can be challenging in clinical practice. We sought to determine whether Aß-positivity in MCI patients can be predicted with only a single tau PET scan.

Methods We prospectively recruited 105 MCI patients and performed two PET scans with 18 F-florbetaben and 18 F-flortaucipir with all patients. Regional 18 F-flortaucipir standardized uptake value ratios (SUVR) were measured using FreeSurfer-generated volumes-of-interest and with the cerebellar crus median as a reference.

Results We classified 49 (46.7%) MCI patients as Aß-positive using visual assessment. In 12 regions showing greater tau uptake in the MCI-Aβ+ patients compared to the MCI-Aβ- patients, tau uptake in the entorhinal cortex showed the greatest area under the curve (AUC) value (AUC = 0.835, sensitivity/specificity = 73.5% /85.7%) for discriminating Aß-positivity. The second and third largest AUCs were obtained with tau uptake in the amygdala (AUC = 0.814, sensitivity/specificity = 65.3%/94.6%) and the parahippocampal cortex (AUC = 0.802, sensitivity/specificity = 67.4%/91.1%). However, post-hoc analyses revealed no statistical differences between the three regions.

Conclusions Single tau PET scans may be helpful in the evaluation of disease state and stage at the same time in MCI patients.

Background

Amyloid-ß (Aß) and tau are important biomarkers for the evaluation of Alzheimer's disease (AD) state and stage particularly in the early stage [1]. Aß-positive mild cognitive impairment (MCI) is considered to be the prodromal, or earliest stage of AD [2]. Previous amyloid positron emission tomography (PET) studies have demonstrated that 40 to 60% of MCI patients are Aß-positive and Aß-positivity on PET (PET-Aß-positivity) is highly correlated with clinical progression from MCI to dementia. [1] Meanwhile, tau PET visualizes distinct topographical distribution patterns of neurofibrillary tangles (NFT), thereby reflecting the clinical and pathological severity of AD [3]. Tau first accumulates in the entorhinal cortex and spreads dorsally toward the neocortex, while tau accumulation beyond the medial temporal regions occurs almost exclusively in Aß-positive patients. As expected due to this distinct spreading pattern, tau accumulation has been found predominantly in the medial and basal temporal regions in Aß-positive MCI patients in previous tau PET studies [4, 5].

Although these two imaging biomarkers provide complementary information, it can be challenging to obtain both PET images in clinical practice. Moreover, Aß-positivity is significantly more important for MCI patients than clinical AD patients who typically show up to 90% of Aß-positivity [6]. In this study, we sought to determine whether PET-Aß-positivity can be predicted with only a single tau PET scan, and which region may be the most predictive of PET-Aß-positivity in MCI patients.

Methods

Participants

From January 2015 to August 2017, we prospectively included 105 MCI patients at the Memory Disorder Clinic of Gangnam Severance Hospital. All MCI patients were diagnosed using Petersen's criteria [7]. All participants underwent clinical interviews, a neuropsychological test battery, genotyping for apolipoprotein E (ApoE), brain magnetic resonance (MR) imaging, and two PET scans with ^{18}F-florbetaben (for Aß) and ^{18}F-flortaucipir (for tau). PET-Aß-positivity was determined by consensus between two nuclear medicine specialists using a validated visual assessment method [8, 9], and the MCI patients were dichotomized into two groups based on PET-Aß-positivity (MCI-Aβ+ and MCI-Aβ-). This study was approved by the Institutional Review Board of Gangnam Severance Hospital and written informed consent was obtained from all subjects.

Image processing steps

We used the Freesurfer 5.3 software (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu) to create participant-specific volume-of-interest (VOI) images. In brief, T1-weighted MR images were first resliced to FreeSurfer space (256×256×256 matrix with 1 mm isovoxels), segmented into gray and white matter, and their 3D-surfaces were reconstructed. Cortical regions were segmented with the curvature information of the white matter surface, and subcortical regions with the probabilistic registration technique. Finally, participant-specific composite VOI mask images for 20 cortical and subcortical regions were created after merging anatomically-related regions.

Statistical parametric mapping 12 (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK) and in-house software implemented in MATLAB 2015b (MathWorks, Natick, MA, USA) were used for integrative analysis of the PET and MR images. PET images were first co-registered to individual MR images in FreeSurfer space and regional standardized uptake value ratio (SUVR) images were created using the cerebellar crus median obtained from spatially-normalized PET images. Finally, regional SUVR values were measured by overlaying the participant-specific VOI mask images on individual SUVR images.

Statistical analysis

Statistical analyses were performed with SPSS 23 (IBM Corp., Armonk, NY, USA) and MedCalc for Windows, version 18.1 (MedCalc Software, Ostend, Belgium). Demographic data and neuropsychological tests were compared between the MCI-Aβ+ and MCI-Aβ- groups with independent t-test for continuous variables or Chi-square test for categorical variables. Independent t-test was used for unadjusted comparisons of regional ^{18}F-flortaucipir uptake between the MCI-Aβ+ and MCI-Aβ- groups, and multivariate logistic regression analysis was used to evaluate independent associations between the

regional ^{18}F-flortaucipir uptake and PET-Aß-positivity after adjusting for age, education, sex, duration, and ApoE ε4 genotype. We excluded the hippocampus due to the effects of off-target binding of ^{18}F-flortaucipir to the choroid plexus. [10] By using the receiver-operating characteristic (ROC) analysis, the accuracy of tau PET to discriminate PET Aß-positivity was then assessed for the regions showing statistically significant differences between the MCI-Aβ+ and MCI-Aβ- groups (unadjusted-$P < 0.05$). Comparisons of area under the ROC curves (AUC) was performed using the DeLong method. Youden's method was used to identify an optimal cut-off point on the ROC curves to maximize the sensitivity and specificity of tau uptake in each region.

Results

Of the 105 MCI patients, 49 (46.7%) were Aß+ on visual assessment. Detailed demographic characteristics are shown in Table 1.

To determine which region is most suitable for PET-Aß-positivity screening, we first compared regional ^{18}F-flortaucipir uptake between the MCI-Aβ+ and MCI-Aβ- patients. The MCI-Aβ+ patients showed greater ^{18}F-flortaucipir uptake in most of the cortical regions except the sensorimotor and anterior cingulate cortices, most prominently in the inferior parietal and lateral and medial temporal cortices when compared to MCI-Aβ- patients (Table 2). The results of multivariate logistic regression analysis adjusted for demographic variables were almost consistent with the unadjusted results (Table 2).

Of the 12 tau uptake regions with significant differences between the MCI-Aβ+ and MCI-Aβ- patients, the entorhinal cortex showed the greatest AUC value (AUC = 0.835) with a sensitivity of 73.5% and specificity of 85.7%. The second and third greatest AUCs were obtained in the amygdala (AUC = 0.814) with a sensitivity of 65.3% and specificity of 94.6%, as well as the parahippocampal cortex (AUC = 0.802) with a sensitivity of 67.4% and specificity of 91.1%. However, post-hoc analyses of the AUC revealed that there were no statistical differences between the entorhinal cortex and amygdala or parahippocampal cortex using DeLong's method (Table 3).

Discussion

In this study, we found that ^{18}F-flortaucipir uptake in the entorhinal cortex was the best predictor for discriminating PET-Aß-positivity, and those in the amygdala or parahippocampal cortex also showed similar accuracy. This suggests that tau PET can serve as a predictor for PET-Aß-positivity in MCI patients.

For predicting PET-Aß-positivity in MCI, several clinical or MR-based methods have been developed, including the use of nomograms based on neuropsychological tests [11], informant-based reporting of cognitive symptoms [12], and MR-based brain morphometry or hippocampal volumetry [13]. However, while morphometry which provided up to 80% of the sensitivity and specificity for predicting PET-Aß-positivity without clinical variables, other methods were suboptimal. Cerebrospinal fluid (CSF) Aß is also

a powerful biomarker for predicting Aß pathology in AD [14]. Previous studies have consistently shown a negative relationship between the CSF $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio and Aß burden measured by PET and high agreement in Aß-positivity status between CSF studies and amyloid PET [14-17]. Nevertheless, the invasiveness required to obtain CSF limits its usage in clinical practice.

Like the previous ^{18}F-flortaucipir studies that showed greater uptake in the medial and inferior temporal regions in MCI patients when compared to healthy controls [4, 5, 18], the MCI-Aβ+ patients in our study showed greater ^{18}F-flortaucipir uptake in the parietal, lateral and medial temporal regions when compared to the MCI-Aβ- patients. ^{18}F-flortaucipir uptake in these regions was also useful for discriminating AD from other neurodegenerative diseases.[14] We therefore believe it is reasonable to select an optimal area from the regions with greater uptake in MCI-Aβ+ patients for predicting PET Aβ-positivity.

In our study, the highest sensitivity was achieved with ^{18}F-flortaucipir uptake in the entorhinal (73.5%) and parahippocampal (67.4%) cortices, as expected by the early appearance of NFT pathology in these regions in AD [19]. Expansion of Aβ throughout the neocortex without tau burden in the entorhinal cortex sufficient to exceed the cut-off threshold in ^{18}F-flortaucipir PET might reduce the sensitivity. Similarly, ^{18}F-flortaucipir uptake in the entorhinal, amygdala and parahippocampal cortices provided 85.7 to 94.6% of the specificity. Small false positivity for predicting PET-Aβ-positivity might be attributable to primary age-related tauopathy (PART) [20]. However, there was no interaction between age and ^{18}F-flortaucipir uptake in the entorhinal and parahippocampal cortices.

Although the greatest AUC value was achieved with the entorhinal cortex, followed by the amygdala and parahippocampal cortex, the post-hoc comparison of AUC values between the entorhinal cortex and the other two regions did not exhibit superiority of one region over any others for predicting PET-Aβ-positivity. However, compared to the entorhinal cortex, the amygdala and parahippocampal cortex provided lower sensitivity (< 70%) and higher specificity (> 90%). When focusing on the screening of PET-Aß-positivity, the entorhinal cortex may be the best region for predicting PET-Aβ-positivity.

This study was limited by the visual assessment for deciding Aβ-positivity, although this has been validated [9]. In addition, absence of an external validation can be a limitation. Nevertheless, our study first added the usefulness of tau PET for predicting PET-Aß-positivity in MCI patients.

Conclusions

In conclusion, ^{18}F-flortaucipir uptake in the medial temporal regions may be used to predict PET-Aß-positivity in MCI patients without considering clinical information. Single tau PET scans may be helpful for discriminating Aß-positivity with uptake in the medial temporal regions as well as for monitoring the disease progression in MCI patients.

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Tables

Table 1. Demographic characteristics of the study participants

	Total MCI	MCI-Aβ-	MCI-Aβ+
n	105	56	49
Age (years)	71.1 ± 9.1	68.9 ± 9.7	73.7 ± 7.6*
Sex (M : F)	41 : 64	17 : 39	24 : 25
Education (years)	11.2 ± 4.5	11.0 ± 4.3	11.4 ± 4.7
Duration (years)	2.3 ± 1.3	2.0 ± 1.2	2.6 ± 1.3*
ApoE ε4+	30 (29%)	7 (13%)	23 (47%)*
MMSE	25.7 ± 2.7	26.2 ± 2.1	25.1 ± 3.2*
CDR-SB	1.5 ± 1.0	1.3 ± 1.0	1.8 ± 0.9*
^{18}F-flortaucipir SUVR	1.21 ± 0.15	1.16 ± 0.09	1.27 ± 0.19*
^{18}F-florbetaben SUVR	1.62 ± 0.31	1.38 ± 0.08	1.89 ± 0.26*

Data are presented as mean ± SD. $^{*}P < 0.05$ for the comparisons between MCI-Aβ- and MCI-Aβ+ groups

Abbreviations: MCI = mild cognitive impairment, Aβ+/- = amyloid-positivity, ApoE = apolipoprotein E, MMSE = Mini-Mental State Examination, CDR-SB = Clinical Dementia Rating sum-of-boxes

Table 2. Comparison of ^{18}F-flortaucipir binding values and multiple logistic regression associated with amyloid positivity in MCI

	Unadjusted[a]			Adjusted[b]	
	MCI-Aβ-	MCI-Aβ+	*P*-value	*OR*[c] *(95% CI)*	*P*-value
Prefrontal	1.20±0.09	1.26±0.18	**0.028**	1.461 (0.992 - 2.151)	0.055
Sensorimotor	1.08±0.09	1.10±0.14	0.475	1.218 (0.801 - 1.854)	0.356
Superior parietal	1.09±0.10	1.17±0.21	**0.013**	1.466 (1.038 - 2.071)	**0.030**
Inferior parietal	1.14±0.11	1.28±0.26	**< 0.001**	1.620 (1.149 - 2.286)	**0.006**
Precuneus	1.20±0.10	1.31±0.25	**0.004**	1.517 (1.056 - 2.178)	**0.024**
Occipital	1.14±0.08	1.21±0.20	**0.010**	1.456 (0.976 - 2.174)	0.066
Superior temporal	1.10±0.09	1.21±0.19	**< 0.001**	1.908 (1.231 - 2.956)	**0.004**
Middle temporal	1.18±0.09	1.42±0.31	**< 0.001**	2.177 (1.427 - 3.321)	**< 0.001**
Inferior temporal	1.21±0.09	1.46±0.30	**< 0.001**	2.076 (1.389 - 3.102)	**< 0.001**
Entorhinal	1.27±0.17	1.72±0.40	**< 0.001**	1.856 (1.374 - 2.508)	**< 0.001**
Parahippocampal	1.20±0.11	1.48±0.29	**< 0.001**	1.953 (1.394 - 2.735)	**< 0.001**
Amygdala	1.32±0.14	1.72±0.41	**< 0.001**	1.629 (1.251 - 2.121)	**< 0.001**
Anterior cingulate	1.23±0.10	1.28±0.15	0.081	1.429 (0.975 - 2.093)	0.067
Posterior cingulate	1.23±0.10	1.35±0.25	**0.001**	1.606 (1.137 - 2.268)	**0.007**

[a]Data are presented as mean ± SD. [b]Adjusted for age, education, sex, disease duration, and ApoE ε4 genotype. [c]OR was analysed by regional SUVR per 0.1 units.
Abbreviations: MCI = mild cognitive impairment, Aβ+/- = amyloid-positivity, OR = odds ratio, CI = confidence interval

Table 3. Comparison of AUC values between entorhinal and other regional tau uptake and determination of optimal cut-off point in MCI

	AUC (95% CI)	*P*-value*	*P*-value**	cut-off++	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Prefrontal	0.611 (0.499 - 0.723)	0.050	**< 0.001**	> 1.32	30.6 (18.3 - 45.4)	94.6 (85.1 - 98.9)
Superior parietal	0.574 (0.459 - 0.689)	0.192	**< 0.001**	> 1.26	32.7 (19.9 - 47.5)	94.6 (85.1 - 98.9)
Inferior parietal	0.650 (0.540 - 0.760)	**0.008**	**< 0.001**	> 1.31	42.9 (28.8 - 57.8)	94.6 (85.1 - 98.9)
Precuneus	0.610 (0.497 - 0.723)	0.052	**< 0.001**	> 1.29	46.9 (32.5 - 61.7)	85.7 (73.8 - 93.6)
Occipital	0.607 (0.493 - 0.722)	0.059	**< 0.001**	> 1.23	40.8 (27.0 - 55.8)	92.9 (82.7 - 98.0)
Superior temporal	0.686 (0.580 - 0.792)	**0.001**	**< 0.001**	> 1.22	45.5 (30.4 - 61.2)	94.3 (82.7 - 99.4)
Middle temporal	0.778 (0.681 - 0.875)	**< 0.001**	0.060	> 1.30	63.6 (47.8 - 77.6)	94.3 (82.7 - 99.4)
Inferior temporal	0.786 (0.692 - 0.881)	**< 0.001**	0.056	> 1.31	65.3 (50.4 - 78.3)	91.1 (80.4 - 97.0)
Entorhinal	0.835 (0.752 - 0.918)	**< 0.001**	-	> 1.41	73.5 (58.9 - 85.1)	85.7 (73.8 - 93.6)
Parahippocampal	0.802 (0.709 - 0.896)	**< 0.001**	0.076	> 1.32	67.4 (52.5 - 80.1)	91.1 (80.4 - 97.0)
Amygdala	0.814 (0.725 - 0.904)	**< 0.001**	0.222	> 1.51	65.3 (50.4 - 78.3)	94.6 (85.1 - 98.9)
Posterior cingulate	0.641 (0.530 - 0.752)	**0.013**	**< 0.001**	> 1.32	49.0 (34.4 - 63.7)	85.7 (73.8 - 93.6)

*P-value for the comparison of AUC between each region and 0.5 for null hypothesis, **P-value for comparison of AUC between each region and the entorhinal cortex

Abbreviations: MCI = mild cognitive impairment, AUC = area under the curve

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB-No 3-2014-0286).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restriction.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

HC contributed to conceptualization of the study, collection and assembly of data, data analysis and drafting. MSB contributed to data analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. HSL, JYC, JHL, and YHR contributed to collection and assembly of data, statistical analyses, and interpretation of data. CHL contributed to the conceptualization of the study, interpretation of data, critical revision of the manuscript for important intellectual content, and supervision. All authors read and approved the final manuscript.

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