The correlation of neuropsychological evaluation with ^{11}C-PiB and ^{18}F-FC119S amyloid PET in mild cognitive impairment and Alzheimer disease

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Abstract

For the diagnosis of mild cognitive impairment (MCI) and Alzheimer disease (AD), variable neuroimaging and neuropsychological tests have been used. We aimed to evaluate the correlation of neuropsychological domain with new amyloid positron emission tomography (PET) study and to validate the availability of new PET tracer.

We enrolled 20 patients who underwent ^{11}C-PiB-PET/CT, new PET tracer ^{18}F-FC119S PET/CT from November, 2014 to July, 2015. Among them, 10 patients were diagnosed with AD and 10 patients with MCI. The current version of Seoul Neuropsychological Screening Battery (SNSB) II was performed for cognitive evaluation. Each parameter of SNSB was compared between 2 patient groups. Spearman correlation analysis between value of SNSB domain and standardized uptake value ratio (SUVR) of PET was also performed.

The AD group presented significant poor z-score in Korean-Boston Naming Test(K-BNT) ($P = .01$),copy score of Rey Complex Figure Test (RCFT) ($P = .049$), immediate ($P = .028$)and delayed memory of Seoul Verbal Learning Test (SVLT) ($P = .028$), recognition of RCFT ($P = .004$), "animal" of Controlled Oral Word Association Test (COWAT) ($P = .041$), color reading of Korean-Color Word Stroop test (K-CWST) ($P = .014$), and Digit Symbol Coding (DSC) ($P = .007$) compared with MCI group. That means, except attention domain, all other cognitive domains were relatively impaired in AD compared with MCI. In correlation analysis, we found that poor performances on copy score of RCFT in MCI groups were associated with great beta amyloid burden in frontal area in both ^{11}C-PiB-PET/CT and ^{18}F-FC119S PET/CT. In AD group, ^{18}F-FC119S PET presented more extensive correlation in each cognitive domain with multiple cortical areas compared with ^{11}C-PiB-PET.

The degree of amyloid burden assessed on ^{18}F-FC119S PET was significantly correlated with neuropsychological test in AD, and also MCI patients. The combination of neuropsychological evaluation with novel ^{18}F-FC119S PET/CT can be used for valid biomarker for MCI and AD.

Abbreviations: ^{11}C-PiB = ^{11}C-Pittsburgh compound B, AD = Alzheimer disease, Aß = beta amyloid, B-ADL = Barthel-activities of daily living, CDR = Clinical Dementia Rating, CDT = Clock Drawing Test, COWAT = Controlled Oral Word Association Test, CR = color reading, DSC = Digit Symbol Coding, DST = Digit Span Test, K-BNT = Korean-Boston Naming Test, K-CWST = Korean-Color Word Stroop test, K-IADL = Korean-Instrumental Activities of Daily Living, K-MMSE = Korean-Mini Mental State Examination, MCI = mild cognitive impairment, PET = positron emission tomography, RCFT = Rey Complex Figure Test, SNSB = Seoul Neuropsychological Screening Battery, SPECT = single-photon emission computed tomography, SUVR = standardized uptake value ratio, SVLT = Seoul Verbal Learning Test.

Keywords: ^{18}F-FC119S PET, Alzheimer disease, amyloid positron emission tomography, mild cognitive impairment, Seoul Neuropsychological Screening Battery

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1. Introduction

Alzheimer disease (AD) is the most common type of dementia, and progressive neurodegenerative disease characterized by cognitive dysfunction and daily activity impairment.[1] Definite diagnosis of AD could only be made by post-mortem neuropathological analysis. The pathologic hallmarks of AD have been known to be deposition of neurofibrillary tangles and beta amyloid (Aß) plaques.[1,2] On the contrary, mild cognitive impairment (MCI) is characterized by cognitive dysfunction with relatively preserved activities of daily living and without dementia.[3] MCI patients tend to progress to AD at a rate of 10% to 15% per year,[4,5] but some of the patients still remain stable.[6] Many studies have been described about risk factors for dementia, such as age, sex, hippocampus, or medial temporal area reduction[7,8]; however, the risk factors for this progression and definite clinical predictive markers have not been fully evaluated.

At present, dementia has become a major healthcare problem. One meta-analysis of epidemiological studies of dementia in South Korea showed that the prevalence of AD was 5.7% and vascular dementia was 2.1%, indicating that AD was the most prevalent type in Korea.[9] As dementia inevitably leads to significant increase in economic and social burden, early diagnosis and disease modification of high-risk MCI would be important in clinical practice.

Until now, the variable neuroimaging and neuropsychological tests have been studied for the diagnosis and prediction of progress in MCI and AD patients. Cognitive evaluation using neuropsychological test has performed a crucial role in diagnosis of dementia and MCI. It is useful in differentiation of MCI subtypes and is cost-effective in diagnosis of AD.[10] The Seoul Neuropsychological Screening Battery (SNSB) is one of the most commonly used neuropsychological test in South Korea.[11] This battery is composed of 5 cognitive domains: attention, language, memory, visuospatial, and frontal/executive functions.[11] It is a reliable and valid test which may take 1.5 to 2 hours to complete. The current version of SNSB (SNSB II) analyzes the 45 to 90-year-old criteria. It based on nationwide large Korean sample (1100 people), and the continuous data values were converted to z-score which were standardized with educational level and age.[12,13] A z-score < -1 presents an abnormal value by SNSB II criteria.[13] Additionally, SNSB II includes Korean-Mini Mental State Examination (K-MMSE), Clinical Dementia Rating (CDR), Korean-Instrumental Activities of Daily Living (K-IADL), and Barthel-Activities of Daily Living (B-ADL).

In addition to neuropsychological test, imaging of brain Aß using positron emission tomography (PET) also has been widely used for early identification of AD, and differentiation AD from non-AD patients.[14] ^{11}C-Pittsburgh compound B (PiB) is the first amyloid imaging, which showed significant retention in brain of AD patients.[1,14] Also, ^{11}C-PiB-PET appeared to positive in 50% to 60% of MCI subjects.[1] However, short radioactive half-life has been the major limitation of ^{11}C-PiB PET, preventing its widespread use, and therefore, other ^{18}F-labeled PET tracers have been developed.[2] Among them, ^{18}F-FC119S was introduced as a new Aß PET tracer which showed excellent binding affinity for synthetic Aß$_{1-42}$ aggregates and rapid clearance in preclinical study.[15] In the previous study with 10 MCI and 10 AD patients, we showed that the cortical uptakes of ^{18}F-FC119S were significantly correlated with those of ^{11}C-PiB-PET/CT, and so this new PET tracer can be effectively available for Aß imaging with longer radioactive half-lives.[2] However, except for imaging

comparison of ^{18}F-FC119S and ^{11}C-PiB-PET, comprehensive analysis of neuropsychological tests in MCI and AD patients has not been performed. For the widespread clinical application of novel PET tracer, correlation between novel PET tracer and current standard neuropsychological tests need to be defined.

This study aimed to evaluate the correlation between neuropsychological domain and new amyloid PET study in patients with MCI and AD, and to assess the potential as useful imaging biomarker for extensive clinical application.

2. Methods

2.1. Subjects

In the previous study,[2] 28 healthy controls, 10 patients with MCI, and 10 patients with AD were included. Among them, the datasets of 10 MCI and 10 AD patients were analyzed for present study. The inclusion criteria for MCI were as follows: aged 55 years or older; had objective cognitive impairment; and no disability in their daily activities.[16] The inclusion criteria for AD were as follows: aged 55 years or older with definite AD or probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association Alzheimer criteria.[2,17] The subjects with severe medical illnesses or other neurological disease were excluded. All subjects underwent a neuropsychological evaluation using SNSB II and were subjected to ^{11}C-PiB-PET/CT and ^{18}F-FC119S PET/CT. This study was approved by the Institutional Review Board of KIRAMS.

2.2. Neuropsychological assessment

The current version of SNSB (SNSB II) was used for neuropsychological evaluations. These batteries involve attention, language, memory, visuospatial, and frontal/executive functions.[11] Domain of memory function is composed of Seoul Verbal Learning Test (SVLT) (immediate, 20 minutes delayed recall, recognition) and the Rey Complex Figure Test (RCFT) (immediate, 20 minutes delayed recall, recognition). Domain of frontal/executive function includes motor impersistence, contrasting program, go-no-go, fist-edge-palm, alternating hand movement, alternating square and triangle, luria loop, Controlled Oral Word Association Test (COWAT), Korean-Color Word Stroop test (K-CWST), Digit Symbol Coding (DSC), and Korean-Trail Making test. Domain of language function includes Korean-Boston Naming Test (K-BNT), right-left orientation, and calculation. Domain of attention function includes Digit Span Test (DST), letter cancellation, and vigilance test. Domain of visuospatial function is composed of Clock Drawing Test (CDT) and RCFT. The continuous raw data values were converted to z-score, which were standardized with educational level and age. We analyzed these z-scores because the z-scores are elaborately defined and enable to minimize the effects of illiteracy.[18] Thus z-score allows precise comparative analysis between the various subjects. Additionally, K-MMSE and CDR were also evaluated.

2.3. Neuroimaging analysis

All patients underwent ^{11}C-PiB-PET/CT and ^{18}F-FC119S PET/CT within 3 months after the neuropsychological test.[2] Quantitative PET image analysis was performed to obtain the standardized uptake value (SUV) for each brain region including

frontal cortex, temporal cortex, parietal cortex, occipital cortex, anterior cingulate, posterior cingulated, and global SVUR.[2] SUV ratios (SUVRs) were calculated using cerebellar cortex as a reference region. The detail protocols were described in previous study.[2]

2.4. Statistical analysis

Demographics and clinical data of MCI and AD patients were compared using Mann-Whitney U test. Neuropsychological data of SNSB II adjusted by age and educational level were compared between MCI and AD patients using Mann-Whitney U test. The correlation between neuropsychological tests and SUVR of ^{11}C-PiB-PET/CT and ^{18}F-FC119S PET/CT was evaluated using Spearman correlation in each MCI and AD groups. Commercially available software program (SPSS ver 21.0, SPSS, Chicago, IL) was used for all analyses. The level of statistical significance was at $P < .05$.

3. Results

3.1. Clinical and neuropsychological results

Ten patients with MCI and 10 patients with AD were evaluated in this study. Demographic characteristics are summarized in Table 1. Age and sex showed no significant difference between MCI and AD patients. AD patients had significantly poorer K-MMSE and CDR than MCI patients. To analyze the differences in cognition between MCI and AD subjects, the comparison of neuropsychological data was performed. The values were presented as z-score. AD groups presented significant poorer z-score in K-BNT ($P = .01$), copy score of RCFT ($P = .049$), immediate ($P = .028$), and delayed memory of SVLT ($P = .028$), recognition of RCFT ($P = .004$), "animal" of COWAT ($P = .041$), and color reading of K-CWST ($P = .014$) and DSC ($P = .007$) (Table 2).

3.2. Correlations between the neuropsychological domain and PET

Table 3 showed correlation of neuropsychological domain with ^{11}C-PiB-PET/CT in patients with MCI and AD. In MCI groups, poor copy score of RCFT was associated with high SUVR in frontal cortex (Fig. 1). In AD groups, poor value of copy time of RCFT was associated with high SUVRs in frontal, temporal, parietal, occipital, anterior cingulate, posterior cingulate, and global area. Also, recognition of SVLT and RCFT showed negative correlation with SUVRs of frontal cortex in AD patients. Also, immediate memory of RCFT and recognition of SVLT showed negative correlation with SUVRs of global area in AD

Table 1

Demographic and clinical data of MCI and AD subjects.

Parameter	MCI (n = 10)	AD (n = 10)	P
Age (y, mean ± SD)	72.3 ± 8.0	73.5 ± 9.3	.570
Sex (M:F)	3:7	3:7	1.000
K-MMSE (mean ± SD)	26.8 ± 1.8	17.1 ± 7.6	*.001*
CDR (mean ± SD)	0.5 ± 0.0	1.20 ± 0.95	*.030*

AD = Alzheimer disease, CDR = Clinical Dementia Rating, K-MMSE = Korean-Mini Mental State Examination, MCI = mild cognitive impairment.
The bold italic data means statistically significant $P < .05$.

Table 2

Neuropsychological data of MCI and AD subjects.

		MCI (n = 10)	AD (n = 10)	P
Attention				
Digit span	Forward	2.03 ± 0.79	0.91 ± 2.17	.427
Digit span	Backward	0.53 ± 1.86	−1.14 ± 2.30	.140
Language				
K-BNT		−0.20 ± 1.71	−3.08 ± 2.98	*.010*
Visuospatial				
RCFT	Copy score	0.30 ± 1.11	−3.18 ± 4.30	*.049*
RCFT	Copy time	0.03 ± 0.65	−0.56 ± 2.25	1.000
Memory				
SVLT	Immediate	−0.99 ± 0.91	−2.23 ± 1.25	*.028*
SVLT	Delayed	−1.47 ± 0.79	−2.28 ± 0.63	*.028*
SVLT	Recognition	−1.26 ± 1.83	−2.66 ± 1.52	.112
RCFT	Immediate	−0.60 ± 1.64	−1.45 ± 0.83	.212
RCFT	Delayed	−0.66 ± 1.85	−1.49 ± 0.99	.241
RCFT	Recognition	−0.49 ± 1.69	−2.90 ± 1.32	*.004*
Frontal/executive				
COWAT	Animal	−0.78 ± 0.84	−1.84 ± 1.69	*.041*
COWAT	Supermarket	−0.39 ± 1.22	−1.42 ± 1.29	.059
COWAT	ㄱ	−0.86 ± 0.72	−1.30 ± 0.94	.344
	ㅇ	−0.64 ± 0.96	−1.30 ± 0.99	.162
	ㅅ	−0.37 ± 0.81	−1.27 ± 1.01	.054
	Phonemic	−0.73 ± 0.85	−1.52 ± 1.16	.140
K-CWST	CR	0.30 ± 1.31	−2.00 ± 1.90	*.014*
DSC		0.00 ± 1.26	−1.94 ± 1.54	*.007*

P value was determined by using Mann-Whitney U test.
AD = Alzheimer disease, COWAT = Controlled Oral Word Association Test, CR = color reading, DSC = Digit Symbol Coding, K-BNT = Korean-Boston Naming Test, K-CWST = Korean-Color Word Stroop Test, MCI = mild cognitive impairment, RCFT = Rey Complex Figure Test, SVLT = Seoul Verbal Learning Test.
The bold italic data means statistically significant $P < .05$.

groups. Significant correlations were not observed with other neuropsychological values.

Table 4 showed correlation of neuropsychological domain in SNSB with ^{18}F-FC119S PET/CT. In MCI groups, copy score of RCFT showed significant negative correlation with SUVR of frontal cortex (Fig. 2), which presents similar results with ^{11}C-PiB-PET/CT. The poor value of tests including K-BNT, immediate memory of RCFT, "ㄱ" of COWAT were also associated with high SUVRs in frontal cortex in MCI. In AD group, ^{18}F-FC119S PET presented more extensive correlations of cognitive domains with many cortical areas including frontal, temporal, parietal, anterior cingulate, and posterior cingulate areas compared with ^{11}C-PiB-PET.

4. Discussion

This study was conducted to explore association between cognitive function and anatomical lesion on new amyloid PET, and to assess the potential as useful biomarker for extensive clinical application in MCI and AD patients. To our knowledge, this is the first study to analyze the correlation between novel ^{18}F-FC119S PET and detail cognitive function.

Our previous study suggested that[18]F-FC119S might be appropriate for imaging Aß.[2] The uptake of ^{18}F-FC119S was significantly correlated with that of ^{11}C-PiB-PET/CT. Although ^{18}F-FC119S has shown the potential for imaging biomarker of MCI and dementia, correlation between this new PET tracer and cognitive function has yet to be determined. We present here the correlation between novel PET tracer and current standard

Table 3

Correlations between SUVRs of ^{11}C-PiB and neuropsychological tests in MCI and AD patients.

^{11}C-PiB

Cognitive domain			Frontal cortex MCI	Frontal cortex AD	Temporal cortex MCI	Temporal cortex AD	Parietal cortex MCI	Parietal cortex AD	Occipital cortex MCI	Occipital cortex AD	Anterior cingulate MCI	Anterior cingulate AD	Posterior cingulate MCI	Posterior cingulate AD	Global MCI	Global AD
Attention	Digit span	Forward	−0.061 (0.868)	−0.321 (0.365)	0.371 (0.291)	−0.321 (0.365)	0.006 (0.987)	−0.079 (0.829)	0.620 (0.056)	−0.139 (0.701)	0.097 (0.789)	−0.321 (0.365)	0.000 (1.000)	−0.115 (0.751)	−0.067 (0.834)	−0.200 (0.580)
	Digit span	Backward	−0.073 (0.841)	−0.248 (0.489)	−0.395 (0.258)	−0.248 (0.489)	0.091 (0.802)	−0.030 (0.934)	0.146 (0.688)	−0.164 (0.651)	0.134 (0.713)	−0.224 (0.533)	0.109 (0.763)	−0.018 (0.960)	−0.018 (0.960)	−0.152 (0.676)
Language	K-BNT		−0.340 (0.293)	−0.042 (0.907)	−0.297 (0.405)	−0.030 (0.934)	−0.091 (0.803)	0.200 (0.580)	−0.358 (0.310)	0.018 (0.960)	0.091 (0.803)	−0.030 (0.934)	0.018 (0.960)	0.164 (0.651)	−0.067 (0.855)	0.067 (0.855)
Visuospatial	RCFT	Copy score	**−0.661 (0.038)**	**−0.648 (0.043)**	−0.139 (0.701)	−0.188 (0.603)	−0.467 (0.174)	−0.152 (0.676)	−0.467 (0.174)	−0.152 (0.676)	−0.212 (0.556)	−0.079 (0.829)	−0.321 (0.365)	−0.018 (0.960)	−0.394 (0.260)	−0.188 (0.603)
	RCFT	Copy time	0.079 (0.829)	−0.413 (0.235)	−0.333 (0.347)	**−0.758 (0.011)**	0.188 (0.603)	**−0.770 (0.009)**	0.115 (0.751)	**−0.782 (0.008)**	−0.079 (0.829)	**−0.782 (0.008)**	−0.042 (0.907)	**−0.855 (0.002)**	−0.006 (0.987)	**−0.782 (0.008)**
Memory	SVLT	Immediate	−0.333 (0.347)	0.552 (0.098)	−0.103 (0.777)	−0.292 (0.413)	0.042 (0.907)	−0.134 (0.713)	0.200 (0.580)	−0.286 (0.424)	0.067 (0.855)	−0.195 (0.590)	−0.030 (0.934)	−0.109 (0.763)	−0.139 (0.701)	−0.261 (0.466)
	SVLT	Delayed	−0.224 (0.533)	−0.224 (0.533)	−0.042 (0.907)	−0.576 (0.082)	0.115 (0.751)	−0.539 (0.108)	−0.236 (0.511)	−0.576 (0.082)	0.018 (0.960)	−0.467 (0.174)	−0.006 (0.960)	−0.467 (0.174)	−0.030 (0.934)	−0.624 (0.054)
	SVLT	Recognition	−0.321 (0.365)	−0.321 (0.365)	−0.018 (0.960)	−0.042 (0.907)	−0.091 (0.803)	−0.515 (0.128)	−0.079 (0.829)	−0.624 (0.054)	−0.333 (0.347)	−0.491 (0.150)	−0.370 (0.293)	−0.442 (0.200)	−0.261 (0.467)	**−0.636 (0.048)**
	RCFT	Immediate	−0.333 (0.347)	**−0.685 (0.029)**	−0.224 (0.533)	−0.576 (0.082)	0.030 (0.934)	−0.515 (0.128)	−0.248 (0.489)	−0.576 (0.082)	0.030 (0.934)	−0.442 (0.200)	−0.067 (0.855)	−0.588 (0.074)	−0.067 (0.855)	**−0.648 (0.043)**
	RCFT	Delayed	**−0.636 (0.048)**	−0.612 (0.060)	0.212 (0.556)	−0.624 (0.054)	−0.345 (0.328)	−0.588 (0.074)	−0.394 (0.260)	−0.564 (0.090)	−0.455 (0.187)	−0.503 (0.138)	−0.527 (0.117)	−0.564 (0.090)	−0.479 (0.855)	−0.612 (0.060)
	RCFT	Recognition	−0.394 (0.260)	−0.600 (0.067)	0.103 (0.777)	0.042 (0.907)	−0.200 (0.580)	−0.515 (0.128)	0.258 (0.425)	−0.564 (0.090)	−0.115 (0.751)	−0.539 (0.108)	−0.224 (0.533)	−0.442 (0.200)	−0.285 (0.425)	−0.612 (0.060)
Frontal/executive	COWAT	Animal	−0.042 (0.907)	**−0.648 (0.043)**	0.127 (0.726)	0.042 (0.907)	0.345 (0.328)	0.212 (0.556)	0.345 (0.328)	0.091 (0.803)	0.152 (0.676)	−0.067 (0.855)	0.103 (0.777)	0.139 (0.701)	0.055 (0.881)	0.127 (0.726)
	COWAT	Supermarket	0.127 (0.726)	−0.503 (0.138)	0.127 (0.726)	−0.430 (0.214)	0.418 (0.229)	−0.261 (0.467)	0.467 (0.174)	−0.370 (0.293)	0.212 (0.556)	−0.370 (0.293)	0.176 (0.627)	−0.236 (0.511)	0.164 (0.651)	−0.382 (0.276)
	COWAT	ㄱ	−0.297 (0.405)	−0.418 (0.229)	−0.103 (0.777)	−0.358 (0.310)	0.006 (0.987)	−0.273 (0.446)	−0.115 (0.751)	−0.309 (0.385)	0.127 (0.726)	−0.285 (0.425)	0.055 (0.881)	−0.164 (0.651)	−0.042 (0.907)	−0.333 (0.347)
	COWAT	ㅇ	0.188 (0.603)	−0.479 (0.162)	0.042 (0.907)	−0.442 (0.200)	0.467 (0.174)	−0.382 (0.276)	0.091 (0.803)	−0.418 (0.229)	0.527 (0.117)	−0.345 (0.328)	0.503 (0.138)	−0.273 (0.446)	0.442 (0.200)	−0.442 (0.200)
	COWAT	ㅅ	0.248 (0.489)	−0.442 (0.200)	0.297 (0.405)	−0.406 (0.244)	0.297 (0.405)	−0.285 (0.425)	0.370 (0.293)	−0.394 (0.260)	0.455 (0.187)	−0.345 (0.328)	0.467 (0.174)	−0.212 (0.556)	0.382 (0.276)	−0.382 (0.276)
	COWAT	Phonemic	0.176 (0.627)	−0.406 (0.244)	0.261 (0.467)	−0.345 (0.328)	0.370 (0.293)	−0.261 (0.467)	0.236 (0.511)	−0.321 (0.365)	0.491 (0.150)	−0.273 (0.446)	0.467 (0.174)	−0.152 (0.676)	0.406 (0.244)	−0.321 (0.365)
	K-CWST	CR	−0.418 (0.229)	−0.285 (0.425)	−0.091 (0.803)	−0.236 (0.511)	−0.067 (0.855)	−0.103 (0.777)	0.248 (0.489)	−0.212 (0.556)	−0.030 (0.934)	−0.212 (0.556)	−0.127 (0.726)	−0.091 (0.803)	−0.261 (0.467)	−0.212 (0.556)
	DSC		−0.539 (0.108)	−0.564 (0.090)	0.006 (0.987)	−0.564 (0.090)	−0.309 (0.385)	−0.418 (0.229)	0.152 (0.676)	−0.418 (0.229)	−0.127 (0.726)	−0.515 (0.128)	−0.224 (0.533)	−0.358 (0.310)	−0.388 (0.310)	−0.503 (0.138)

P value of Spearman correlation coefficient is given in parenthesis.

^{11}C-PiB = ^{11}C-Pittsburgh compound B, AD = Alzheimer disease, COWAT = Controlled Oral Word Association Test, CR = color reading, DSC = Digit Symbol Coding, K-BNT = Korean-Boston Naming Test, K-CWST = Korean-Color Word Stroop Test, MCI = mild cognitive impairment, RCFT = Rey Complex Figure Test, SVLT = Seoul Verbal Learning Test.
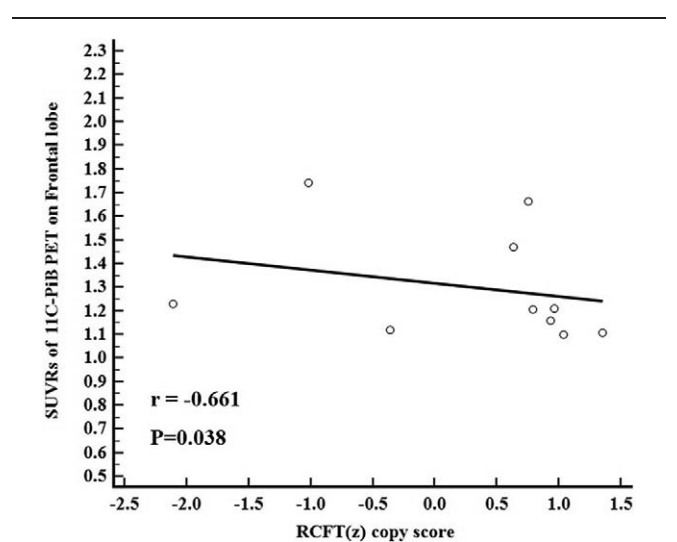

Figure 1. Scatter-plot shows significant negative correlation between SUVR of ^{11}C-PiB-PET on frontal lobe and copy score of RCFT.

r = −0.661
P = 0.038

neuropsychological tests in Korea for widespread clinical application based on the results of previous study.

In our study, the new Aß PET tracer, ^{18}F-FC119S PET, showed similar correlation with ^{11}C-PiB-PET in several cognitive tests, and uptakes in amyloid PET was significantly correlated with cognitive domain in neuropsychological test.

Many neuropsychological tests contribute to the detection and differentiation of AD from normal aging or other types of dementia and MCI. In our neuropsychological analysis, AD patients had significantly poorer K-MMSE and CDR than MCI patients. The comparison of subsets of SNSB showed that language (K-BNT), visuospatial (copy score of RCFT), memory (immediate and delayed memory of SVLT, recognition of RCFT), frontal/executive (COWAT [animal], K-CWST [color reading], DSC) domains were significantly impaired in the AD group compared with the MCI group; that is, except attention, all other cognitive domains were relatively impaired in the AD group.

Many studies have presented that AD patients showing impaired episodic memory may be due to ineffective consolidation.[19] Also, patients with AD present visuospatial dysfunction even in early preclinical stage and mild AD.[19,20] Early-onset AD patients performed poorly on forward, backward digit, visual spans, visual counting, and Rey complex figure test, which suggested poor attention and visuospatial function.[21] Our results are in agreement with these reports which showed specific cognitive dysfunction in AD patients.[19–21]

Neuropsychological dysfunction in MCI is also common. One meta-analysis showed that verbal memory and many language testes had high predictive accuracy in predicting progression from MCI to AD, and executive functions and visual memory had better specificity.[22]

In correlation analysis using ^{11}C-PiB-PET, we found that in MCI patients, poor performance on copy score of RCFT was associated with great Aß burden in frontal area. The new Aß PET tracer, ^{18}F-FC119S PET, showed similar correlation with ^{11}C-PiB-PET in this cognitive test. That means, in MCI patients, the visuospatial function was commonly associated with degree of Aß burden in frontal area. In AD groups, copy time of RCFT showed negative correlation with SUVRs in frontal, temporal, parietal, occipital, anterior cingulate, posterior cingulate, and

Figure 2. Scatter-plot shows significant negative correlation between SUVR of ¹⁸F-FC119S-PET on frontal lobe and copy score of RCFT.

global area using ¹¹C-PiB-PET. However, ¹⁸F-FC119S PET presented more extensive correlations of each cognitive domain with cortical areas in AD compared with ¹¹C-PiB-PET. However, in advanced stage of dementia, specific cognitive domain boundaries can be obscured, so neuropsychological study is most useful in early stage of disease.[19]

There have been many studies about correlation of neuropsychological characteristics with brain imaging including PET, MR, and single-photon emission computed tomography (SPECT) in MCI and AD patients. One study reported that amnestic MCI had early amyloid deposition in precuneus, frontal, and posterior cingulate areas in ¹⁸F-AV-45 PET.[23] MCI patients showed poor visuospatial memory and atrophy in frontal and mediotemporal areas compared with normal group.[24] The low blood flow of the left frontal area and cognitive test of orientation in MCI patients were good predictive factors for risk of developing dementia.[8] It is not simple to decide which area performs dominant role in cognition because complex brain networks are involved in cognitive function. Because the amyloid burden of MCI and AD patients can affect the neuropsychological function, the degree of cortical uptake can be predictive factor of the severity of cognitive dysfunction.

This study has some limitations. The sample size of patients was small and diagnosis of patients was performed by clinical criteria. Also, we did not subdivide the MCI group into amnestic and nonamnestic MCI. Future studies including a larger number of patients in multicenter could be helpful to verify our results.

5. Conclusions

In conclusions, the degree of amyloid burden assessed on ¹⁸F-FC119S PET was significantly correlated with neuropsychological test in AD as well as MCI patients, and which showed similar results with ¹¹C-PiB-PET. So, considering good clinical utility of new Aß tracer, ¹⁸F-FC119S would be a candidate PET imaging biomarker in MCI and AD.

Author contributions

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Table 4

Correlations between SUVRs of ¹⁸F-FC119S and neuropsychological tests in MCI and AD patients.

¹⁸F-FC119S Cognitive domain			Frontal cortex MCI	Frontal cortex AD	Temporal cortex MCI	Temporal cortex AD	Parietal cortex MCI	Parietal cortex AD	Occipital cortex MCI	Occipital cortex AD	Anterior cingulate MCI	Anterior cingulate AD	Posterior cingulate MCI	Posterior cingulate AD	Global MCI	Global AD
Attention	Digit span	Forward	0.225 (0.532)	−0.164 (0.651)	−0.267 (0.455)	−0.236 (0.511)	−0.267 (0.455)	−0.261 (0.467)	0.195 (0.590)	−0.212 (0.556)	0.462 (0.179)	−0.152 (0.676)	−0.024 (0.947)	−0.418 (0.229)	0.170 (0.638)	−0.200 (0.580)
	Digit span	Backward	−0.201 (0.578)	−0.333 (0.347)	0.377 (0.283)	0.055 (0.881)	0.377 (0.283)	−0.188 (0.603)	0.158 (0.663)	0.055 (0.881)	0.001 (0.999)	−0.127 (0.726)	0.511 (0.132)	−0.321 (0.365)	0.195 (0.590)	−0.127 (0.726)
Language	K-BNT		**−0.697 (0.025)**	−0.164 (0.651)	**−0.673 (0.033)**	0.200 (0.580)	−0.055 (0.881)	0.018 (0.960)	**−0.661 (0.038)**	0.152 (0.676)	−0.358 (0.310)	0.006 (0.987)	0.042 (0.907)	−0.164 (0.651)	−0.576 (0.082)	0.042 (0.907)
Visuospatial	RCFT	Copy score	**−0.673 (0.033)**	**−0.648 (0.043)**	−0.612 (0.060)	−0.200 (0.528)	−0.467 (0.174)	−0.382 (0.276)	**−0.685 (0.029)**	−0.212 (0.556)	−0.236 (0.511)	−0.285 (0.425)	−0.200 (0.580)	−0.406 (0.244)	**−0.745 (0.013)**	−0.418 (0.229)
	RCFT	Copy time	0.321 (0.365)	−0.442 (0.200)	0.394 (0.260)	−0.297 (0.405)	0.224 (0.533)	−0.455 (0.187)	0.297 (0.405)	−0.394 (0.260)	0.091 (0.803)	**0.661 (0.038)**	0.297 (0.405)	−0.479 (0.162)	0.479 (0.162)	−0.442 (0.200)
Memory	SVLT	Immediate	−0.309 (0.385)	−0.377 (0.283)	−0.297 (0.405)	−0.140 (0.700)	0.188 (0.603)	−0.353 (0.318)	−0.273 (0.446)	−0.030 (0.934)	0.030 (0.934)	−0.164 (0.650)	−0.067 (0.855)	−0.432 (0.213)	−0.152 (0.676)	−0.213 (0.555)
	SVLT	Delayed	−0.394 (0.260)	**−0.794 (0.006)**	−0.479 (0.162)	−0.491 (0.150)	0.248 (0.489)	**−0.685 (0.029)**	−0.539 (0.108)	−0.345 (0.328)	−0.333 (0.347)	**−0.733 (0.016)**	−0.018 (0.960)	**−0.709 (0.022)**	−0.479 (0.162)	−0.624 (0.054)
	SVLT	Recognition	−0.285 (0.425)	−0.624 (0.054)	−0.152 (0.676)	−0.297 (0.405)	−0.188 (0.603)	**−0.636 (0.048)**	−0.236 (0.511)	−0.285 (0.425)	−0.248 (0.489)	−0.382 (0.276)	−0.212 (0.556)	−0.576 (0.082)	−0.236 (0.162)	−0.503 (0.138)
	RCFT	Immediate	**−0.673 (0.033)**	**−0.782 (0.008)**	−0.612 (0.060)	**−0.661 (0.038)**	−0.006 (0.987)	**−0.758 (0.011)**	−0.600 (0.067)	−0.370 (0.293)	−0.491 (0.150)	**−0.794 (0.006)**	−0.127 (0.726)	**−0.770 (0.009)**	**−0.636 (0.048)**	**0.648 (0.043)**
	RCFT	Delayed	**−0.636 (0.048)**	**−0.745 (0.013)**	−0.515 (0.128)	−0.539 (0.108)	−0.333 (0.347)	**−0.661 (0.038)**	−0.612 (0.060)	−0.333 (0.347)	−0.491 (0.150)	**−0.794 (0.006)**	−0.067 (0.855)	**−0.758 (0.011)**	−0.576 (0.082)	−0.576 (0.082)
	RCFT	Recognition	0.067 (0.855)	−0.624 (0.054)	−0.030 (0.934)	−0.261 (0.467)	0.430 (0.214)	−0.600 (0.067)	−0.030 (0.934)	0.430 (0.214)	0.297 (0.405)	−0.455 (0.187)	0.236 (0.511)	−0.552 (0.098)	−0.200 (0.580)	−0.430 (0.214)
Frontal/executive	COWAT	Animal	−0.055 (0.881)	−0.079 (0.829)	−0.079 (0.829)	0.491 (0.150)	0.430 (0.214)	0.285 (0.425)	0.261 (0.467)	−0.103 (0.777)	0.030 (0.934)	−0.091 (0.803)	0.321 (0.365)	0.115 (0.751)	0.018 (0.960)	0.309 (0.385)
	COWAT	Supermarket	−0.067 (0.855)	−0.576 (0.082)	0.055 (0.881)	−0.139 (0.701)	0.527 (0.117)	−0.406 (0.244)	−0.406 (0.244)	−0.030 (0.934)	0.042 (0.907)	−0.382 (0.276)	0.006 (0.987)	−0.515 (0.128)	0.224 (0.533)	−0.321 (0.365)
	COWAT	ㄱ	**0.697 (0.025)**	−0.564 (0.090)	−0.588 (0.074)	−0.067 (0.855)	−0.018 (0.960)	−0.370 (0.293)	−0.103 (0.777)	−0.067 (0.855)	−0.321 (0.365)	−0.273 (0.446)	0.455 (0.187)	−0.370 (0.293)	−0.527 (0.117)	−0.297 (0.405)
	COWAT	ㅇ	−0.309 (0.385)	−0.588 (0.074)	−0.224 (0.533)	−0.164 (0.651)	0.467 (0.174)	−0.479 (0.162)	0.042 (0.907)	−0.042 (0.907)	−0.055 (0.881)	−0.321 (0.365)	0.515 (0.128)	−0.430 (0.214)	−0.042 (0.907)	−0.370 (0.293)
	COWAT	ㅅ	0.200 (0.580)	−0.467 (0.174)	0.309 (0.385)	0.006 (0.987)	0.552 (0.098)	−0.345 (0.328)	0.321 (0.365)	−0.042 (0.907)	0.503 (0.138)	−0.200 (0.580)	0.309 (0.385)	−0.333 (0.347)	0.042 (0.907)	−0.261 (0.467)
	COWAT	Phonemic	−0.164 (0.651)	−0.515 (0.128)	−0.042 (0.907)	−0.18 (0.960)	0.418 (0.229)	−0.333 (0.347)	0.042 (0.907)	−0.139 (0.701)	0.176 (0.627)	−0.200 (0.580)	0.261 (0.467)	−0.430 (0.214)	−0.115 (0.751)	−0.273 (0.446)
	K-CWST	CR	−0.176 (0.627)	−0.576 (0.082)	−0.200 (0.580)	−0.091 (0.803)	0.164 (0.651)	−0.297 (0.405)	−0.236 (0.511)	−0.152 (0.676)	0.152 (0.676)	−0.358 (0.310)	0.309 (0.385)	−0.576 (0.082)	−0.236 (0.511)	−0.309 (0.385)
	DSC		−0.127 (0.726)	**−0.648 (0.043)**	−0.127 (0.726)	−0.273 (0.446)	−0.285 (0.425)	−0.527 (0.117)	−0.285 (0.425)	−0.152 (0.676)	0.273 (0.446)	−0.503 (0.138)	0.261 (0.467)	−0.576 (0.082)	−0.236 (0.511)	−0.430 (0.214)

P value of Spearman correlation coefficient is given in parenthesis.

AD = Alzheimer disease, COWAT = Controlled Oral Word Association Test, CR = color reading, DSC = Digit Symbol Coding, K-BNT = Korean-Boston Naming Test, K-CWST = Korean-Color Word Stroop Test, MCI = mild cognitive impairment, RCFT = Rey Complex Figure Test, SVLT = Seoul Verbal Learning Test.
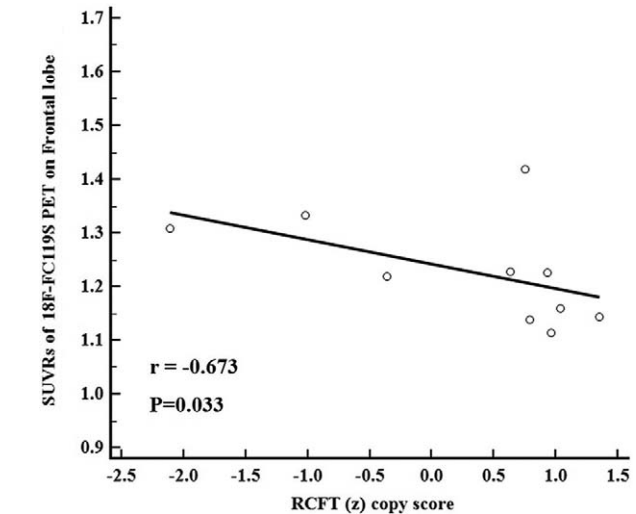
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