

## Amyloid PET and Voxel-based Morphometry Analysis Using MRI in Mild Cognitive Impairment and Alzheimer's Disease

著者	Waragai M., Okamura N., Furukawa K., Tashiro M., Watanuki S., Furumoto S., Funaki Y., Kato M., Iwata R., Yanai K., Kudo Y., Arai H.
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## VIII. 2. Amyloid PET and Voxel-based Morphometry Analysis Using MRI in Mild Cognitive Impairment and Alzheimer's Disease

Waragai M.<sup>1</sup>, Okamura N.<sup>2</sup>, Furukawa K.<sup>1</sup>, Tashiro M.<sup>3</sup>, Watanuki S.<sup>3</sup>, Furumoto S.<sup>2,4</sup>, Funaki Y.<sup>5</sup>, Kato M.<sup>2</sup>, Iwata R.<sup>5</sup>, Yanai K.<sup>2</sup>, Kudo Y.<sup>6</sup>, and Arai H.<sup>1</sup>

<sup>1</sup>Department of Geriatrics and Gerontology, Division of Brain Sciences, Institute of Development, Aging and Cancer, Tohoku University,

<sup>2</sup>Department of Pharmacology, Tohoku University School of Medicine,

<sup>3</sup>Division of Cyclotron Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University,

<sup>4</sup>Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University,

<sup>5</sup>Division of Radiopharmaceutical Chemistry, Cyclotron and Radioisotope Center, Tohoku University,

<sup>6</sup>Innovation of New Biomedical Engineering Center, Tohoku University,

### Introduction

Currently, amyloid PET imaging using a tracer that binds to amyloid  $\beta$  (A $\beta$ ) fibrils can noninvasively and reliably assess A $\beta$  deposition and be applied as a biomarker for AD<sup>1)</sup>. Pittsburgh Compound-B (PIB) has been the most commonly used tracer for the amyloid PET imaging. Our group has recently developed a novel PET tracer, 2-(2-[2-demethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole (BF-227), and reported that this compound is able to finely detect A $\beta$  deposition primarily in the posterior association area of AD patients<sup>2,3)</sup>. It might be speculated that BF-227 detects neuritic plaques containing dense amyloid fibrils preferentially, compared to PIB-PET, and provides unique and specific information about the A $\beta$  pathology in AD patients<sup>2,3)</sup>.

It should be important to detect A $\beta$  deposition as early as possible in order to begin medication to prevent or treat cognitive decline before the symptoms of dementia become obvious because it is considered that deposition as well as aggregation of A $\beta$  starts much earlier before patients indicate symptoms of dementia<sup>2,3)</sup>.

On the other hand, it has been found that cognitive decline strongly correlates with cortical atrophy in AD supporting cortical degeneration as the primary basis for cognitive decline in AD<sup>4)</sup>. Thus, an increased rate of cerebral atrophy evaluated with MRI using voxel-based morphometry (VBM) is a diagnostic feature of AD that correlates with clinical stage/severity and is thought to represent the macroscopic consequences of neuronal

destruction<sup>5</sup>). However, it is still unclear the amounts of A $\beta$  deposition in the brain directly correlate with progression and brain atrophy because recent studies suggested that amyloid deposition in the brain reaches a plateau by the early stage of AD. Moreover, clearance of amyloid plaques in patients with AD using immunisation with A $\beta$ 42 did not prevent progressive neurodegeneration<sup>6</sup>. In this study, we studied comparison of amyloid-imaging PET using novel  $\beta$ -amyloid probe [<sup>11</sup>C]BF-227 and structural MRI analysis for the diagnosis and tracking the severity of AD.

## **Materials and Methods**

### ***Subjects***

Patients recruited in the present study included 12 normal age-matched controls, 13 subjects with amnesic MCI, and 15 patients with AD. Diagnoses of probable AD were based on criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease Related Disorders Association (NINCDS-ADRDA)<sup>7</sup>. The diagnosis of amnesic MCI was made according to the published criteria described previously<sup>8</sup>. The MCI subjects were divided into two groups, MCI converters (n=6) and MCI non-converters (n=7). The MCI converters were defined as patients who eventually developed AD within a mean follow-up of 27.0 $\pm$ 7.9 months (range 14–30 months). The MCI non-converters were defined as having a transient memory loss or remaining cognitively stable through at least a 2-year follow-up (27.7 $\pm$ 2.2 months; range 25–30 months). All subjects were screened using a questionnaire and medical history, and subjects with medical conditions potentially affecting the central nervous system were excluded. In addition, none of the subjects had asymptomatic cerebral infarction detected via T2-weighted MRI. The Committee on Clinical Investigation at Tohoku University School of Medicine and the Advisory Committee on Radioactive Substances at Tohoku University approved the study protocol.

### ***MRI methods***

All subjects underwent MRI with a 1.5 Tesla MR scanner (GE Signa Hispeed, Milwaukee, WI). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin axial sections using a vascular TOF SPGR sequence (echo time/repetition time, 2.4/50 ms; flip angle, 45 $^\circ$ ; acquisition matrix, 256 $\times$ 256; 1 excitation; field of view, 22 cm; slice thickness, 2.0 mm). Cerebral atrophy

was evaluated by voxel-based morphometry (VBM) implemented in the Voxel-Based Specific Regional Analysis System for AD (VSRAD) software developed by Matsuda et al<sup>9)</sup>. VSRAD software is an adjunctive diagnostic tool for early AD which can automatically analyze three dimensional T1-weighted MRI data as a series of segmentation, anatomical standardization and smoothing using SPM5, and Z-score analysis;  $Z\text{-score} = ([\text{control mean}] - [\text{individual value}]) / (\text{control S.D.})$  as previously reported by Minoshima et al. in a PET study [37]. The degree of the gray matter atrophy was calculated as ratio (%) of total area in which the Z score of the voxel is more than 2.0 to the whole brain.

### ***PET procedure***

Radiosynthesis of [<sup>11</sup>C]BF-227 and the procedure used for BF-227-PET were performed as described previously<sup>2)</sup>. BF-227 and its N-desmethylated derivative (a precursor of [<sup>11</sup>C]BF-227) were custom-synthesized by Tanabe R&D Service Co. [<sup>11</sup>C]BF-227 was synthesized from its precursor by N-methylation in dimethyl sulfoxide using [<sup>11</sup>C]methyl triflate. The [<sup>11</sup>C]BF-227 PET study was performed using a PET SET-2400W scanner (Shimadzu Inc., Japan). After an intravenous injection of 211-366 MBq [<sup>11</sup>C]BF-227, dynamic PET images were obtained for 60 min with the subject's eyes closed. Standardized uptake value (SUV) images of [<sup>11</sup>C]BF-227 were obtained by normalizing the tissue radioactivity concentration to the injected dose and body weight. ROIs were placed on individual axial MR images in the cerebellar hemisphere and the frontal, lateral temporal, parietal and posterior cingulate cortices. The ROI information was then copied onto the dynamic PET SUV images, and regional SUVs were sampled using Dr.View/LINUX software. The ratio of the regional to cerebellar SUV (SUVR) at 40-60 min post injection was calculated, and averaged SUVR values in the frontal, temporal, parietal and posterior cingulate cortices were considered representative of BF-227 retention in the neocortex (neocortical SUVR).

### ***Statistical analysis***

Statistical comparison of PET and MRI measurements in the four groups was performed via an analysis of variance followed by a Bonferroni multiple comparisons test with a significance level of  $p < 0.05$ . Statistical comparisons of age and MMSE scores in the four groups were performed using a Kruskal-Wallis test followed by a Dunn's multiple comparison test with a significance level of  $p < 0.05$ . Correlations between the MMSE score and BF-227 retention in the neocortex or the cerebral atrophy index were examined

using a non-parametric Spearman's rank correlation analysis. Correlations between the brain atrophy index and BF-227 retention were determined using Pearson's correlations. A linear model was applied to the data to obtain a correlation coefficient and *p* value. These analyses were performed using GraphPad Prism5 software (GraphPad, San Diego, CA).

## Results

Representative images of [<sup>11</sup>C]BF-227-PET and T1-weighted MRI in a normal control (70-year-old female, MMSE score 29), a MCI non-converter (76-year-old male, MMSE score 27), a MCI converter (85-year-old male, MMSE score 23), and an AD patient (62-year-old female, MMSE score 20) are shown in Figure 1.

We examined comparison of BF-227 SUVR in the neocortex (left) and the parahippocampal ROI value from gray matter MR images processed by SPM5 the percent global atrophy (right). Significant inter-group difference between the MCI-converter and the MCI-nonconverter was observed in the frontal and the average neocortical SUVR assayed by BF227-PET, but not in the percent global atrophy or parahippocampal ROI value obtained by VBM-MRI (Fig. 2).

Next, we analyzed the correlations of MMSE scores with the BF-227 SUVR in the neocortex (left), the percent global atrophy (middle), the parahippocampal region of interest (ROI) value from gray matter images processed by SPM5 (right). We observed a significant correlation only between the percent global atrophy and the MMSE score (Spearman  $r=-0.459$ ,  $p=0.036$ ). In contrast, no significant correlation was observed between the parahippocampal ROI from SPM5 and the MMSE (Spearman  $r=0.181$ ) or between the BF-227 SUVR in the neocortex and the MMSE (Spearman  $r=-0.200$ ). Finally, no significant correlation was observed between the BF-227 SUVR and the percent global atrophy or parahippocampal atrophy in the analysis of all subjects (Fig. 3).

## Discussion

In the present study, MCI converters were more clearly distinguished from MCI non-converters by BF-227 PET than by VBM-MRI. BF-227 PET achieved higher sensitivity and specificity in the discrimination between MCI converters and MCI non-converters than did VBM-MRI. Our results strongly suggest that amyloid imaging using BF-227 PET will be a useful tool to predict conversion from MCI to AD, as previously shown for PIB-PET<sup>1</sup>). However, cerebral gray matter loss as determined by VBM-MRI was better correlated with the clinical severity of AD than BF-227 PET. Used

together, BF-227 PET and VBM-MRI could be an effective method for the early diagnosis and severity tracking of AD.

We hope to explore the relationship between these imaging measurements and the impairment of episodic memory function in a future study. Additional longitudinal studies are also needed to confirm the findings we have obtained and to examine the time course of AD, including changes in the pre-symptomatic subjects, and to determine the relationship between amyloid deposition and brain atrophy as underlying factors in the pathogenesis of AD.

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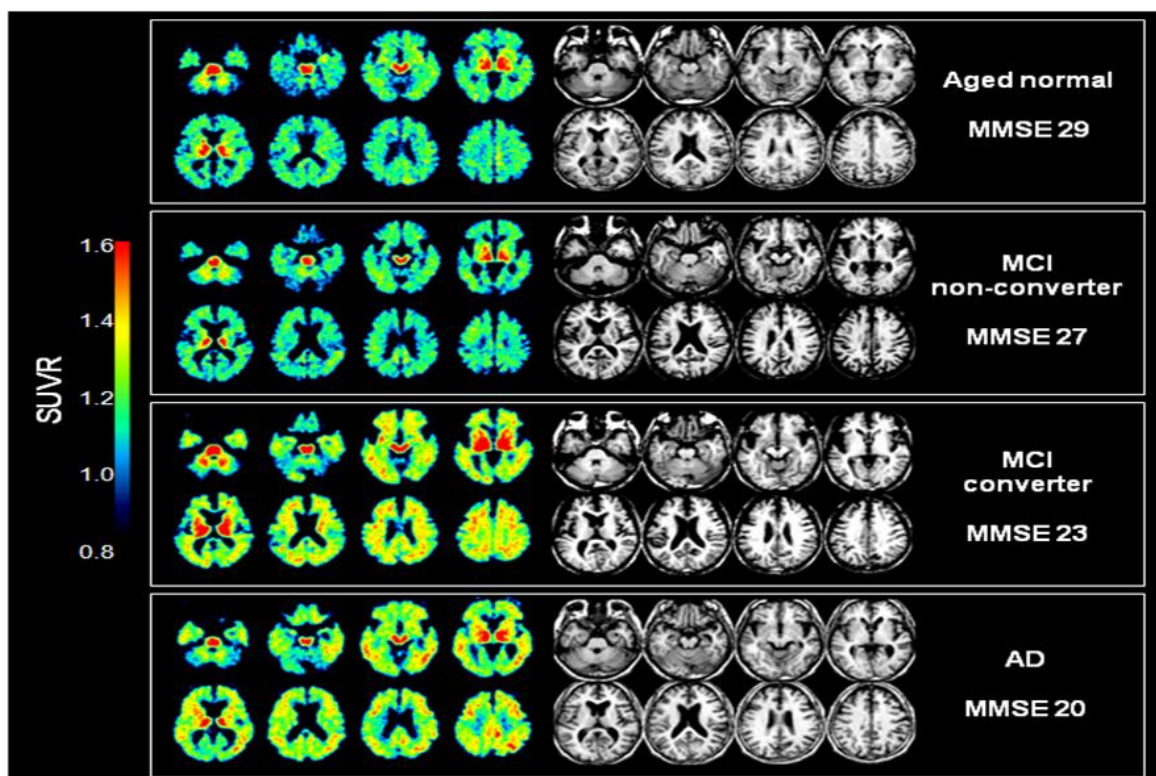


Figure 1. Representative images of  $[^{11}\text{C}]\text{BF-227-PET}$  SUVR between 20 and 40 min post-injection (left) and T1-weighted MRI (right) in a control subject, a MCI non-converter, a MCI converter and an AD subject. The degree of  $[^{11}\text{C}]\text{BF-227}$  retention is shown by color intensity from yellow to red in the cortex.

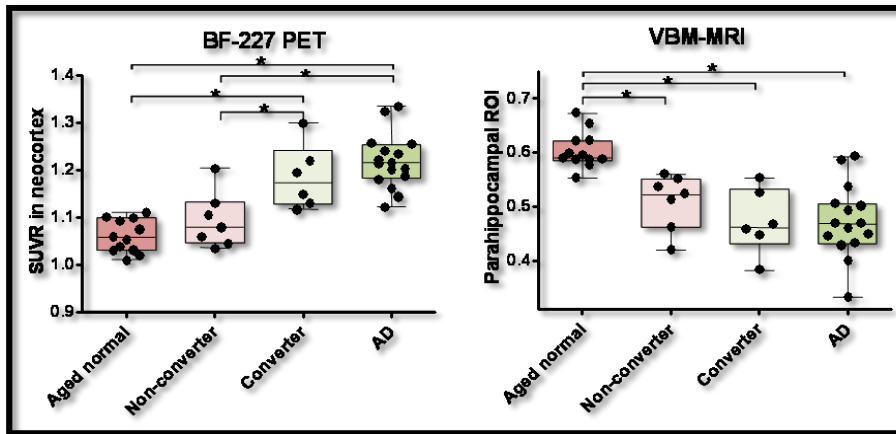


Figure 2. Statistical analysis showed that both of the BF-227 PET and the VBM-MRI could distinguish MCI and early AD from aged normal. Only BF-227 PET could statistically differentiate MCI converter from MCI non-converter.

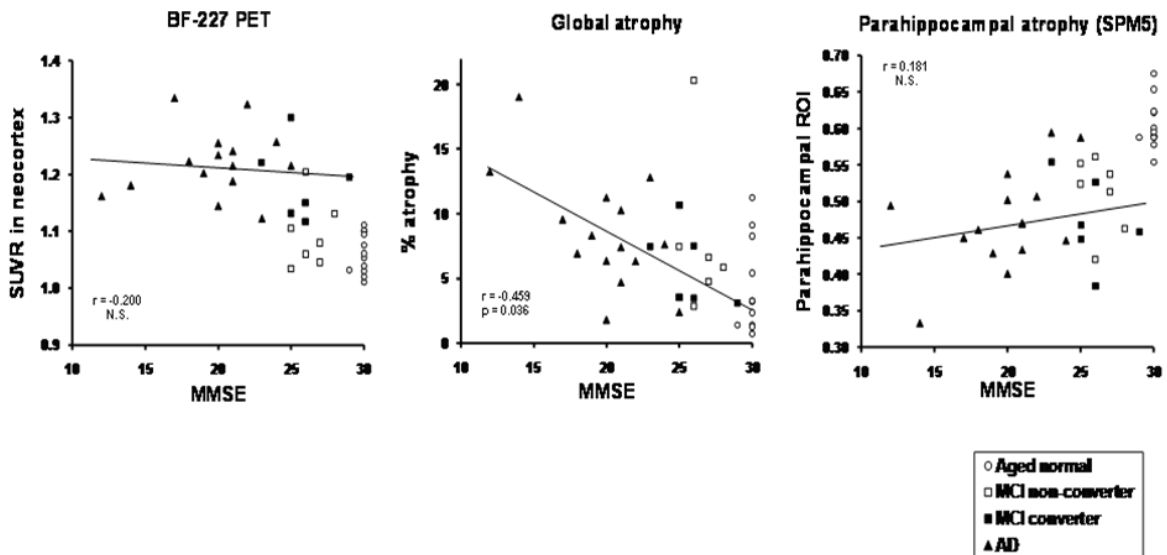


Figure 3. The correlations of MMSE scores with the BF-227 SUVR in the neocortex (right), the percent global atrophy (middle) and the parahippocampal region of interest (ROI) value from gray matter images processed by SPM5 (left).