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Correlation of Early-Phase F-18 Florapronal PET with F-18 FDG PET in Alzheimer's Disease and Normal Brain

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Abstract

Purpose F-18 florapronol (FPN) is the commercially recognized beta-amyloid positron emission tomography (PET) radiotracer in Korea. This study compared the early F-18 florapronol PET with F-18 fluorodeoxyglucose (FDG) PET between healthy controls (HC) and Alzheimer's dementia (AD) patients.

Methods A total of 29 subjects (15 HC and 14 AD subjects) underwent F-18 FPN PET and F-18 FDG PET. F-18 FDG PET image was acquired from 30 to 60 min and F-18 FPN PET for 0 to 10 min. F-18 FPN and F-18 FDG images were spatially normalized with transformation matrices obtained from individual CT images and standardized uptake value ration (SUVR) from cerebellum area, and the global mean was calculated using PMOD 3.6. Pearson's correlation coefficients between F-18 FDG and early F-18 FPN for predefined cortical brain regions were calculated.

Results We compared the F-18 FDG and F-18 FPN for SUVR of a specific region in global mean normalization and cerebellum normalization, and most of the correlation coefficient was higher in global mean normalization. In global mean normalization, the correlation coefficient for SUVR of HC was higher than that of AD in all brain regions.

Conclusions Early F-18 FPN study can be used as a proxy marker for the F-18 FDG PET.

Keywords Alzheimer's disease · F-18 florapronol · Dual time · F-18 FDG

Introduction

Alzheimer's dementia (AD) is the most common type of senile dementia, and intracellular neurofibrillary tangles and extracellular amyloid plaques together constitute the characteristic neuropathology of AD [1]. Amyloid positron emission tomography (PET) can identify amyloid plaque accumulation in the brain known as the initial pathogenesis of AD. And through F-18 fluorodeoxyglucose (FDG) brain PET, metabolic abnormalities can be detected which are associated with neuronal injury and clinical symptom. Atypical AD (those with AD pathology but atypical clinical presentations) can present with aphasia and visual or executive dysfunction rather than a predominant memory impairment. That is, the combination of amyloid PET with F-18 FDG PET or perfusion SPECT delivers complementary information that helps to assure the accuracy and specificity of AD diagnosis [2–4].

It is considered that cerebral blood flow and glucose metabolism are tightly coupled [5, 6]. It is known that early-phase amyloid PET with lipophilic tracers might replace F-18 FDG PET by delivering perfusion pattern which is reflecting metabolic information. Since glucose consumption in the brain correlates with the regional cerebral blood flow (CBF) which is shown in early-phase amyloid PET, a number of studies have been conducted that relate early-phase distribution patterns of amyloid tracers to F-18 FDG PET [7–9]. Thus, dual-phase amyloid PET is gaining prominence as an attractive tool to simultaneously measure both the neuronal activity and amyloid deposition. F-18 florapronol (FPN) is the first amyloid tracer for PET developed in Korea. Its New Drug Application (NDA) approval was obtained in 2018.

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The purpose of this study was to investigate the comparability of early-phase PET images of novel amyloid tracer F-18 FPN to FDG PET images. Therefore, we performed visual crosstalk analysis and relative quantitative crossover analysis of early-phase F-18 FPN PET and F-18 FDG PET imaging from normal and AD patients.

Materials and Methods

Participants

We retrospectively studied 17 healthy controls and 16 AD patients aged 50s through 80s in the neurology department of Dong-A University Medical Center. Participants completed neuropsychological assessments, as well as imaging tests including F-18 FDG brain PET and F-18 FPN amyloid PET. Participants with any neurological, medical, or psychiatric diseases were excluded from this study. Informed consent was obtained from all participants. The study protocol was reviewed and approved by the Institutional Review Board of our hospital.

PET Acquisition

All PET examinations were performed using a Biograph 40 mCT Flow PET/CT scanner (Siemens Healthcare, Knoxville, TN). The UltraHD-PET (TrueX-TOF) was used to reconstruct all PET images. And all participants underwent F-18 FDG and F-18 FPN PET, within an interval of 4 weeks.

- F-18 FDG scans: After fasting for at least 8 h, participants received 185 MBq of F-18 FDG injections. Serum glucose levels were < 180 mg/dL in all participants before radiotracer injection. Thereafter, participants rested in a bed within a quiet room and dim lighting for 30 min. PET/computed tomography (CT) acquisition commenced 30 min after radiotracer injection. Helical CT was performed with a rotation time of 0.5 s at 100 kVp and 228 mAs, without an intravenous contrast agent. PET followed immediately and was acquired over 30 min in 3-dimensional mode. All images were obtained from the skull vertex to the skull base.
- F-18 FPN scan: All participants were intravenously injected 370 MBq of F-18 florapronol (Alzavue, FutureChem Pharma), with dynamic images acquired immediately afterward for 10 min. For the delayed image, PET/CT acquisition was started 30 min after radiotracer injection. Velcro straps secured the participant's head to minimize motion artifacts. Helical CT was performed using the same protocol as the F-18 FDG PET. PET followed immediately and was acquired for 30 min in 3-dimensional mode. All images were acquired from the skull vertex to the skull base.

Image Analysis

PMOD 3.6 (PMOD Technologies, Zurich, Switzerland) was used for image quantitative analysis. The transformation matrix of each participant was obtained by fusing the CT template of the PMOD and the CT image of the participant. PET images were then spatially normalized through the transformation matrix of each participant and applied to an automated anatomical labeling template of PMOD (Hammers atlas). All pairs of early-phase F-18 FPN and F-18 FDG PET images were spatially normalized to different MNI (Montreal Neurological Institute) spatial templates. Hammers atlas was applied to spatially normalized early-phase F-18 FPN and FDG PET images. Data from 83 gray matter VOIs are combined to result in the amyloid composite brain regions and more such as frontal cortex, temporal cortex, parietal cortex, occipital cortex, striatum, anterior cingulate, posterior cingulate, and cerebral white matter. We selected whole cerebellum and whole brain as reference regions for intensity normalization.

Statistical Analysis

Normal distributions for all continuous variables were evaluated using the Kolomogorov-Smirnov test. Since SUVR distributions of temporal, occipital, parietal cortex, education year, Mini-Mental State Examination (MMSE) score, and age did not meet the normality, non-parametric test was performed for analysis. Other variables satisfied the distribution of normality. Categorical variable such as sex ratio was assessed using Fisher's exact test. To evaluate the correlation of the SUVR values obtained from the early-phase F-18 FPN and F-18 FDG PET images, we

Table 1 Demographics of the study population

Study groups	*N*	Age (years ± SD)	Male	Female	Education (years ± SD)	MMSE (score ± SD)
All	33	68.8 ± 8.7	13	20	8.8 ± 4.4	20.2 ± 7.3
HC	17	68.6 ± 7.9	9	8	10.4 ± 3.8	27.4 ± 2.1
AD	16	69.0 ± 9.8	4	12	6.9 ± 4.4	14.4 ± 3.9

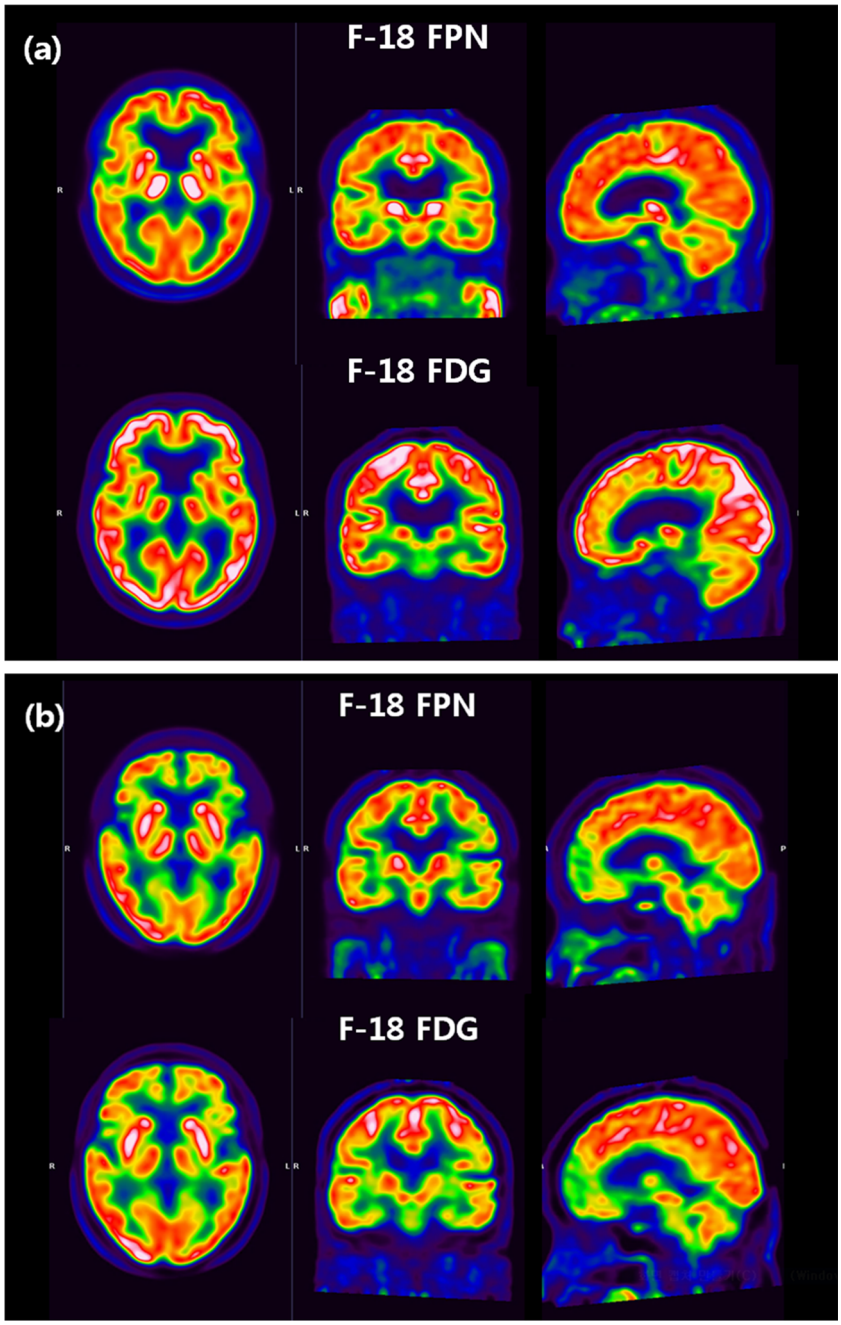

Fig. 1 Representative images obtained from HC and AD group using early F-18 FPN (top rows) and F-18 FDG (bottom rows). HC brain showed normal metabolism and perfusion (**a**). AD brain showed decreased metabolism and perfusion in the frontotemporal area with both tracers (**b**)

performed a rank correlation analysis with SUVRs of temporal, occipital, and parietal cortex whereas Pearson correlation analysis for the rest of the brain regions. To investigate agreement between F-18 FPN and F-18 FDG PET images, we performed paired *t* test (Wilcoxon test for non-normally distributed variables), calculated intraclass correlation coefficient, and outlined Bland-Altman plot. Statistical analyses were performed using MedCalc Statistical Software version 16.4.3. All *p* values were two-sided. Statistical significance was considered when *p* values were < 0.05.

Results

Demographics

A summary of the demographic characteristics of the two populations is shown in Table 1. According to Mann-Whitney *U* test, AD patients had significantly lower mean MMSE score (14.4 ± 3.9, $p < 0.05$) and education year (6.9 ± 4.4, $p < 0.0001$) than HC subjects. HC subjects had higher proportions of men whereas AD patients had higher (more than three times) proportions of women.

Table 2 Average within-subject correlations for early 18F-FPN image and 18F-FDG image

R (correlation coefficient)	Total (*R* ± SD)	AD (*R* ± SD)	HC (*R* ± SD)
FPN – FDG (global mean normalization)	0.83 ± 0.11	0.87 ± 0.08	0.78 ± 0.11

Visual Assessment

In the images from HC subjects, we could not find any abnormally decreased cortical uptake in F-18 FPN and FDG PET (Fig. 1a). The AD group showed diseased patterns of regional perfusion and hypometabolism (Fig. 1b). A visual inspection was always performed as quality control to find out possible missteps in the co-registration process.

Quantitative Analysis

We calculated the average within-subject correlation coefficient *R* of SUVR in HC subjects and AD patients with global mean normalization and cerebellum normalization, respectively. With global mean normalization, the correlation *R* values were 0.78 ± 0.11 in HC, 0.87 ± 0.08 in AD, and 0.83 ± 0.11 in total between F-18 FPN and F-18 FDG (Table 2). We also compared the F-18 FDG and F-18 FPN for SUVR of a specific region in global mean normalization (Table 3). Except for the region of the occipital cortex, most of the SUVRs of target brain regions correlate well with each other in global mean normalization. The least correlation was found in the occipital lobe ($R = 0.49$), and the highest correlation was found in the posterior cingulate ($R = 0.93$). Bland-Altman plots shown in Fig. 2 suggest a reasonable level of agreement between the two measurements. The SUVRs of FDG revealed higher value in all regions except temporal, striatum, and anterior cingulate. In addition, to analyze the similarity between the two examinations, we carried out the paired *t* test and intraclass correlation coefficient (ICC) test (Fig. 3). From the results of the *t* test (Wilcoxon test for non-normally distributed variables), only posterior cingulate ($p = 0.33$) and cerebral white matter ($p = 0.33$) showed the similarity. However, for all SUVR values, there was no significant difference between F-18 FPN and F-18 FDG ($p = 0.10$) and showed high correlation agreement (ICC = 0.91).

Discussion

In this study, the relationship between early-phase cerebral cortical perfusion using F-18 FPN SUVR and F-18 FDG SUVR is explored. The use of the protocol with dual time-point image acquisition is attractive since it allows obtaining information from two biomarkers in a single procedure, lowering the costs of using different PET tracers and radiation exposure, patient discomfort, and shortening the scanning time.

Our results showed a strong correlation of regional tracer uptake (SUVR) in investigated cortical brain regions between early F-18 FPN and F-18 FDG PET. However, there was significant partial uncoupling in occipital lobes on cerebral perfusion and metabolism. These results agree with earlier study that showed uncoupling of cerebral blood flow (CBF) and cerebral metabolic rate for glucose (CMRgl) in those areas [5]. Limbic regions and occipital lobes are significantly hyperperfused with higher relative CBF than CMRgl. It is postulated in previous study that limbic and posterior regions need to be hyperperfused for active activation because of their role in arousal and stimulus encoding. We can see higher uptake in basal ganglia and thalamus in scans of early FPN compared with FDG (Fig. 1).

Table 3 Regional SUVRs and correlation coefficients of early 18F-FPN image and 18F-FDG image

Region (global mean normalization)	F-18 FPN (SUVR ± SD)	F-18 FDG (SUVR ± SD)	*r*	rho	*p*
Frontal cortex	1.00 ± 0.03	1.03 ± 0.03	0.75		< 0.0001*
Temporal cortex	0.99 ± 0.04	0.93 ± 0.04		0.70	< 0.0001*
Parietal cortex	0.95 ± 0.04	1.00 ± 0.05		0.60	0.0003*
Occipital cortex	1.09 ± 0.04	1.15 ± 0.06		0.49	0.0041*
Striatum	0.92 ± 0.11	0.82 ± 0.10	0.81		< 0.0001*
Antertior cingulate	1.03 ± 0.12	0.97 ± 0.12	0.89		< 0.0001*
Posterior cingulate	1.04 ± 0.17	1.05 ± 0.19	0.93		< 0.0001*
Cerebral white matter	0.86 ± 0.05	0.86 ± 0.05	0.83		< 0.0001*

r, Pearson's correlation coefficient; *rho*, Spearman's coefficient of rank correlation

*$p < 0.05$

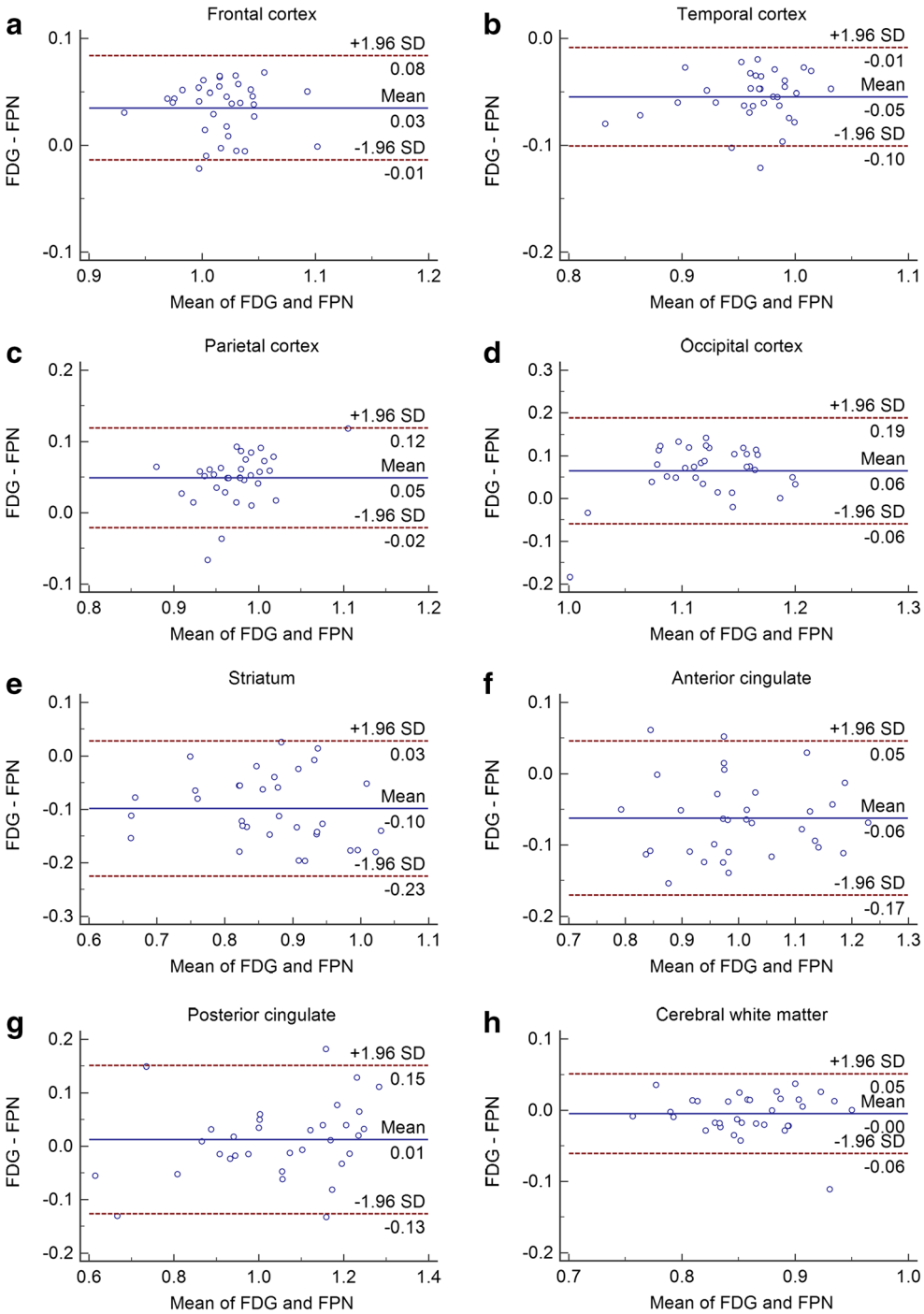

Fig. 2 Bland-Altman plots for SUVR of each brain regions. **a** Frontal cortex. **b** Temporal cortex. **c** Parietal cortex. **d** Occipital cortex. **e** Striatum. **f** Anterior cingulate. **g** Posterior cingulate. **h** Cerebral white matter. Limits of agreement were established as ± 1.96 SD and delineated by dotted lines

With the paired *t* test, the equivalence between early FPN and FDG images were analyzed. For each brain region, the null hypothesis from *t* test was rejected for most of them ($p < 0.05$) except for posterior cingulate ($p = 0.33$) and cerebral white matter($p = 0.33$). On this wise, we cannot say those two images have the same mean intensity values. But for the all SUVR data-driven, there was no significant difference between the two scans. Moreover, we can see through Bland-Altman plot(Fig. 2) that no important discrepancies exist between early FPN and FDG scans.

The present study had several limitations. First, participants were diagnosed using only clinical criteria and various clinical parameters were not considered and compared. Genetic markers, such as APOE or MR imaging, which can help to compensate for atrophic changes using scaled values such as medial temporal atrophy (Sheltens scale), were unavailable. Second, unfortunately, MR information was unavailable in

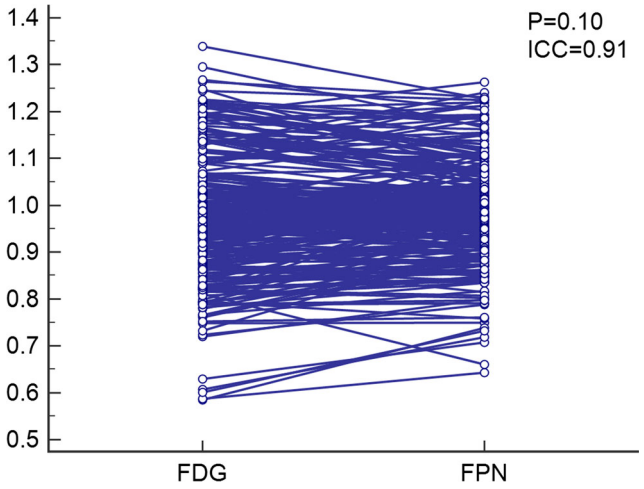

Fig. 3 Dot and line diagram of SUVR by two examinations ($p = 0.10$, ICC = 0.91). ICC stands for the intraclass correlation coefficient

this study. Therefore, CT-based spatial normalization was performed during the computation process. Third, it is needed to compare early-phase PET with absolute measures of brain perfusion, such as arterial spin labeling MRI or O-15 water PET. Last, since this study was performed with a relatively limited sample size in a single institution, our results may be difficult to generalize to the population as a whole.

Conclusion

Early F-18 FPN images well correlated with 18F-FDG PET images; thus, a single F-18 FPN study with dual-phase acquisition could convey both metabolic and molecular information. We assumed that use of dual-phase amyloid PET will reinvigorate F-18 FPN PET in the near future.

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Compliance with Ethical Standards

Conflict of Interest Jieun Jeong, Yong Jin Jeong, Kyung Won Park, and Do-Young Kang declare that they have no conflict of interest.

Ethical Statement This study was performed in accordance with the ethical standards laid down in the Helsinki declaration of 1964 and its later revisions.

Informed Consent Informed consent was obtained from all individual participants included in this prospective study.

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