Neuroimaging
Utility of perfusion PET measures to assess neuronal injury in Alzheimer’s disease


Abstract

Introduction: ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is commonly used to estimate neuronal injury in Alzheimer’s disease (AD). Here, we evaluate the utility of dynamic PET measures of perfusion using ¹¹C-Pittsburgh compound B (PiB) to estimate neuronal injury in comparison to FDG PET.

Methods: FDG, early frames of PiB images, and relative PiB delivery rate constants (PiB-R1) were obtained from 110 participants from the Dominantly Inherited Alzheimer Network. Voxelwise, regional cross-sectional, and longitudinal analyses were done to evaluate the correlation between images and estimate the relationship of the imaging biomarkers with estimated time to disease progression based on family history.

Results: Metabolism and perfusion images were spatially correlated. Regional PiB-R1 values and FDG, but not early frames of PiB images, significantly decreased in the mutation carriers with estimated year to onset and with increasing dementia severity.

Discussion: Hypometabolism estimated by PiB-R1 may provide a measure of brain perfusion without increasing radiation exposure.

Keywords: Alzheimer’s disease; Neuronal injury; Perfusion; FDG; PiB

*Corresponding author. Tel.: + (602) 839 4851; Fax: +(602) 839 3498.
E-mail address: yi.su@bannerhealth.com

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1. Introduction

Alzheimer’s disease (AD) can be staged with biomarkers including positron emission tomography (PET), magnetic resonance imaging (MRI), and cerebrospinal fluid to detect β-amyloid (Aβ), neurofibrillary tangle burden, and neurodegeneration [1–3]. 11C-Pittsburgh compound B (PiB) PET is commonly used to detect cerebral Aβ burden [4,5]. 18F-fluorodeoxyglucose (FDG) PET is an analogue of glucose that accumulates in brain cells thus allowing visualization and measurement of local metabolic activity. Decrease in FDG uptake is thought to reflect local neuronal dysfunction [6] and is used as a reliable imaging biomarker for AD diagnosis.

Models of AD pathophysiology propose a sequential progression of brain changes that are reflected by imaging abnormalities starting with an early increase in Aβ-PET tracer retention, followed by a decrease in glucose metabolism, followed by a decrease in cortical thickness as seen with volumetric MRI [2,7]. Imaging participants with multiple PET tracers help characterize different stages of the disease but is limited by cumulative radiation exposure, greater participant burden, and increased study costs. To address this, several recent investigations have evaluated perfusion-weighted PET or cerebral blood flow (CBF) as potential estimates of glucose metabolism measurements [8–12]. Good spatial correlations were found between CBF estimates and FDG, including in regions affected by hypometabolism in symptomatic sporadic AD [8,10,12]. The gold standard for CBF measurement is 15O-H2O PET [13,14]; however, its 2-minute half-life prevents its widespread use [13]. 15O-H2O has been used to validate perfusion weighted measurements derived from PiB PET [15] based upon influx of the PiB tracer into the brain [16] using either the early frames of the PiB scan (ePiB) or a relative tracer influx rate [PiB-R1] [15,17]. Several studies on sporadic AD showed that a perfusion image with ePiB, in addition to a common Aβ burden PiB image, improves discrimination between AD pathology and other Aβ- and tau-related clinical disorders [10,18,19]. ePiB also helps distinguish the earliest symptomatic stage of AD from healthy controls [20]. Another study from Meyer et al. showed that PiB-R1 and FDG images were similar in a population with dementia and suggested that PiB-R1 can be used as a good surrogate for FDG [9].

To our knowledge, changes in PiB-R1 and ePiB with the progression of the disease have not been evaluated either cross-sectionally or longitudinally. Here, we compared PiB-R1 and ePiB with FDG in a model of AD progression to evaluate their utility in clinical research and trials of dynamic Aβ PET measures as markers of neuronal injury. A validation sub-study compared PiB-R1 and ePiB with the perfusion gold standard, 15O-H2O PET.

We focused on a population with autosomal dominant AD (ADAD) to facilitate the evaluation of disease progression and preclinical AD stages. ADAD is a rare familial form of AD with early onset of clinical symptoms (typically before 65 years old) caused by a mutation in the amyloid precursor protein (APP), presenilin 1 (PS1), or presenilin 2 (PS2) genes, resulting in overproduction of Aβ. These forms of familial AD have essentially 100% penetrance and show similar age of symptom onset in each family across generations [21]. Because the disease course is well characterized, ADAD provides an important model for staging preclinical AD [21]. The Dominantly Inherited Alzheimer Network (DIAN) has described disease progression in ADAD, finding that glucose metabolism is primarily diminished in regions including the precuneus and inferior parietal cortices, beginning ~10 years before symptom onset [22]. We investigated in an ADAD cohort from the DIAN whether PiB-R1 and ePiB values derived from dynamic PiB PET show similar declines in the parietal and temporal lobes as seen with FDG PET, with the aim to evaluate a potential alternative to the FDG neuronal injury marker of AD that would minimize radiation exposure, experiment time, and participant burden in the context of clinical research and trials.

2. Methods

2.1. Participants

Participants were enrolled at DIAN sites, including three sites that performed full-dynamic PiB PET scans: Washington University, Columbia University, and University of California Los Angeles. Each site’s institutional review board approved all study procedures. All participants or their caregivers provided written informed consent approved by their local institution’s review board. Standardized clinical and imaging assessments were obtained according to DIAN study protocols [23]. Data were from the DIAN Data Freeze 7 (May 2014) and had passed strict quality control procedures. This data set included 110 participants with at least one full-dynamic PiB PET scan available for analysis. Sixty-five participants were mutation carriers (MCs) of the genes APP, PS1, or PS2. Forty-five participants with an MC parent were themselves noncarriers (NCs) and were considered as controls (see demographics Table 1). All participants had baseline MRI, PiB, and FDG PET scans, genetic analyses, and clinical assessments using the clinical dementia rating (CDR) with both a global score and a more detailed CDR sum of boxes (CDR-SB) score based on several cognitive and behavioral categories [24,25]. Longitudinal analyses were performed on a subset of 30 participants with at least one follow-up session including dynamic PiB and FDG scans (see demographics in Table 2). Of the 110 participants with baseline dynamic data, 30 participants at the Washington University site additionally underwent an 15O-H2O PET scan for CBF assessment (see demographics in Supplementary Table S1).

2.2. Image acquisition

Standard procedures were used at all DIAN sites and ensured consistency in the data collection [21,23]. Two
Table 1
Demographics of cross-sectional data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NC</th>
<th>MC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>.1</td>
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<tr>
<td>Age, mean (SD) years</td>
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<tr>
<td>EYO, mean (SD) years</td>
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<tr>
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<td>Male, n (%)</td>
<td>22</td>
<td>36</td>
<td>.50</td>
</tr>
<tr>
<td>CDR &gt; 0, n (%)</td>
<td>5</td>
<td>22</td>
<td>.012</td>
</tr>
<tr>
<td>MCBP &gt; .18, n (%)</td>
<td>1</td>
<td>40</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; NC, noncarrier; MC, mutation carrier; EYO, estimated year to symptom onset; CDR, clinical dementia rating.

Table 2
Demographics of longitudinal data at baseline

<table>
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<th>Parameters</th>
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<th>MC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
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<td>15</td>
<td>.6</td>
</tr>
<tr>
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</tr>
<tr>
<td>EYO, mean (SD) years</td>
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<td>−4.2</td>
<td>.983</td>
</tr>
<tr>
<td>Education, mean (SD)</td>
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<td>14.9</td>
<td>.831</td>
</tr>
<tr>
<td>Male, n (%)</td>
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<td>10</td>
<td>.272</td>
</tr>
<tr>
<td>CDR &gt; 0, n (%)</td>
<td>0</td>
<td>7</td>
<td>.034</td>
</tr>
<tr>
<td>MCBP &gt; .18, n (%)</td>
<td>1</td>
<td>12</td>
<td>.044</td>
</tr>
<tr>
<td>MCBP value, mean (SD)</td>
<td>0.09</td>
<td>0.53</td>
<td>.05</td>
</tr>
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</table>

Abbreviations: SD, standard deviation; NC, noncarrier; MC, mutation carrier; EYO, estimated year to symptom onset; CDR, clinical dementia rating; MCBP, mean cortical binding potential.

For each participant, the PET images were processed using regions of interest (ROIs) from FreeSurfer brain segmentation software (http://surfer.nmr.mgh.harvard.edu/)

2.3. Image processing and image analysis

2.4. Statistical analysis

The cross-sectional relationship of FDG, PiB-R1, and ePiB with the estimated year to symptom onset (EYO) was evaluated per mutation group using general linear mixed-models on each ROI. The models included fixed effects for mutation status, EYO, and the interaction between the mutation status and EYO, and random intercepts at the family level. The potential presence of nonlinear trajectories was examined with the inclusion and testing of quadratic and cubic EYO terms, along with appropriate interaction terms with the mutation status indicator. Owing to the preliminary hypothesis-generating nature of the present study, no adjustment for multiple comparisons was performed.

The relationship with CDR-SB was evaluated across the subset of 65 MCs with Spearman’s rank correlation for each region. To evaluate the differences between FDG/CDR-SB, PiB-R1/CDR-SB, and ePiB/CDR-SB, we computed the 95% confidence interval for the difference in
Spearman’s rank correlation coefficients based on the percentile method using 10,000 bootstrap replications [33].

For the longitudinal analyses, to quantify the within-person annual rate of change in FDG, PiB-R1, or ePiB, general linear mixed models were used with random intercepts and random slopes at the participant level, along with random effects at the family level. Fixed effects included a mutation status indicator, EYO at baseline, and time from baseline. The interactions between time from baseline and the two other fixed effects were also included.

All general linear mixed models were estimated using restricted maximum likelihood estimation. F-test denominator degrees of freedom were approximated using the Satterthwaite method [34]. All statistical analyses were performed with SAS, version 9.4 (SAS Institute Inc.).

3. Results

3.1. Participant characteristics

The demographics of the cross-sectional cohort, the longitudinal cohort, and the \(^{15}\)O-H\(_2\)O-PET cohort are summarized in Table 1, Table 2, and Supplementary Table S1, respectively. The NC and MC groups were similar in age, EYO, and education for all cohorts. The two groups were different in CDR and MCBP as expected, with higher prevalence of symptomatic (CDR > 0) and PiB-positive (MCBP > .18) participants in the MC group.

3.2. Comparison of perfusion measures and FDG

To test whether FDG, PiB-R1, and ePiB displayed strong perfusion characteristics, we compared these measures with \(^{15}\)O-H\(_2\)O the gold standard of perfusion, regardless of the mutation status. In the 30 DIAN participants with \(^{15}\)O-H\(_2\)O data, the spatial average Pearson’s \(r\) values for FDG, PiB-R1, and ePiB were 0.69 ± 0.05, 0.74 ± 0.09, and 0.71 ± 0.06 for the entire brain, and 0.57 ± 0.04, 0.64 ± 0.10, and 0.58 ± 0.05 for cortical gray matter, respectively. The average Pearson’s \(r\) values for the correlation of PiB-R1 and \(^{15}\)O-H\(_2\)O, and of ePiB and \(^{15}\)O-H\(_2\)O, were similar for the entire brain. However, the average Pearson’s \(r\) value for the correlation of PiB-R1 and \(^{15}\)O-H\(_2\)O was significantly higher than that of ePiB and \(^{15}\)O-H\(_2\)O on the cortical level (\(P < .0001\)). This suggests better perfusion characteristics of the PiB-R1 values.

Visual comparison of the FDG, PiB-R1, ePiB, and A\(\beta\) uptake PiB images within participants revealed that PiB-R1 was more similar to FDG than ePiB was (Fig. 1). Across all the 110 participants, the PiB-R1 values better correlated with FDG in the precuneus (\(r = 0.48, P < .0001\)) and the inferior parietal (\(r = 0.42, P < .0001\)) than did ePiB values (precuneus: \(r = 0.08,\) n.s.; inferior parietal: \(r = 0.22,\) n.s.), whereas ePiB correlated better in the hippocampus (\(r = 0.52, P < .0001\)) than did PiB-R1 (\(r = 0.40, P < .0001\)) (Fig. 2 and Supplementary Table S3).

3.3. Comparison of perfusion measures and MCBP

PiB is a PET ligand designed for imaging cerebral fibrillar A\(\beta\) [4]. We tested whether PiB-R1 and ePiB were contaminated by A\(\beta\) binding by evaluating their correlation with MCBP. Across all 110 participants, the PiB-R1 values were not correlated with MCBP for all regions. However, ePiB positively correlated with A\(\beta\) burden in several regions (e.g., \(r = 0.59, P < .0001\); and \(r = 0.37, P < .0001\) in the precuneus and the inferior parietal cortex, respectively, Supplementary Fig. S5 and Supplementary Table S4). This demonstrates that ePiB measurement displays some contamination from specific binding, whereas PiB-R1 does not.

3.4. Cross-sectional evaluation with estimated year to onset

Results for FDG, PiB-R1, and ePiB in the precuneus, the inferior parietal, and the hippocampus were compared in Fig. 3. Based on cross-sectional regional analyses, the MC participants showed a significant decrease of glucose uptake.
metabolism with EYO (all regions, \( P < .05 \)), whereas the NC participants remained stable for all regions (see Fig. 3 top row and Supplementary Table S5). The interaction between mutation and EYO was significant only for the precuneus and the inferior parietal. PiB-R1 decreased for the inferior and superior parietal (\( P < .05 \)) and had a tendency to decrease in the precuneus (\( P = .053 \)) within the MC participants, but the interactions were not significant (see Fig. 3 middle row and Supplementary Table S5). ePiB was significantly increased in the MC population in the precuneus (\( P < .0005 \)), the inferior parietal cortex (\( P < .05 \)), and showed positive interaction in the precuneus (see Fig. 3, bottom row, and Supplementary Table S5).

3.5. Cross-sectional evaluation with clinical status

FDG SUVR inversely correlated with the severity of dementia, estimated with CDR-SB, in MC participants (\( n = 65 \)), with a strong correlation in the precuneus and the inferior and the superior parietal (e.g., \( \rho = -0.47 \), \( P < .0001 \) for the superior parietal, see Table 3). Similarly, PiB-R1 values were inversely correlated with CDR-SB in all regions except for the lateral occipital and the hippocampus (e.g., \( \rho = -0.44 \), \( P < .0005 \) for the superior parietal, see Table 3). However, ePiB SUVR values did not significantly correlate with the CDR-SB in any regions (Table 3).

3.6. Longitudinal evaluation

Within the MC participants, the longitudinal data demonstrated a significant decrease in FDG in all cortical regions except the lateral occipital and hippocampus (Supplementary Table S6). Similar results were observed for PiB-R1 in the superior parietal, but no significant changes were observed for ePiB within MC participants (Supplementary Table S6). However, examining the differences in slope between MC and NC participants, these changes observed over time in the MC group were not significantly different from the NC group in these regions for all three measurements (Supplementary Table S6).

4. Discussion

We demonstrated that PiB-R1, a perfusion-weighted parameter derived from PiB PET, was correlated with FDG and decreased with disease progression in an ADAD population. This was the first study to examine a PET measure of perfusion with disease progression in AD to assess its utility in clinical research and trials as a marker of neuronal injury.

For this purpose, it was necessary to confirm the reliability of our FDG measurements in terms of decreases in our ADAD cohort. Regional hypometabolism begins early in disease...
progression and can be reliably measured with FDG. Using an ADAD population, it is possible to model the relative progression of the disease with EYO [2,22]. Previous FDG cerebral metabolism findings in ADAD showed decreases, particularly, in the precuneus, parietal, and cingulate areas [2,22]. In the present study, the cortical glucose metabolism decrease was observed in MC participants in both cross-sectional and longitudinal analyses, and this decrease was linked to cognitive impairment. Our findings are consistent with previous studies indicating that FDG glucose metabolism is a sensitive marker of disease progression in ADAD.

When both PiB-R1 and ePiB were compared with FDG from the same participant and visit, PiB-R1 showed a better spatial correlation. Across DIAN participants, the correlations were stronger between PiB-R1 and FDG than ePiB and FDG in most cortical areas. These findings demonstrate that PiB-R1 is better correlated with FDG both within and across subjects and provides a closer proxy of FDG than ePiB. In our study, PiB-R1 values showed greater similarity to FDG during disease progression than did ePiB. First, PiB-R1 decreased in regions such as the inferior and superior parietal with EYO cross-sectionally, whereas ePiB increased with EYO in these regions. Second, decreases in PiB-R1 with CDR-SB were found in all areas greatly affected by hypometabolism, whereas ePiB did not show any interaction with clinical status. Finally, longitudinally, in MC participants, the PiB-R1 measures showed a consistent trend of decrease, which reached significance in the superior parietal, whereas ePiB did not show any significant changes in the MC participants. The evaluated relationships were stronger in parietotemporal areas than in lateral occipital. Early in the disease course, parietotemporal areas are first to show hypometabolism, whereas lateral occipital areas are only affected later [22].

The counterintuitive increase in ePiB with EYO in regions affected by hypometabolism and the lack of decrease with cognitive impairment are consistent with
correlation between the tracers and dementia in mutation carriers \( n = 65 \). Spearman’s rank correlation coefficient (rho) and \( P \) values are displayed for FDG and CDR-SB, ePiB, and CDR-SB, and for PiB-R1 and CDR-SB. There were strong negative correlations between values are displayed for FDG and CDR-SB, ePiB, and CDR-SB, and for PiB-R1 and CDR-SB. There were strong negative correlations between FDG and CDR-SB, but no correlation between ePiB and CDR-SB.

contamination by early binding to \( \alpha \beta \) deposits. This early binding caused overestimation of perfusion in ePiB, but not PiB-R1. Different profiles of progression were thus observed between the two perfusion PET measures in the present study. Chen et al. showed that ePiB and PiB-R1 displayed similar spatial profiles \([15]\), but the progression of the disease was not considered. In ADAD, as the disease progresses, the \( \alpha \beta \) deposition and thus the MCBP increase \([2,22]\). The precuneus and the inferior parietal are particularly affected by the increase of \( \alpha \beta \) deposition \([22]\). In the present study, the precuneus and the inferior parietal displayed strong positive correlation between the ePiB measure and MCBP. This may have been due to contamination by \( \alpha \beta \) binding, as these increases were not observed in PiB-R1.

Besides \( \alpha \beta \) deposition, AD progression is associated with atrophic processes in more advanced stages \([1,2,22]\). PET SUVR can be strongly affected by atrophic processes, due to the partial volume effect \([35,36]\). A voxel-based morphometry gray matter comparison between NC and MC participants showed that very few voxels survived correction for multiple comparisons, suggesting that the association observed was not due to differential atrophic process between the groups \([Supplemental Fig. S4]\) \([37]\). A correction for partial volume effects was applied to our ePiB and PiB-R1 data to obtain a more accurate measure, not contaminated by atrophy. Our group and other groups have shown the importance of partial volume correction \( (PVC) \) in PET-image processing \([25,38,39]\). However, the use of PVC may lead to different outcomes in PET studies \([25,40]\). Although our main ePiB \( (corrected) \) results showed increase with ADAD progression in the MC participants, the same noncorrected data tend to decrease with EYO \( (see \ Supplemental Fig. S2) \). PiB-R1 showed the same trend with or without PVC. Thus, PVC is not necessary for PiB-R1, resulting in simpler processing.

The current results also support the hypothesis that decreases in perfusion and in cerebral glucose metabolism are coupled during the course of ADAD. However, the findings with the \( ^{18} \)F-fluorodeoxyglucose; PiB, \( ^{11} \)C-Pittsburgh compound B; ePiB, early frames of the PiB scan.

NOTE. Statistically significant values are listed in bold \( (P \ value < .05) \). NOTE. Evaluation of correlation between the tracers and dementia in mutation carriers \( n = 65 \). Spearman’s rank correlation coefficient (rho) and \( P \) values are displayed for FDG and CDR-SB, ePiB, and CDR-SB, and for PiB-R1 and CDR-SB. There were strong negative correlations between FDG and CDR-SB, but no correlation between ePiB and CDR-SB.

<table>
<thead>
<tr>
<th>Region</th>
<th>FDG and CDR-SB</th>
<th>PiB-R1 and CDR-SB</th>
<th>ePiB and CDR-SB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \rho )</td>
<td>( P ) value</td>
<td>( \rho )</td>
</tr>
<tr>
<td>Precuneus</td>
<td>-0.45</td>
<td>.0001</td>
<td>-0.27</td>
</tr>
<tr>
<td>Inferior Parietal</td>
<td>-0.47</td>
<td>&lt;.0001</td>
<td>-0.28</td>
</tr>
<tr>
<td>Superior Parietal</td>
<td>-0.47</td>
<td>&lt;.0001</td>
<td>-0.44</td>
</tr>
<tr>
<td>Lateral Occipital</td>
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<td>-0.17</td>
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<tr>
<td>Hippocampus</td>
<td>-0.30</td>
<td>.014</td>
<td>-0.22</td>
</tr>
</tbody>
</table>

Abbreviations: CDR-SB, Clinical Dementia Rating–Sum of Boxes; FDG, \( ^{18} \)F-fluorodeoxyglucose; PiB, \( ^{11} \)C-Pittsburgh compound B; ePiB, early frames of the PiB scan.

The results of the present study show clear utility for using the PiB-R1 in clinical research or trials to measure physiologic changes. However, two potential issues can be encountered in practical terms: the dropout rate and the multisite implementation. First, PiB-R1 calculation requires a long scan session that may not be well tolerated by individuals with cognitive impairment. In our study, one out of over 30 participants with follow-up assessments switched to a short protocol. The dropout rate was not an issue in our DIAN longitudinal cohort. Second, not all DIAN sites acquired the full-dynamic scan. Some acquire only a late 30-minute frame beginning 40 minutes after tracer injection. Other sites additionally acquire the first 10 minutes for calculating ePiB in addition to the amyloid load, attempting to minimize study cost and participant burden. Although these approaches decrease the amount of time a participant spends in the scanner, the advantages of PiB-R1 over ePiB lead us to conclude that a full-dynamic acquisition is preferable.

Some studies suggested using other \( \alpha \beta \)-PET ligands such as flurbetapir \([43–45]\), flurbetaben \([11,46]\), or tau PET ligands \([17]\) to measure perfusion and compare with FDG measurements. Further investigation using other PET tracers could be of interest to fully assess the utility of alternative perfusion proxies using PET tracers in an ADAD population.

These perfusion PET imaging modalities do not measure the same feature as FDG but still possess utility for clinical research and trials. This investigation of ePiB and PiB-R1 measures in an ADAD cohort gives a better characterization of alternative measurements and their potential further applications. PiB-R1 may provide a new measure of neuronal injury. Although the current evidence does not suggest that PiB-R1 is a better measure of neuronal injury than FDG, for participants already receiving a PiB PET scan for assessment of \( \alpha \beta \) deposition, substitution of PiB-R1 for FDG would minimize radiation exposure, experiment time, and participant burden by acting as a surrogate for the FDG scan without causing significant dropout on longitudinal follow-up visits during clinical research and trials. Further study evaluating the applicability of PiB-R1 in sporadic AD and other conditions is of interest.

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Supplementary data

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References


