Evaluation across the spectrum of cognitive decline
Chapter 4

Detection of Alzheimer pathology *in vivo* using both [\(^{11}\)C]PIB and [\(^{18}\)F]FDDNP positron emission tomography

Nelleke Tolboom, Maqsood Yaqub, Wiesje M. van der Flier
Ronald Boellaard, Gert Luurtsema, Albert D. Windhorst
Frederik Barkhof, Philip Scheltens, Adriaan A. Lammertsma
Bart N.M. van Berckel

Abstract

Objective: [11C]PIB and [18F]FDDNP have been developed as positron emission tomography tracers for in vivo imaging of pathology in Alzheimer’s disease (AD). The purpose of this study was to directly compare these tracers in AD, mild cognitive impairment (MCI) and healthy controls.

Methods: Paired [11C]PIB and [18F]FDDNP scans were performed in 14 patients with AD, 11 with amnestic MCI and 13 controls. For both tracers, parametric images of binding potential (BPND) were generated. Global cortical BPND was assessed using ANOVA. In addition, regional patterns of BPND were compared between diagnostic groups using ANOVA for repeated measures.

Results: Global cortical BPND of [11C]PIB showed higher binding in patients with AD than in controls and MCI patients. [18F]FDDNP uptake in AD was higher than in controls, but MCI could not be distinguished from AD or controls. Global BPND values of both tracers were moderately correlated (r=0.45; p=0.005). In MCI, BPND of [11C]PIB showed a bi-modal distribution, whilst values for [18F]FDDNP were more widespread with more MCI patients demonstrating increased uptake. Regional [11C]PIB binding showed different patterns across diagnostic groups, as AD patients showed an overall increase in binding, with relatively lowest binding in the medial temporal lobe (MTL). With [18F]FDDNP patterns were similar across diagnostic groups. For all groups, highest values were observed in the MTL.

Conclusion: Differences in BPND between patients with AD, MCI and controls were more pronounced for [11C]PIB. The difference in regional binding, the moderate correlation and the discrepant findings in MCI suggest that they measure related, but different, characteristics of the disease.
Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder. The diagnosis of AD during life is based on clinical criteria, which have low sensitivity and specificity in the early stages of the disease (1). Mild cognitive impairment (MCI) is characterised by mild cognitive deficits. Although at the time of diagnosis MCI patients do not have dementia, they have an increased risk of progression to dementia (2). Ongoing developments in AD therapy dictate the need for developing techniques that identify subjects with incipient AD among patients with MCI. In vivo imaging of the pathology underlying AD holds promise for providing such a method.

Neuropathologically AD is characterised by the accumulation of amyloid-beta (Aβ) in senile plaques and hyperphosphorylated tau in neurofibrillary tangles. Neurofibrillary tangles are thought to be present mainly in medial temporal as well as lateral temporal lobe and to a lesser extent in frontal, parietal, and occipital lobes. Amyloid plaques are more evenly distributed throughout the cortex with relatively mild involvement of the hippocampal formation (3).

Over the past two decades, positron emission tomography (PET) tracers have been developed for in vivo imaging of AD pathology. Of these ligands, [11C]PIB (Pittsburgh Compound-B) (4) and [18F]FDDNP (2-(1-{6-[2-[F-18]fluoroethyl](methyl)amino}-2-naphthyl)ethylidene) malononitrile) (5) have been used most widely.

First results with [11C]PIB showed greater cortical retention in patients with AD compared to controls (4 6-8). This finding has been replicated several times in AD and has been extended to MCI patients where a more bi-modal distribution has been described (9 13). Using [18F]FDDNP, it was also possible to distinguish AD, MCI and controls, but presently these findings have not been replicated (5).

Paired studies in the same subjects with validated tracer kinetic models are needed for a meaningful comparison. The aim of the present study was to directly compare global and regional uptake of [11C]PIB and [18F]FDDNP using validated quantitative methods in the same healthy control subjects, AD patients and MCI patients.

Materials and Methods

Subjects

Fourteen AD patients, 11 patients with amnestic MCI and 13 healthy controls were included in this study. All patients received a standard dementia screening that included medical history, physical and neurological examinations, screening laboratory tests, brain MRI, and extensive neuropsychological testing. Among neuropsychological tests were the Mini Mental State Examination (MMSE) (14) and the Dutch version (15) of the Ray Auditory Verbal Learning Test (RAVLT) (16), a test specifically for episodic memory. Clinical diagnosis was established by consensus in a multidisciplinary team, without knowledge of the PET results. All AD patients met NINCDS-ADRDA (17) criteria for “probable AD”. Seven of the 14 AD subjects were
taking acetylcholine esterase inhibitors. Two AD patients used psychotropic medication (1 used a benzodiazepine and 1 a selective serotonin reuptake inhibitor). MCI subjects met the Petersen criteria (2) based on subjective and objective cognitive impairment, predominantly affecting memory, in the absence of dementia or significant functional loss. Two MCI subjects used psychotropic medication (1 used a benzodiazepine and 1 a selective serotonin reuptake inhibitor). Control subjects were recruited through advertisements in newspapers, and underwent the same diagnostic procedures. None of the controls used psychotropic medication.

Exclusion criteria were a history of major psychiatric or neurological (other than AD) illness and the use of non-steroidal anti-inflammatory drugs (NSAIDS), since these have been reported to compete with $[^{18}F]FDDNP$ for binding to Aβ fibrils in vitro and to Aβ plaques ex vivo (18). Additional exclusion criteria for controls were: subjective memory complaints or clinically significant abnormalities on the magnetic resonance imaging (MRI) scan (as determined by a neuroradiologist). Written informed consent was obtained from all subjects after a complete written and verbal description of the study. The study was approved by the Medical Ethics Review Committee of the VU University Medical Centre.

**PET**

PET scans were performed on an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, USA), equipped with a neuro-insert to reduce the contribution of scattered photons. This scanner enables the acquisition of 63 transaxial planes over a 15.5 cm axial field of view, thus allowing the whole brain to be imaged in one bed position. The properties of this scanner have been reported elsewhere (19). All subjects received a venous cannula for tracer injection. First, a 10 minute transmission scan was performed in 2D acquisition mode using three retractable rotating line sources. This scan was used to correct the subsequent emission scan for photon attenuation. Next, a dynamic emission scan in 3D acquisition mode was started simultaneously with the intravenous injection of 351±82 MBq $[^{11}C]PIB$ (20), with an specific activity (SA) of 41±22 GBq/µmol using an infusion pump (Med-Rad, Beek, the Netherlands) at a rate of 0.8 ml/sec, followed by a flush of 42 ml saline at 2.0 ml/sec. This scan consisted of 23 frames with progressive increase in frame duration (1x15, 3x5, 3x10, 2x30, 3x60, 2x150, 2x300, 7x600 s) for a total duration of 90 minutes. Finally, after a resting period of at least 1 hour to allow for decay of $^{11}C$, exactly the same procedure was repeated, but now using an injection of 177±14 MBq $[^{18}F]FDDNP$ (21) with an SA of 86±51 GBq/µmol. Patient motion was restricted by the use of an immobilisation device and monitored by checking the position of the head using laser beams.

**MRI**

All subjects underwent a structural MRI scan using a Siemens 1.5 T Sonata scanner (Siemens Medical Solutions, Erlangen, Germany). The scan protocol included a coronal T1-weighted 3D MPRAGE (magnetization prepared rapid acquisition gradient echo; slice thickness 1.5 mm, 160 slices; matrix size 256x256; voxel size 1x1x1.5 mm; echo time=3.97 ms; repetition time=2700
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ms; inversion time=950 ms; flip angle 8°), which was used for co-registration and region of interest (ROI) definition.

**Image and data analysis**

All PET sinograms were corrected for dead time, tissue attenuation using the transmission scan, decay, scatter and randoms, and were reconstructed using a standard filtered back projection algorithm and a Hanning filter with a cut-off at 0.5 times the Nyquist frequency. A zoom factor of 2 and a matrix size of $256 \times 256 \times 63$ were used, resulting in a voxel size of $1.2 \times 1.2 \times 2.4$ mm and a spatial resolution of approximately 7 mm full-width at half-maximum at the centre of the field of view. Images were then transferred to workstations (Sun Microsystems, Santa Clara, CA, USA) for further analysis.

MRI images were aligned to corresponding PET images using a mutual information algorithm. Data were further analysed using PVE lab, a software program that uses a probability-map based on 35 delineated ROIs that has been validated previously (22). No correction for partial volume effects was applied to the PET data.

ROIs were projected onto $[^{11}C]$PIB and $[^{18}F]$FDDNP parametric images of binding potential (BPND). These parametric images were generated by applying a “two-step” basis function implementation of the simplified reference tissue model with cerebellar grey matter as reference tissue (RPM2) (23) to the full dynamic 90 minute PET data. RPM2, a fully quantitative method for assessing the data, was identified as the parametric method of choice since it provided best results for both tracers (24,25). The outcome measure BPND is a quantitative measure of specific binding. It reflects the concentration of specifically bound tracer relative to the concentration of free and non-specifically bound tracer in tissue under equilibrium (26). For regional analyses, BPND of frontal (volume weighted average of orbital frontal, medial inferior frontal and superior frontal), parietal and temporal (volume weighted average of superior temporal and medial inferior temporal) cortex and MTL (volume weighted average of enthorinal cortex and hippocampus) and posterior cingulate was used. In addition, a global cortical ROI was defined, based on the volume weighted average of all these regions. Cerebellar grey matter was chosen as reference tissue because of its (histopathological) lack of Congo red and thioflavin-S–positive plaques (27,28).

**Statistics**

Data are presented as mean±SD, unless otherwise stated. Differences between groups were assessed using analysis of variance (ANOVA) with post-hoc LSD tests and age as covariate. Associations between $[^{11}C]$PIB and $[^{18}F]$FDDNP were assessed using Pearson’s correlation coefficient. Regional binding pattern of both $[^{11}C]$PIB and $[^{18}F]$FDDNP between subject groups was assessed using ANOVA for repeated measures with diagnosis as between subjects factor, brain region as within subjects factor and age as covariate. Separate models were run with $[^{11}C]$PIB and $[^{18}F]$FDDNP as dependent variables. A p value below 0.05 was considered to be significant.
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Results

\(^{[1]}\text{C}\)PIB and \(^{[18]}\text{F}\)FDDNP studies were performed on the same day, except for 1 AD patient, 3 MCI patients and 2 healthy controls who were scanned with an average interval of 3 weeks due to radiosynthesis failure. The three groups were similar with respect to age and gender (Table 1). MMSE scores were available of all subjects. AD patients had lower MMSE scores than controls and MCI patients. MMSE scores between the latter two groups did not differ. The Dutch version of the RAVLT was performed in all subjects, except for 3 AD patients.

Visual inspection of the PET images (Figure 1) confirmed the known high cortical \(^{[1]}\text{C}\)PIB binding in AD with predominantly white matter uptake in controls. The specific component of \(^{[18]}\text{F}\)FDDNP was less distinct and high binding was observed in striatum.

![Examples of parametric \(^{[1]}\text{C}\)PIB (panel A) and \(^{[18]}\text{F}\)FDDNP (panel B) BP\(_{\text{ND}}\) images in a control subject and an AD patient. \(^{[1]}\text{C}\)PIB and \(^{[18]}\text{F}\)FDDNP scans were performed in the same subjects. In each panel the control subject is on the left and the AD patient on the right. Note the high level of \(^{[18]}\text{F}\)FDDNP binding in subcortical structures suggesting non specific binding.](image-url)
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Average global cortical BP\(_{ND}\) for [11C]PIB was 0.85±0.10 in patients with AD, 0.28±0.29 in MCI patients and 0.11±0.15 in controls (Figure 2, left panel). ANOVA with adjustment for age showed a significant difference between groups (p<0.0001). Post-hoc LSD tests showed higher [11C]PIB binding in AD than in controls and MCI (both p<0.0001). Furthermore, MCI differed from controls (p=0.03). In AD, average [18F]FDDNP global cortical BP\(_{ND}\) was approximately 9-fold lower than average [11C]PIB global cortical BP\(_{ND}\). Values were 0.09±0.02 in AD, 0.08±0.05 in MCI and 0.05±0.03 in controls (Figure 2, right panel). ANOVA with adjustment for age showed a difference between groups (p=0.04). Post-hoc LSD testing showed higher global [18F]FDDNP BP\(_{ND}\) in AD than in controls (p=0.01), but MCI could not be distinguished from either AD (p=0.54) or controls (p=0.07). [11C]PIB BP\(_{ND}\) values in MCI patients appeared to be bi-modal with values either similar to those in AD patients or controls. In contrast, [18F]FDDNP BP\(_{ND}\) values for MCI patients were quite dispersed, with some MCI patients having lower values than most controls, whereas others even had higher values than AD patients. Across diagnostic groups,

**Table 1**: Demographic and clinical characteristics according to diagnostic group

<table>
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<tr>
<th>Variable</th>
<th>Diagnostic group</th>
<th>MCI</th>
<th>AD</th>
<th>P Value</th>
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<tr>
<td>Age, year</td>
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<td>68±10</td>
<td>63±7</td>
<td>0.21</td>
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<td>Sex % f (f/m)</td>
<td>39% (5/8)</td>
<td>18% (2/9)</td>
<td>43% (6/8)</td>
<td>0.40</td>
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<td>MMSE</td>
<td>29±1</td>
<td>27±3</td>
<td>23±3</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless indicated otherwise.
MCI, Mild cognitive impairment; AD, Alzheimer’s disease; f, female; m, male; MMSE, Mini-Mental-State Examinations.
Differences between groups (P value) were assessed using analysis of variance.
* Post-hoc LSD-tests: AD<MCI, p<0.0001; AD<Controls, p<0.0001; MCI<Controls, p=0.15.

![Figure 2](image.png)

*Figure 2*: Scatter plots of global cortical [11C]PIB BP\(_{ND}\) (panel A) and global cortical [18F]FDDNP BP\(_{ND}\) (panel B), by diagnostic group (controls: squares; MCI = mild cognitive impairment: triangles; AD = Alzheimer’s disease: circles). Horizontal lines between symbols represent mean values. Note the 6-fold lower scale in Figure B compared to A. Differences between groups were assessed using ANOVA (adjusted for age, post-hoc LSD correction), and are indicated by asterisks: * p<0.05; **p<0.0001.
there was a moderate correlation of $BP_{ND}$ values between both tracers ($r=0.45$; $p=0.005$; Figure 3). Within diagnostics groups, however, there was no significant correlation (AD $r=-0.18$; MCI $r=0.34$; controls $r=0.42$; all $p>0.15$). This discrepancy in binding between tracers within subjects is best demonstrated by three MCI subjects. They displayed relatively high $[^{18}F]FDDNP$ uptake compared to controls whereas $[^{11}C]PIB$ binding was similar to controls (Figure 3).

There was a strong correlation between $[^{11}C]PIB$ and MMSE scores across diagnostic groups ($r=-0.75$; $p<0.0001$). $[^{18}F]FDDNP$ showed a moderate correlation with MMSE ($r=-0.39$, $p=0.02$) across groups. Furthermore, there was a strong correlation across diagnostic groups between $[^{11}C]PIB$ and the Dutch version of the RAVLT ($r=-0.63$; $p<0.0001$). $[^{18}F]FDDNP$ showed a reasonably good correlation with the Dutch version of the RAVLT ($r=-0.47$; $p<0.01$). Subsequently, regional binding patterns were investigated (Table 2, Figure 4). In case of $[^{11}C]PIB$, ANOVA for repeated measures showed a significant main effect of diagnostic group ($p<0.0001$) and brain region ($p=0.02$). Moreover, an interaction between diagnostic group and brain region ($p<0.0001$) was found, indicating different regional binding patterns between diagnostic groups. In controls, $[^{11}C]PIB$ binding was equal in all regions. Patients with AD, and to a lesser extent patients with MCI, showed marked increased $[^{11}C]PIB$ binding in all regions, except in MTL, where binding was relatively low compared to the uptake in the other regions (Figure 4A). For $[^{18}F]FDDNP$ there was a main effect of diagnostic group ($p=0.05$) and region ($p=0.001$). No interaction was found, indicating that regional differences were similar across diagnostic groups. AD patients displayed an overall increase in binding compared to controls, with MCI patients in between. Highest binding was seen in the (medial) temporal lobe and lower binding in the frontal, parietal, and posterior cingulate areas, with comparable patterns for the three diagnostic groups (Figure 4B).

**Figure 3:** Correlation between $[^{11}C]PIB$ BP$_{ND}$ and $[^{18}F]$ FDDNP BP$_{ND}$. Across diagnostic groups, there was a moderate correlation between BP$_{ND}$ values of both tracers ($r=0.45$; $p=0.005$, Pearson's correlation). AD patients are represented with circles, MCI with filled triangles and controls with squares. The discrepancy in binding between tracers within subjects is best demonstrated by the three MCI subjects at the top of the figure. They displayed relatively high $[^{18}F]FDDNP$ uptake compared to controls, whereas $[^{11}C]PIB$ binding was similar to controls.

Discussion

This study directly compared global cortical and regional binding of [11C]PIB and [18F]FDDNP in the same AD, MCI and control subjects. The present study revealed marked differences between the two tracers: global cortical binding of both tracers was only moderately correlated, binding in MCI patients varied between tracers and regional binding patterns of both tracers differed substantially. These results all suggest that both tracers bind to different aspects of the neuropathology underlying cognitive decline associated with dementia.

Assessment of global cortical binding showed that both tracers were able to distinguish AD patients from controls on a group level. However, the specific binding of [11C]PIB in AD patients was substantially higher than that of [18F]FDDNP. Moreover, all AD patients displayed increased

| Table 2: Regional [11C]PIB and [18F]FDDNP binding (BPND) data by diagnostic group |
|-----------------------------------|-------------------------------|-----------------|-----------------------------------|-------------------------------|
| Diagnosis            | Controls | [11C]PIB | AD | Controls | [18F]FDDNP |
| Brain region          |          |          |  |          |           |        |
| Global               | 0.11±0.15| 0.28±0.29| 0.85±0.10| 0.05±0.03| 0.08±0.05| 0.09±0.02|
| Frontal              | 0.12±0.21| 0.31±0.34| 0.92±0.10| 0.05±0.04| 0.09±0.07| 0.10±0.02|
| Medial temporal       | 0.07±0.07| 0.05±0.08| 0.15±0.10| 0.11±0.03| 0.13±0.05| 0.14±0.05|
| Temporal             | 0.09±0.12| 0.26±0.25| 0.78±0.11| 0.07±0.03| 0.10±0.06| 0.10±0.03|
| Posterior cingulate  | 0.11±0.10| 0.31±0.29| 0.80±0.16| 0.04±0.04| 0.06±0.07| 0.07±0.05|
| Parietal             | 0.09±0.13| 0.29±0.32| 0.94±0.18| 0.03±0.04| 0.04±0.04| 0.06±0.03|

Data are presented as mean ± SD.
MCI, Mild cognitive impairment; AD, Alzheimer’s disease

Figure 4: Regional binding pattern of both [11C]PIB (panel A) and [18F]FDDNP (panel B) between subject groups. Binding was assessed using ANOVA for repeated measures adjusted for age with diagnosis as between subjects factor, brain region as within subjects factor. Separate models were run with [11C]PIB and [18F]FDDNP as dependent variables. A p value below 0.05 was considered significant. Regional [11C]PIB binding pattern had a significant main effect in subject group (p<0.0001) and brain region (p=0.02) and an interaction between subject group and brain region (p<0.0001). Regional [18F]FDDNP binding pattern had a significant main effect in subject group (p=0.05) and brain region (p=0.001), but without interaction. AD patients are represented by circles, MCI with triangles and controls with squares.
global cortical \([^{11}C]PIB\) binding without overlap with control subjects. In contrast, global cortical \([^{18}F]FDDNP\) binding in AD patients showed substantial overlap between AD patients and control subjects. This overlap is probably due to the fact that there is a higher level of non-specific binding (binding other than to amyloid or tangles) in both groups leading to a lower specific to non-specific binding ratio. Consequently, at a group level differentiation is possible, but identification of increased uptake in individual cases may prove to be difficult with \([^{18}F]FDDNP\), whilst this is possible with \([^{11}C]PIB\). These results suggest that the accuracy of \([^{18}F]FDDNP\) as a differential diagnostic tool for detection of Alzheimer pathology in individual subjects will be lower than that of \([^{11}C]PIB\).

For both tracers, MCI patients showed average binding intermediate between AD patients and control subjects. \([^{11}C]PIB\) binding in MCI was similar to that of either controls or AD patients. This bi-modal distribution of \([^{11}C]PIB\) binding in MCI patients is consistent with results from other studies \((10-13)\). With \([^{18}F]FDDNP\), the distribution of binding was more widespread. A larger number of MCI patients displayed increased global cortical \([^{18}F]FDDNP\) uptake, in some patients even exceeding that of AD patients. In the only other report on \([^{18}F]FDDNP\) in MCI \((5)\), MCI patients as a group showed intermediate \([^{18}F]FDDNP\) binding, and all subjects displayed lower binding than that in the highest AD patients, which is somewhat discrepant with the present results and probably due to patient selection.

Regional binding showed different patterns between the two tracers. For \([^{11}C]PIB\), there was a difference in regional binding patterns between diagnostic groups. AD patients showed increased binding in all brain regions compared to healthy controls, with relatively smallest increase in the MTL. For \([^{18}F]FDDNP\), regional binding patterns were comparable between diagnostic groups. AD patients displayed an overall increase in binding compared to controls, with MCI patients in between. For all three groups highest values across brain regions were found in MTL. The differences in regional binding can be explained by the binding characteristics of \([^{11}C]PIB\) and \([^{18}F]FDDNP\): the \textit{in vivo} cortical uptake of \([^{11}C]PIB\) primarily reflects Aβ related cerebral amyloidosis \((29)\), whilst uptake of \([^{18}F]FDDNP\) results from binding to both amyloid depositions and neurofibrillary tangles \((30)\). Different binding sites for \([^{11}C]PIB\) and \([^{18}F]FDDNP\) as a cause for differences in binding patterns is further supported by a recently published study comparing both tracers in aged and young macaques \((31)\). Relatively low binding of \([^{11}C]PIB\) in MTL of AD patients is consistent with the low level of amyloid depositions in this region \((32)\). Therefore, the relatively high binding of \([^{18}F]FDDNP\) in MTL suggests that this could be due to \textit{in vivo} binding to neurofibrillary tangles, which are abundant in MTL. In the present study three MCI subjects displayed high \([^{18}F]FDDNP\) binding, whereas \([^{11}C]PIB\) binding was within the normal range. It is appealing to speculate that these MCI subjects may suffer from a prodromal dementia other than AD, for instance a tauopathy, contributing to the relatively high \([^{18}F]FDDNP\) uptake. Further studies are needed, however, to substantiate this hypothesis.

In general, present results are in line with those reported in previous \([^{11}C]PIB\) studies (mostly expressed as distribution volume ratio DVR, which equals BP\text{ND} + 1) \((48-1133)\). Previously published levels of global and regional binding (also expressed as DVR) for \([^{18}F]FDDNP\) were
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slightly higher for AD (5), AD patients in the present study, however, were, on average, ten years younger than in the previously published study. Therefore, these differences could be due to differences in age, as tangle load has been reported to increase with age (34). To date, two studies have compared both amyloid tracers in human subjects. The first study was performed in two different individuals with a hereditary prion disease, still making it very difficult to provide an objective comparison of the two tracers (35). In a more recent study Shin et al. (36) presented the first intrasubject comparison of $[^{11}C]$PIB and $[^{18}F]$FDDNP in healthy controls and AD subjects. They reported negligible $[^{11}C]$PIB, but strong $[^{18}F]$FDDNP uptake in the medial temporal lobe in AD subjects, whereas there was significant uptake of both tracers in neocortical areas. Although rather similar in design, there are several important differences in methods between this multi tracer study and the present study. AD patients were, on average, ten years older and had more severe AD with a mean MMSE score of 13. No MCI patients were included and scans were performed on separate days. The average injected dose of $[^{11}C]$PIB was similar, whilst the average injected dose of $[^{18}F]$FDDNP was lower. The total amount of injected $[^{18}F]$FDDNP (labeled and non-labeled) and thus the occupation of the number of binding sites, however, was approximately equal. PET data were analysed using only semi-quantitative methods. For $[^{11}C]$PIB, SUVR$_{40-60}$ has been used to quantify PET data. Although this method has been validated for visualising $[^{11}C]$PIB accumulation (7), it may suffer from bias due to flow effects. Simple tissue ratios using 40-60 minutes data, such as SUVR$_{40-60}$, have been reported to overestimate specific binding by around 18% compared to a more quantitative model (37). $[^{18}F]$FDDNP PET data has been quantified using SUVR$_{60-120}$. Currently no formal validation of SUVR$_{60-120}$ has been published for $[^{18}F]$FDDNP. The use of this non-validated analytical method for $[^{18}F]$FDDNP warrants caution since a relatively small bias can lead to large effects in measured values due to the low specific to non-specific binding ratio of $[^{18}F]$FDDNP. Despite these essential differences, results were partly in line with each other. Levels of global and regional binding for $[^{11}C]$PIB were in good agreement with the present study, both for controls and AD patients. However, levels of global and regional binding for $[^{18}F]$FDDNP in AD patients were substantially higher as well as levels of $[^{18}F]$FDDNP binding in the medial temporal lobe in controls. Although most of the discrepancies found in the results could largely be attributable to differences in patient selection, as tangle load has been reported to increase with age (34) and disease severity (38), potential bias due to the use of non-validated analytical methods could also have confounded some of their results.

The main strength of the present study is its unique design, in which dynamic 90 minute PET scans with both ligands were performed in the same subjects along the spectrum of cognitive decline and on the same day. This design eliminated intersubject differences and thus enabled a balanced comparison.

Due to the longer radioactive decay of the $[^{18}F]$ labeled FDDNP (110 minutes) compared to $[^{11}C]$PIB (20 minutes), the study was set up with $[^{11}C]$PIB as the first scan. $[^{11}C]$PIB with high specific activity was injected in tracer amounts (nanograms) leading to a negligible occupancy of $[^{11}C]$PIB binding sites. In addition, analysis of the six subjects of which $[^{11}C]$PIB and $[^{18}F]$FDDNP scans
were performed on separate days revealed no difference of $[^{18}F]$FDDNP binding compared to $[^{18}F]$FDDNP binding values of studies performed on a single day. Therefore it is highly unlikely that the order of the scans have influenced final results.

**Conclusion**

The regional binding patterns, the moderately correlated global cortical binding and the findings in MCI patients together imply that $[^{11}C]$PIB and $[^{18}F]$FDDNP measure related, but different aspects of the neuropathology associated with AD. The binding of $[^{18}F]$FDDNP to pathology other than amyloid may lead to its complementary use to $[^{11}C]$PIB in the differential diagnosis of dementia. More specially, $[^{18}F]$FDDNP might be useful in $[^{11}C]$PIB negative MCI subjects, which could have prodromal dementias other than AD. Inclusion of more subjects, especially MCI patients, and clinical follow-up is needed to substantiate these findings.

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