Chapter 6

Differential association of $[^{11}\text{C}]\text{PIB}$ and $[^{18}\text{F}]\text{FDDNP}$ binding with cognitive impairment

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Abstract

Objective: To evaluate associations of $[^{11}C]$PIB and $[^{18}F]$FDDNP with impairment in specific cognitive domains over the broader spectrum comprising cognitively normal elderly subjects, MCI and AD.

Methods: Twelve Alzheimer’s disease (AD) patients, 13 mild cognitive impairment (MCI) patients and 15 cognitively normal elderly subjects were included. Paired $[^{11}C]$PIB and $[^{18}F]$FDDNP positron emission tomography (PET) scans were performed in all subjects. Binding potential (BP_{ND}) was calculated using parametric images of BP_{ND} for global, frontal, parietal, temporal and medial temporal and posterior cingulate. Cognitive functions were assessed using a battery of neuropsychological tests. Linear regression analyses were used to assess associations of $[^{11}C]$ PIB and $[^{18}F]$FDDNP binding with cognitive measures.

Results: Adjusted for age, sex and $[^{18}F]$FDDNP binding, higher global $[^{11}C]$PIB binding was associated with lower scores on MMSE, immediate and delayed recall of the RAVLT, VAT and TMT part B. Conversely, higher $[^{18}F]$FDDNP binding was independently associated with lower scores on immediate recall of the RAVLT. After additional adjustment for diagnosis, higher $[^{11}C]$ PIB binding remained independently associated with delayed recall (standardised β=-0.39, p=0.01) whilst higher $[^{18}F]$FDDNP binding remained independently associated with immediate recall (standardised β=-0.32, p=0.03). When regional binding was assessed using stepwise models, both increased frontal $[^{11}C]$PIB and temporal $[^{18}F]$FDDNP binding were associated with memory, whilst increased parietal $[^{11}C]$PIB binding was associated with non-memory functions.

Conclusion: Increased $[^{18}F]$FDDNP binding is specifically associated with impairment of episodic memory, whilst increased $[^{11}C]$PIB binding is associated with impairment in a broader range of cognitive functions.
Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder. The diagnosis of AD can be preceded by a preclinical phase, which is characterised primarily by episodic memory impairment, often referred to as mild cognitive impairment (MCI) (1,2). A clinical diagnosis of AD is made when, in addition to progressive memory impairment, impairment in at least one other cognitive domain, e.g. aphasia, apraxia, agnosia or executive dysfunctioning is present (3).

The neuropathology of AD is characterised by the accumulation of amyloid-beta (Aβ) in senile plaques and hyperphosphorylated tau in neurofibrillary tangles. Over the past two decades, positron emission tomography (PET) tracers have been developed for in vivo imaging of AD pathology. Of these ligands, $[^{11}C]$PIB (4) and $[^{18}F]$FDDNP (5) have been used most widely. $[^{11}C]$PIB was designed to measure the amount of fibrillar Aβ deposits (6,7), whilst $[^{18}F]$FDDNP has been reported to label not only amyloid but also other proteins (8) including neurofibrillary tangles (9). Recently, using a paired study in the same subjects, we have shown that both tracers were able to distinguish AD patients from cognitively normal elderly subjects at a group level, although $[^{11}C]$PIB had the largest discriminative power (10).

To date, several studies have reported associations between increased $[^{11}C]$PIB binding and episodic memory impairment in cognitively normal elderly subjects and MCI patients (4,11-12). For $[^{18}F]$FDDNP, associations between increased frontal, temporal and parietal binding and impairment of memory have been found (5)(13). At present, no studies have been performed evaluating relationships between tracer binding and cognitive impairment using both tracers in the same subjects. The aim of this study was to assess the independent associations of $[^{11}C]$PIB and $[^{18}F]$FDDNP with impairment in the cognitive domains of memory, language, executive functioning and visuoconstructive praxis over the spectrum comprising cognitively normal elderly subjects, MCI and AD.

Methods

Subjects

Twelve AD patients, 13 patients with amnestic MCI and 15 age matched cognitively normal elderly subjects, for which paired $[^{11}C]$PIB and $[^{18}F]$FDDNP scans and neuropsychological data were available, were included between November 2005 and September 2008. Global and regional $[^{11}C]$PIB and $[^{18}F]$FDDNP binding of an overlapping sample have been presented before (10).

All patients received a standard dementia screening that included medical history, physical and neurological examinations, screening laboratory tests and brain magnetic resonance imaging (MRI). Clinical diagnosis was established by consensus in a multidisciplinary team, without knowledge of PET results. All AD patients met NINCDS-ADRDA criteria for “probable AD” (3). MCI patients met Petersen criteria based on subjective and objective cognitive impairment,
predominantly affecting memory, in the absence of dementia or significant functional impairment (2). Cognitively normal elderly subjects were recruited through advertisements in newspapers, and underwent the same diagnostic procedures. The level of education was classified using the system of Verhage (14), ranging from 1 (low) to 7 (high). Exclusion criteria were history of major psychiatric or neurological (other than AD) illness and use of non-steroidal anti-inflammatory drugs (NSAIDS), as these have been reported to compete with [18F]FDDNP for binding to Aβ fibrils in vitro and to Aβ plaques ex vivo (15). Additional exclusion criteria for cognitively normal elderly subjects were subjective memory complaints or clinically significant abnormalities on the MRI scan (as determined by a neuroradiologist).

**Standard Protocol Approvals, Registrations, and Patient Consents**

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 Amsterdam.

**Neuropsychological Assessment**

Detailed neuropsychological assessment was performed using the following tests: Mini Mental State Examination (MMSE) (16), Digit Span (17), immediate and delayed recall of the Dutch version of the Rey Auditory Verbal Learning Task (RAVLT) (18), Visual Association Test (VAT) (19) (ranging from 1 (low) to 12 (high)) together with VAT picture naming (same range as VAT), category fluency, Trail Making Test (TMT) part A and B, Stroop tests with the Word, Colour and Colour-Word subtasks (20), and the Rey Complex Figure Copy test (21). Median time between imaging and neuropsychological assessment was 0.9 month (interquartile range: 1.6 months) with a mean (SD) of 1.2 (1.3) months.

**Positron emission tomography**

PET scans were performed using an ECAT EXACT HR+ scanner (22) (Siemens/CTI, Knoxville, USA), equipped with a neuro-insert to reduce the contribution of outside field of view (FOV) activity. This scanner enables the acquisition of 63 transaxial planes over a 15.5 cm axial FOV, thus allowing the whole brain to be imaged in a single bed position. All subjects received a venous cannula for tracer injection. Patient motion was restricted by the use of a head holder and monitored by checking the position of the head using laser beams. First, a 10 minutes 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 $353 \pm 71$ MBq $[^{11}\text{C}]$PIB with a specific activity (SA) of $43 \pm 24$ GBq/µmol. Using an infusion pump (Med-Rad, Beek, the Netherlands), activity was injected in approximately 4 sec, which was followed by a flush of 40 ml saline at 2.0 ml/sec. Radiolabeled $[^{11}\text{C}]$PIB was synthesised according to a modification (23) of the procedure described by Wilson et al. (24) Each dynamic emission scan consisted of 23 frames with
Association with cognitive impairment

progressive increase in frame length (1x15, 3x5, 3x10, 2x30, 3x60, 2x150, 2x300, 7x600 s) and a total duration of 90 minutes.

After a resting period of at least 1 hour to allow for decay of $^{11}$C (i.e. about 2.5 hours after the administration of $[^{11}$C]PIB), an identical $[^{18}$F]FDDNP protocol was performed using an injection of 179±15 MBq $[^{18}$F]FDDNP (25) with an SA of 78±51 GBq/µmol.

**Magnetic resonance imaging**

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 ms; inversion time=950 ms; flip angle 8°).

**Image 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 cut-off at 0.5 times the Nyquist frequency. A zoom factor of 2 and a matrix size of 256x256x63 were used, resulting in a voxel size of 1.2x1.2x2.4 mm and a spatial resolution of approximately 7 mm full-width at half-maximum at the centre of the field of view.

MR images were aligned to corresponding PET images using a mutual information algorithm (26). Segmentation of MR images and further analysis of PET data was performed using PVE lab, a software program that uses a probability map of 35 delineated (grey matter) regions of interest (ROI) that has been validated previously (27). 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 ($BP_{ND}$). These parametric images were generated by applying a basis function implementation of the “two-step” simplified reference tissue model with cerebellar grey matter as reference tissue (RPM2) (28) to the full dynamic 90 minutes PET data (29,30). $BP_{ND}$ is a quantitative measure of specific binding, reflecting the concentration of specifically bound tracer relative to the concentration of free and non-specifically bound tracer in tissue under equilibrium conditions (31). A global cortical ROI was defined, based on a volume weighted $BP_{ND}$ average of the following ROIs: frontal (volume weighted average of orbital frontal, medial inferior frontal and superior frontal), parietal, temporal (volume weighted average of superior temporal and medial inferior temporal) cortex, medial temporal lobe (MTL) (volume weighted average of entorhinal cortex and hippocampus), and posterior cingulate. Mean (±SD) volumes for the ROIs were: frontal 55±9 ml, parietal 26±5 ml, temporal 41±7 ml, MTL 5±1 ml and posterior cingulate 3±1 ml. Cerebellar grey matter was chosen as reference tissue, because of its (histopathological) lack of Congo red and thioflavin-S–positive plaques (32,33).
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Statistical analysis

Data are presented as mean±SD, unless otherwise stated. Data of TMT and Stroop tests were log-transformed as they were not normally distributed. Frequency distributions for sex were compared with Chi-squared tests. For continuous measures, differences between groups were assessed using analysis of variance (ANOVA) with age and sex as covariates and post-hoc least significant difference (LSD) tests.

Pearson’s correlations were calculated for global and regional \([^{[1]}C]PIB\) and \([^{[1]}F]FDDNP\) binding. For assessment of relationships between global BP\(_{ND}\) data and neuropsychological tests, linear regression analyses were performed. Standardised β’s and standard errors (SE) are reported to allow comparison of effect sizes. R\(^2\) are given for each model. In the first model, the relationship of each PET ligand (independent variable) with each cognitive test (dependent variable) was assessed separately, after adjustment for age and sex. In the second model, both PET ligands were entered simultaneously (independent variables), after adjustment for age and sex. In the third model, the same relationships were examined as in the second model, additionally adjusted for diagnosis (using dummy variables).

Subsequently, an additional analysis was performed to evaluate the relationships between regionally increased ligand binding and performance on neuropsychological tests. After adjustment for age and sex (forced entry), forward step regression analysis was performed with regional \([^{[1]}C]PIB\) and \([^{[1]}F]FDDNP\) BP\(_{ND}\) of frontal, parietal, temporal, MTL and posterior cingulate ROIs as independent variables for each cognitive test (dependent variable). Probability for entry was set at 0.05 and removal at 0.10.

Results

Demographic and clinical characteristics according to diagnostic group are presented in Table 1. The three groups did not differ with respect to age, sex or level of education. Average global cortical BP\(_{ND}\) for \([^{[1]}C]PIB\) differed between groups. Higher \([^{[1]}C]PIB\) binding was found in AD patients compared with cognitively normal elderly subjects and MCI patients. Furthermore, \([^{[1]}C]PIB\) binding in MCI patients was higher than that of cognitively normal elderly subjects. Average global cortical BP\(_{ND}\) for \([^{[1]}F]FDDNP\) did not differ significantly between groups, but tended to be highest in AD patients, lowest in cognitively normal elderly subjects and intermediate in MCI patients. As expected, performance on all neuropsychological tests, except for the forward condition of the Digit span, VAT picture naming and Stroop 2, differed between the three groups. Compared to cognitively normal elderly subjects, poorest results were found for AD patients with MCI patients displaying intermediate values (Table 1).

Across the diagnostic groups, global binding of the two ligands was moderately correlated (Table 2). When regional binding was assessed, similar correlations were found for frontal and parietal ROI but poor correlations were found for temporal, medial temporal and posterior cingulate ROIs.

Linear regression analyses showed that, adjusted for age and sex, higher global \([^{[1]}C]PIB\) binding
Table 1: Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>MCI</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>68±7</td>
<td>67±10</td>
<td>64±7</td>
</tr>
<tr>
<td><strong>Sex (f/m)</strong></td>
<td>5/10</td>
<td>2/11</td>
<td>4/8</td>
</tr>
<tr>
<td><strong>Level of Education ¥</strong></td>
<td>6±1</td>
<td>6±1</td>
<td>6±1</td>
</tr>
<tr>
<td><strong>Global [11C]PIB BPND</strong></td>
<td>0.15±0.25</td>
<td>0.41±0.39*</td>
<td>0.86±0.12*,**</td>
</tr>
<tr>
<td><strong>Global [18F]FDDNP BPND</strong></td>
<td>0.06±0.03</td>
<td>0.07±0.05</td>
<td>0.09±0.02</td>
</tr>
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<td><strong>MMSE</strong></td>
<td>29±1</td>
<td>28±2*</td>
<td>24±2*,**</td>
</tr>
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<td><strong>Digit span, forward</strong></td>
<td>6±1</td>
<td>6±1</td>
<td>6±1</td>
</tr>
<tr>
<td><strong>Digit span, backward</strong></td>
<td>4±1</td>
<td>5±1*</td>
<td>4±1**</td>
</tr>
<tr>
<td><strong>Immediate recall RAVLT</strong></td>
<td>38±9</td>
<td>31±7*</td>
<td>23±9*,**</td>
</tr>
<tr>
<td><strong>Delayed recall RAVLT</strong></td>
<td>7±2</td>
<td>4±2*</td>
<td>1±2*,**</td>
</tr>
<tr>
<td><strong>VAT</strong></td>
<td>12±1</td>
<td>11±2</td>
<td>6±4*,**</td>
</tr>
<tr>
<td><strong>VAT picture naming2</strong></td>
<td>12±2</td>
<td>12±1</td>
<td>10±3</td>
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<tr>
<td><strong>TMT A ‡</strong></td>
<td>36±16</td>
<td>44±14</td>
<td>76±43*,**</td>
</tr>
<tr>
<td><strong>TMT B ‡</strong></td>
<td>77±27</td>
<td>110±22*</td>
<td>181±113*,**</td>
</tr>
<tr>
<td><strong>Stroop 1 ‡,2</strong></td>
<td>42±5</td>
<td>44±8</td>
<td>56±20*,**</td>
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<tr>
<td><strong>Stroop 2 ‡,2</strong></td>
<td>59±13</td>
<td>59±13</td>
<td>95±66</td>
</tr>
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<td><strong>Stroop 3 ‡,2</strong></td>
<td>107±31</td>
<td>111±17</td>
<td>168±71*,**</td>
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<td><strong>Category fluency1</strong></td>
<td>23±4</td>
<td>19±6</td>
<td>13±5*,**</td>
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<td><strong>Rey Figure Copy1</strong></td>
<td>35±1</td>
<td>34±3</td>
<td>26±8*,**</td>
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</table>

Data are presented as mean±standard deviation

MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning task; VAT: Visual Association Task, TMT: TrailMaking Test; AD: Alzheimer’s disease; MCI: mild cognitive impairment

¥ Education using Verhage’s classification(14)

‡ lower scores indicate better (faster) performances

1 Missing data of 1-3 AD subjects
2 Missing data of 1 MCI subject

Note, that for TMT A and B and Stroop 1, 2 and 3 values are shown as measured, whilst statistical analyses were performed on log-transformed values.

If analysis of variance with age and sex as covariate was p<0.05, then a post-hoc LSD test was performed

* p <0.05 compared with cognitively normal elderly subjects

** p <0.01 compared with MCI

Table 2: Correlations between global and regional [11C]PIB and [18F]FDDNP binding

<table>
<thead>
<tr>
<th>ROI</th>
<th>r</th>
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<tbody>
<tr>
<td>Global</td>
<td>0.45**</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.46**</td>
</tr>
<tr>
<td>Medial Temporal</td>
<td>0.32*</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.36*</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>0.32*</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.47**</td>
</tr>
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</table>


BPND: binding potential, ROI; region of interest

* p<0.05
** p<0.01
### Table 3: Associations of $[^{11}C]PIB$ and $[^{18}F]FDDNP$ BP\(_{ND}\) with cognitive test performance

<table>
<thead>
<tr>
<th>Cognitive functions</th>
<th>Model 1 $[^{11}C]PIB$</th>
<th>R(^2)</th>
<th>St. β (SE)</th>
<th>Model 2 $[^{18}F]FDDNP$</th>
<th>R(^2)</th>
<th>St. β (SE)</th>
<th>Model 3 $[^{11}C]PIB$</th>
<th>R(^2)</th>
<th>St. β (SE)</th>
<th>Model 3 $[^{18}F]FDDNP$</th>
<th>R(^2)</th>
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<tbody>
<tr>
<td>MMSE</td>
<td>-0.67 (0.12)**</td>
<td>0.52</td>
<td>-0.43 (0.14)**</td>
<td>0.28</td>
<td>-0.59 (0.13)**</td>
<td>-0.18 (0.13)</td>
<td>0.54</td>
<td>-0.13 (0.14)</td>
<td>-0.14 (0.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span forward</td>
<td>0.05 (0.15)</td>
<td>0.19</td>
<td>-0.07 (0.15)</td>
<td>0.19</td>
<td>0.11 (0.17)</td>
<td>-0.12 (0.17)</td>
<td>0.20</td>
<td>0.10 (0.22)</td>
<td>-0.11 (0.16)</td>
<td></td>
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</tr>
<tr>
<td>Digit span backward</td>
<td>-0.09 (0.15)</td>
<td>0.19</td>
<td>-0.10 (0.15)</td>
<td>0.19</td>
<td>-0.06 (0.17)</td>
<td>-0.06 (0.17)</td>
<td>0.20</td>
<td>-0.24 (0.21)</td>
<td>-0.06 (0.16)</td>
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<tr>
<td>Immediate recall RAVLT</td>
<td>-0.56 (0.14)**</td>
<td>0.31</td>
<td>-0.52 (0.14)**</td>
<td>0.21</td>
<td>-0.41 (0.15)*</td>
<td>-0.34 (0.15)*</td>
<td>0.40</td>
<td>-0.08 (0.19)</td>
<td>-0.32 (0.14)*</td>
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<tr>
<td>Delayed recall RAVLT</td>
<td>-0.77 (0.11)**</td>
<td>0.56</td>
<td>-0.50 (0.14)**</td>
<td>0.25</td>
<td>-0.67 (0.12)**</td>
<td>-0.21 (0.12)</td>
<td>0.60</td>
<td>-0.39 (0.15)*</td>
<td>-0.19 (0.11)</td>
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<tr>
<td>VAT</td>
<td>-0.50 (0.15)**</td>
<td>0.28</td>
<td>-0.22 (0.16)</td>
<td>0.09</td>
<td>-0.50 (0.17)**</td>
<td>0.01 (0.16)</td>
<td>0.28</td>
<td>0.01 (0.18)</td>
<td>0.02 (0.14)</td>
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<td>VAT picture naming</td>
<td>-0.15 (0.17)</td>
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<td>-0.11 (0.17)</td>
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<td>0.13 (0.19)</td>
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<td>0.24 (0.25)</td>
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<tr>
<td>TMT A</td>
<td>0.32 (0.16)*</td>
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<td>0.11 (0.16)</td>
<td>0.03</td>
<td>0.34 (0.18)</td>
<td>-0.04 (0.18)</td>
<td>0.12</td>
<td>-0.25 (0.20)</td>
<td>-0.09 (0.15)</td>
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<td>TMT B</td>
<td>0.47 (0.15)**</td>
<td>0.25</td>
<td>0.22 (0.17)</td>
<td>0.09</td>
<td>0.47 (0.18)*</td>
<td>0.01 (0.17)</td>
<td>0.25</td>
<td>0.06 (0.20)</td>
<td>-0.03 (0.15)</td>
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<tr>
<td>Stroop 1</td>
<td>0.27 (0.16)</td>
<td>0.13</td>
<td>0.14 (0.16)</td>
<td>0.07</td>
<td>0.09 (0.18)</td>
<td>0.52 (0.18)</td>
<td>0.14</td>
<td>0.01 (0.23)</td>
<td>-0.12 (0.18)</td>
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<tr>
<td>Stroop 2</td>
<td>0.24 (0.16)</td>
<td>0.20</td>
<td>0.03 (0.16)</td>
<td>0.15</td>
<td>0.28 (0.18)</td>
<td>-0.08 (0.17)</td>
<td>0.21</td>
<td>-0.06 (0.22)</td>
<td>-0.09 (0.16)</td>
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<tr>
<td>Stroop 3</td>
<td>0.32 (0.17)</td>
<td>0.12</td>
<td>-0.01 (0.17)</td>
<td>0.02</td>
<td>0.39 (0.19)*</td>
<td>-0.17 (0.18)</td>
<td>0.14</td>
<td>-0.04 (0.23)</td>
<td>-0.17 (0.17)</td>
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<tr>
<td>Category fluency</td>
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<td>0.21</td>
<td>-0.22 (0.16)</td>
<td>0.06</td>
<td>-0.44 (0.17)*</td>
<td>-0.02 (0.17)</td>
<td>0.21</td>
<td>-0.20 (0.20)</td>
<td>-0.10 (0.15)</td>
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<td>Rey Figure Copy</td>
<td>-0.34 (0.15)*</td>
<td>0.23</td>
<td>-0.15 (0.16)</td>
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<td>-0.33 (0.17)</td>
<td>-0.02 (0.17)</td>
<td>0.23</td>
<td>0.15 (0.19)</td>
<td>0.02 (0.14)</td>
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</table>

Associations between $[^{11}C]PIB$ and $[^{18}F]FDDNP$ BP\(_{ND}\) and cognitive functions (dependent variables) were assessed using linear regression analyses. Estimates are represented as standardised beta's, to allow comparison of effect sizes. Model 1: PET ligand, adjusted for age and sex. Model 2: both PET ligands entered simultaneously (independent variables), adjusted for age and sex. Model 3: as model 2, additionally adjusted for diagnosis (using dummy variables).

MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning task; VAT: Visual Association Task, TMT: Trail Making Test. St.β: standardised beta; SE: standard error

* p<0.05; ** p<0.01
Association with cognitive impairment

Figure 1: Scatter plots of $[^{11}C]$PIB binding (global BP$_{ND}$) and (A) immediate and (B) delayed recall of the Rey Auditory Verbal Learning Test (RAVLT) together with scatter plots of $[^{18}F]$FDDNP binding (global BP$_{ND}$) and (C) immediate and (D) delayed recall of the RAVLT. Open circles represent patients with AD, filled triangles patients with MCI and open squares cognitively normal elderly subjects. After adjustment for age, sex, $[^{18}F]$FDDNP binding and diagnosis, higher global $[^{11}C]$PIB binding was associated with lower scores on delayed recall (standardised $\beta$= -0.39, standard error=0.15, p=0.01), but not with lower scores on immediate recall (standardised $\beta$= -0.08, standard error=0.19, p>0.01). After adjustment for age, sex, $[^{11}C]$PIB binding and diagnosis, higher global $[^{18}F]$FDDNP binding was associated with lower scores on immediate recall (standardised $\beta$= -0.32, standard error=0.14, p=0.03) but not with lower scores on delayed recall of RAVLT (standardised $\beta$= -0.19, standard error= 0.11, p=0.08).

The various lines illustrate the different relationships with the cognitive tests for each diagnostic sample; the solid line represents the total sample, the dashed line the AD patients, the dashed-dotted line the MCI patients and the dotted line the controls. Note that, for delayed recall, values of AD patients had limited variability as they were at floor level. Furthermore, in fig. A the trend line of AD patients was affected by the relatively limited variability in $[^{11}C]$PIB binding.
was associated with lower scores on MMSE, immediate and delayed recall on the RAVLT, VAT, TMT parts A and B, category fluency and Rey Figure Copy test (Table 3, model 1). Higher global \(^{[18F]}\)FDDNP binding was associated with lower scores on MMSE and immediate and delayed recall on the RAVLT (model 1). When both ligands were entered in the same model (model 2), higher global \(^{[11C]}\)PIB binding remained associated with lower scores on MMSE, immediate and delayed recall on the RAVLT, VAT and TMT part B. Similarly, increased \(^{[18F]}\)FDDNP remained associated with lower scores on immediate recall, but associations with MMSE and delayed recall disappeared. After additional adjustment for diagnosis (model 3), higher \(^{[11C]}\)PIB binding remained independently associated with delayed recall on the RAVLT and higher \(^{[18F]}\)FDDNP binding remained independently associated with immediate recall on the RAVLT (see also Figure 1).

Finally, forward step regression analysis was used to assess associations between regional binding BP\(_{ND}\) values and cognitive test performance (Table 4). Increased frontal \(^{[11C]}\)PIB binding was associated with lower scores on MMSE and delayed recall on RAVLT. Both increased temporal \(^{[11C]}\)PIB and frontal \(^{[18F]}\)FDDNP binding were associated with lower scores on immediate recall of RAVLT. Parietal \(^{[11C]}\)PIB binding was associated with poorer performance on TMT part A and B, Stroop 3, Category fluency and Rey Figure Copy test. Posterior cingulate \(^{[11C]}\)PIB binding was associated with poorer performance on VAT.

**Discussion**

In this study, associations of \(^{[11C]}\)PIB and \(^{[18F]}\)FDDNP binding with impairment in specific cognitive domains across the spectrum of cognitively normal elderly subjects, MCI and AD were assessed. Increased \(^{[18F]}\)FDDNP binding was associated specifically with impairment of episodic
memory, whilst increased $[^{11}\text{C}]$PIB binding was associated with impairment in a broader range of cognitive functions, especially memory impairment and executive dysfunctioning. Other studies have presented associations with either increased $[^{11}\text{C}]$PIB (11-12,34) or $[^{18}\text{F}]$FDDNP binding (5,13). Increased $[^{11}\text{C}]$PIB binding was associated with both impaired memory performance and impaired non-memory functions (11). Increased $[^{18}\text{F}]$FDDNP signal was found to be associated with decreased composite cognitive score (13). In the present study, $[^{11}\text{C}]$PIB and $[^{18}\text{F}]$FDDNP binding were simultaneously evaluated, revealing both ligands to be independently associated with impaired cognition. Higher global $[^{11}\text{C}]$PIB was independently associated with impairment in a number of cognitive domains, whilst higher global $[^{18}\text{F}]$FDDNP was associated specifically with episodic memory impairment.

While no specific associations between memory and amyloid load in the brain at post mortem examinations have been reported, amyloid deposition in general is associated with a high likelihood of presence of AD. This seemingly is in line with the more widespread impairment in cognition associated with increased global $[^{11}\text{C}]$PIB binding. The specific association between $[^{18}\text{F}]$FDDNP binding and episodic memory impairment, when simultaneously assessing the ligands, is somewhat less straightforward. However, part of the specific signal of $[^{18}\text{F}]$FDDNP may be due to the tangle component (35). Apart from differences in underlying substrate for tracer binding, an alternative explanation for the difference in associations between $[^{11}\text{C}]$PIB and $[^{18}\text{F}]$FDDNP could be the higher specific signal of $[^{11}\text{C}]$PIB. As a result, differences between diagnostic groups were larger and may have driven the observed associations with cognitive functioning. When additional adjustments for diagnosis were performed, association between global binding and episodic memory remained for both tracers. This implies that even after accounting for a diagnosis effect, both amyloid and tangle burden, as estimated using PET, contributed to impairment in episodic memory, the main characteristic of (prodromal) AD (1).

When regional binding was assessed, frontal, temporal and posterior cingulate $[^{11}\text{C}]$PIB binding and frontal $[^{18}\text{F}]$FDDNP binding were associated with memory function, whilst parietal $[^{11}\text{C}]$PIB binding was associated with non-memory domains of language, executive functioning and visuoconstructive praxis. These findings suggest that the association with impairment in specific cognitive domains is at least partly driven by regional tracer uptake.

A limitation of the present study is the relatively small sample size, possibly concealing subtle associations. Nevertheless, the unique design, performing quantitative PET scanning with both ligands and neuropsychological tests in the same subjects along the spectrum of cognitive decline, enabled a direct evaluation of the independent association of both tracers with impairment in specific cognitive domains.

The present findings demonstrate that higher binding of both $[^{11}\text{C}]$PIB and $[^{18}\text{F}]$FDDNP are associated with cognitive impairment. This has relevance in the discussion on using biomarkers to identify the prodromal phase of AD (36) and on biomarkers serving as surrogate markers of disease progression in clinical trials.
Chapter 6

References


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