Amyloid burden and metabolic function in early-onset Alzheimer's disease: parietal lobe involvement

Rik Ossenkoppele,1,2 Marissa D. Zwan,1,2 Nelleke Tolboom,1,2 Danielle M. E. van Assema,1,2 Sofie F. Adriaanse,1,2 Reina W. Kloet,2 Ronald Boellaard,2 Albert D. Windhorst,2 Frederik Barkhof,3 Adriaan A. Lammertsma,2 Philip Scheltens,1 Wiesje M. van der Flier1,4 and Bart N. M. van Berckel2

1 Department of Neurology and Alzheimer Center, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands
2 Department of Nuclear Medicine and PET Research, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands
3 Department of Radiology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands
4 Department of Epidemiology and Biostatistics, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands

Correspondence to: Rik Ossenkoppele, Department of Neurology and Alzheimer Center and Department of Nuclear Medicine and PET Research, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands
E-mail: r.ossenkoppele@vumc.nl

Alzheimer's disease with early onset often presents with a distinct cognitive profile, potentially reflecting a different distribution of underlying neuropathology. The purpose of this study was to examine the relationships between age and both in vivo fibrillary amyloid deposition and glucose metabolism in patients with Alzheimer's disease. Dynamic [11C]Pittsburgh compound-B (90 min) and static [18F]fluorodeoxyglucose (15 min) scans were obtained in 100 patients with Alzheimer's disease and 20 healthy controls. Parametric non-displaceable binding potential images of [11C]Pittsburgh compound-B and standardized uptake value ratio images of [18F]fluorodeoxyglucose were generated using cerebellar grey matter as reference tissue. Nine [11C]Pittsburgh compound-B-negative patients were excluded. The remaining patients were categorized into younger (n = 45, age: 56 ± 4 years) and older (n = 46, age: 69 ± 5 years) groups, based on the median age (62 years) at time of diagnosis. Younger patients showed more severe impairment on visuo-spatial function, attention and executive function composite scores (P < 0.05), while we found a trend towards poorer memory performance for older patients (P = 0.11). Differences between groups were assessed using a general linear model with repeated measures (gender adjusted) with age as between subjects factor, region (frontal, temporal, parietal and occipital and posterior cingulate cortices) as within subjects factor and [11C]Pittsburgh compound-B binding/[18F]fluorodeoxyglucose uptake as dependent variables. There was no main effect of age for [11C]Pittsburgh compound-B or [18F]fluorodeoxyglucose, suggesting that overall, the extent of amyloid deposition or glucose hypometabolism did not differ between groups. Regional distributions of [11C]Pittsburgh compound-B binding and [18F]fluorodeoxyglucose uptake (both P for interaction < 0.05) differed between groups, however, largely due to increased [11C]Pittsburgh compound-B binding and decreased [18F]fluorodeoxyglucose uptake in the parietal cortex of younger patients (both P < 0.05). Linear regression analyses showed negative associations between visuo-spatial functioning and parietal [11C]Pittsburgh compound-B binding for younger patients (standardized β: − 0.37) and between visuo-spatial functioning and occipital binding for older patients (standardized β: − 0.39). For [18F]fluorodeoxyglucose, associations were found between...
The disparity between early- and late-onset Alzheimer’s disease potentially reflects differences in distribution of underlying neuropathology. Post-mortem studies have described higher burdens of amyloid plaques and neurofibrillary tangles in patients with early-onset Alzheimer’s disease (Mann et al., 1984; Hansen et al., 1988; Berg et al., 1998; Bigio et al., 2002; Marshall et al., 2007). The major disadvantages of post-mortem studies, however, are that usually only a few slices of a small number of brain areas are examined and that in general they are performed years after disease onset. Furthermore, the increased pathological burden in early-onset Alzheimer’s disease may be explained by a more advanced stage of the disease at time of death as older patients with Alzheimer’s disease more frequently die due to other age-related conditions. This may introduce a systematic bias in post-mortem studies (Berg et al., 1998; Ho et al., 2002).

Brain amyloid plaque load can be quantified in vivo using PET and carbon-11-labelled Pittsburgh compound-B ([11C]PIB; Klunk et al., 2004). In the first study comparing [11C]PIB retention in early- and late-onset Alzheimer’s disease, these earlier pathological observations could not be replicated in the living human brain as no global and regional differences in amyloid burden were found (Rabinovici et al., 2010). In line with this finding, amyloid-β1-42 and hyperphosphorylated tau levels in CSF did not differ according to age at onset (Bouwman et al., 2009).

The absence of conclusive evidence for an effect of age on deposition of amyloid plaques is remarkable given the distinct phenotype often observed in patients with early-onset Alzheimer’s disease. Differences in downstream processes according to age at onset, however, have been reported more consistently. Patients with early-onset Alzheimer’s disease show more severe cortical atrophy, cerebral hypoperfusion and glucose hypometabolism and more profound abnormalities on EEG than their late-onset counterparts (Augest et al., 1990; Yasuno et al., 1998; Nakamoto et al., 2002; Kemp et al., 2003; Kim et al., 2005; Frisoni et al., 2007; Karas et al., 2007; Rabinovici et al., 2010; de Waal et al., 2011). Furthermore, in early-onset Alzheimer’s disease, the posterior parts of the brain are affected most prominently, whereas in late-onset Alzheimer’s disease this is the case for medial temporal regions (Scheltens et al., 1992; Kemp et al., 2003; Frisoni et al., 2007; Rabinovici et al., 2010).

The purpose of the present study was to examine the extent and distribution of specific [11C]PIB binding and [18F]fluorodeoxyglucose (FDG) uptake in order to test the hypothesis that early-onset Alzheimer’s disease is associated with more posterior-oriented amyloid load and glucose hypometabolism compared with late-onset Alzheimer’s disease.

Materials and methods

Patients

One hundred patients with Alzheimer’s disease and 20 healthy controls were included. Patients with Alzheimer’s disease were categorized into younger and older groups based on median age (62 years) at time of diagnosis. All subjects received a standard dementia screening that included medical history, informant-based history, physical and neurological examinations, screening laboratory tests, brain MRI and neuropsychological testing (Tolboom et al., 2009). Clinical diagnosis was established by consensus in a multidisciplinary team, without awareness of the PET results. All patients with Alzheimer’s disease met criteria proposed by the National Institute on Ageing and the Alzheimer’s Association workgroup for probable Alzheimer’s disease with at least intermediate likelihood due to abnormal [11C]PIB PET (McKhan et al., 2011). Controls were recruited through advertisements in newspapers and underwent the same diagnostic procedures.

Exclusion criteria were a history of major psychiatric or neurological (other than Alzheimer’s disease) illness, drug and/or alcohol abuse, major vascular events such as stroke or haemorrhage, and known genetic mutations (presenilin-1, presenilin-2 and amyloid-β precursor protein). Furthermore, [11C]PIB negative patients with Alzheimer’s disease were excluded. Parametric images of [11C]PIB were assessed visually and scored either positive or negative by an experienced nuclear medicine physician (B.v.b.). [11C]PIB scans were interpreted conservatively and were only considered positive if there was binding in more than one brain region (e.g. frontal, parietal, temporal or occipital) to such an extent that differentiation between grey and white
matter was either blurred or absent, indicating substantial cortical uptake. Consequently, nine patients were excluded, leaving 45 younger and 46 older patients with Alzheimer’s disease for analysis. Additional exclusion criteria for controls were subjective memory complaints or clinically relevant abnormalities on MRI. 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 Center.

Cognition

In 43 younger and 44 older patients with Alzheimer’s disease, cognitive functioning was assessed using a neuropsychological test battery covering five major cognitive domains: memory (immediate recall, recognition and delayed recall of a Dutch version of the Rey Auditory Verbal Learning Test and the Visual Association Test), visuo-spatial functioning (number location, dot counting and fragmented letters derived from the Visual Object Space and Perception battery, and the Rey Complex Figure copy test), executive functions (Digit Span backwards, Trail Making Test part B and Stroop-Colour-Word card subtask), attention (Trail Making Test part A, Stroop test Word and Colour subtasks, and digit span forward), and language (Visual Association Test picture naming and category fluency (animals: 1 min) (Stroop, 1935; Osterrieth, 1944; Reitan, 1958; Luteijn and van der Ploeg, 1982; Saan and Deelman, 1986; Warrington and James, 1991; Lindeboom and Matto, 1994; Lindeboom et al., 2002). For each cognitive task, raw test scores were converted to z-scores. Next, composite z-scores were calculated for each cognitive domain by averaging z-scores for all cognitive tasks within a cognitive domain. Composite z-scores were calculated when at least one neuropsychological task was available in each cognitive domain (n = 43 younger and n = 44 older patients with Alzheimer’s disease). Z-transformation was performed within the Alzheimer’s disease group without taking into account a normative group. The value Z = 0 therefore reflects the average test performance of our patients with Alzheimer’s disease in a given domain. Level of education was rated according to Verhage (1964).

Positron emission tomography

PET scans were obtained on an ECAT® EXACT™ HR+ scanner (Siemens/CTI) equipped with a neuroinsert 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 (16 younger and 34 older patients with Alzheimer’s disease). The scan protocol included a coronal T1-weighted 3D MPRAGE (1.5 T scanner: slice thickness 1.5 mm, 160 slices, matrix size 256 × 256, voxel size 1 × 1 × 1.5 mm, echo time 3.97 ms, repetition time 2700 ms, flip angle 8°; 3 T scanner: slice thickness 1.0 mm, 180 slices, matrix size 256 × 256, voxel size 1 × 1 × 1.5 mm, echo time 3 ms, repetition time 708 ms and flip angle 12°). The MRI scan was used for co-registration, segmentation and region of interest definition. Furthermore, medial temporal lobe atrophy and white matter hyperintensities were assessed visually using standardized rating scales (Fazekas et al., 1987; Scheltens et al., 1992).

Magnetic resonance imaging

All subjects underwent structural MRI using a 1.5 T Sonata (Siemens) scanner (16 younger and 12 older patients with Alzheimer’s disease and all controls) or a 3 T Signa HDxt (General Electric) scanner (29 younger and 34 older patients with Alzheimer’s disease). The scan protocol included a coronal T1-weighted 3D MPRAGE (1.5 T scanner: slice thickness 1.5 mm, 160 slices, matrix size 256 × 256, voxel size 1 × 1 × 1.5 mm, echo time 3.97 ms, repetition time 2700 ms, flip angle 8°; 3 T scanner: slice thickness 1.0 mm, 180 slices, matrix size 256 × 256, voxel size 1 × 1 × 1.5 mm, echo time 3 ms, repetition time 708 ms and flip angle 12°). The MRI scan was used for co-registration, segmentation and region of interest definition. Furthermore, medial temporal lobe atrophy and white matter hyperintensities were assessed visually using standardized rating scales (Fazekas et al., 1987; Scheltens et al., 1992).

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 × 256 × 63 was used, resulting in voxel size of 1.2 × 1.2 × 2.4 mm and spatial resolution of 7 mm full-width at half-maximum at the centre of the field of view.

Magnetic resonance 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 regions of interest that have been validated previously (Svarer et al., 2005). Regions of interest were projected onto [11C]PiB parametric non-displaceable binding potential (BPND) images. These images were generated by applying a two-step basis-function implementation of the simplified reference tissue model (RPM2) (Wu and Carson, 2002), to the full dynamic 90-min PET data. RPM2, a fully quantitative method for assessing the data, was identified as the parametric model of choice (Yaqub et al., 2008). 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. For [18F]FDG, parametric images of standardized uptake value ratio were extracted from the interval between 45 and 60 min after injection. Cerebellar grey matter was chosen as reference tissue for both PET tracers because of its (histopathological) lack of Congo red and thioflavin-S-positive plaques (Yamaguchi et al., 1989) and its relative insensitivity to metabolic changes during disease progression (Soininen et al., 1995).

For regional analysis, BPND ([11C]PiB) and standardized uptake value ratio ([18F]FDG) of frontal (volume weighted average of orbital frontal, medial inferior frontal and superior frontal), parietal (including the
precuneus), occipital and temporal (volume weighted average of superior temporal and medial inferior temporal) cortices and posterior cingulate were calculated. In addition, global cortical BPND and standardized uptake value ratio were calculated, based on the aforementioned regions.

Apolipoprotein E

APOE genotyping was performed after DNA isolation from 10 ml ethylenediaminetetraacetic acid (EDTA) blood, using the LightCycler® APOE mutation detection method (Roche Diagnostics GmbH).

Statistics

Differences between groups for baseline characteristics were assessed using ANOVA, Kruskal–Wallis tests and χ² tests, where appropriate. ANOVAs, adjusted for gender and education in Model 1, and additionally adjusted for Mini-Mental State Examination (MMSE) and APOE in Model 2, were used to compare cognitive test performance between Alzheimer’s disease groups only, and to compare global [11C]PIB BPND and [18F]FDG standardized uptake value ratio between patients and controls. Regional differences in [11C]PIB BPND (binding potential) and [18F]FDG standardized uptake value ratio between younger and older patients with Alzheimer’s disease were assessed using a general linear model with repeated measures (Model 1: adjusted for gender; Model 2: additionally adjusted for education, MMSE and APOE) entering age (dichotomous) as between subjects factor, region (frontal, temporal, parietal and occipital and posterior cingulate cortices) as within subjects factor and regional BPND/standardized uptake value ratio as dependent variables. The analyses were repeated entering age at diagnosis as continuous variable. ANOVAs (Model 1: adjusted for gender; Model 2: additionally adjusted for education, MMSE and APOE) were used to further assess differences between younger and older patients with Alzheimer’s disease in regional BPND/standardized uptake value ratio. Linear regression analyses were used to assess the spatial relationships between [11C]PIB and [18F]FDG and to assess the relationships between regional BPND/standardized uptake value ratio and composite cognitive domain scores for younger and older patients with Alzheimer’s disease separately. Statistical significance was set at $P < 0.05$.

Results

Subject characteristics

Characteristics according to diagnostic group are presented in Table 1. At time of diagnosis, the younger patients with Alzheimer’s disease were on average 56 ± 4 years (median: 56, range: 40–62) and the older patients with Alzheimer’s disease 69 ± 5 years (median: 67, range: 62–78). Younger and older patients did not differ in gender, level of education, disease duration or MMSE scores. Patients with Alzheimer’s disease had a slightly lower level of education than controls ($P < 0.05$).

Adjusted for gender and education, younger patients showed more severe impairment on visuo-spatial function, executive function and attention composite scores than older patients ($P < 0.05$, Table 2). In contrast, there was a trend towards worse memory performance for the older Alzheimer’s disease group compared with younger patients ($P = 0.11$). No differences in language skills were observed ($P = 0.51$). After additional adjustment for MMSE and APOE, the difference in memory performance between groups became significant ($P < 0.05$).

Global $[^{11}C]PIB$ binding potential and $[^{18}F]FDG$ standardized uptake value ratio

Adjusted for gender, global cortical $[^{11}C]PIB$ BPND did not differ between younger (0.75 ± 0.13) and older Alzheimer’s disease (0.69 ± 0.21, $P = 0.29$), both being higher than that of controls (0.12 ± 0.21, both $P < 0.001$, Fig. 1A). Global cortical $[^{18}F]FDG$ uptake was essentially the same in younger (0.98 ± 0.09) and older (0.99 ± 0.10) patients with Alzheimer’s disease ($P = 0.30$), which was lower than in controls (1.10 ± 0.07, both $P < 0.001$, Fig. 1B). Additional adjustment for education, MMSE and APOE did not change the results.

Regional $[^{11}C]PIB$ binding potential and $[^{18}F]FDG$ standardized uptake value ratio

General linear model with repeated measures (adjusted for gender) was used to assess the regional distributions of $[^{11}C]PIB$ and $[^{18}F]FDG$ in relation to age in patients with Alzheimer’s disease only. For $[^{11}C]PIB$ BPND, the main effect for age, treated as a dichotomous variable, was not significant ($P = 0.22$), but there was a main effect for region ($P < 0.001$). Moreover, there was no evidence of an interaction between age and region ($P = 0.40$). For $[^{18}F]FDG$ uptake, there was a main effect for age ($P = 0.006$), but no significant evidence of an interaction between age and region ($P = 0.16$).

### Table 1 Demographic and clinical characteristics according to diagnostic group

<table>
<thead>
<tr>
<th></th>
<th>Younger Alzheimer’s disease (n = 45)</th>
<th>Older Alzheimer’s disease (n = 46)</th>
<th>Controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>56 ± 4ᵃ</td>
<td>69 ± 5</td>
<td>67 ± 7</td>
</tr>
<tr>
<td>Disease duration</td>
<td>3 ± 2</td>
<td>3 ± 2</td>
<td>n/a</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>29/16</td>
<td>26/20</td>
<td>14/6</td>
</tr>
<tr>
<td>Education</td>
<td>5(3–7)b</td>
<td>5(3–7)b</td>
<td>6(2–7)</td>
</tr>
<tr>
<td>MMSE</td>
<td>23 ± 5ᵇ</td>
<td>24 ± 3ᵇ</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>APOE carrier (%)</td>
<td>67</td>
<td>80</td>
<td>18</td>
</tr>
<tr>
<td>Fazekas score</td>
<td>0.9 ± 0.6</td>
<td>1.3 ± 1.0ᵈ</td>
<td>n/a</td>
</tr>
<tr>
<td>MTA score</td>
<td>0.8 ± 0.6</td>
<td>0.9 ± 0.6</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation unless indicated otherwise. Fazekas scores represent the grade of white matter hyperintensities. Differences between groups were assessed using ANOVA with post hoc Bonferroni tests (age and MMSE), independent samples t-test (disease duration), Kruskal–Wallis test (education, medial and temporal lobe atrophy and Fazekas scores) and χ² (gender, APOE genotype).

a Younger Alzheimer’s disease < older Alzheimer’s disease and controls: $P < 0.05$.
b Younger and older Alzheimer’s disease < controls: $P < 0.05$.
c Education using Verhage’s classification (Verhage, 1964) on a 1–7 scale, median (range).
d Older Alzheimer’s disease > Younger Alzheimer’s disease: $P = 0.06$.
m = male; f = female; APOE = apolipoprotein E; MTA = medial temporal lobe atrophy.
an interaction between age and region (P < 0.01), which could be attributed to increased [11C]PIB binding in the parietal cortex of younger patients with Alzheimer’s disease (Fig. 2A). Additional adjustment for education, MMSE and APOE did not change the results (P for interaction < 0.05). Results were comparable when the analysis was repeated using age as continuous variable (interaction between age and region P < 0.01). ANOVAs with adjustment for gender, education, MMSE and APOE showed higher parietal [11C]PIB BPND in younger patients compared with older patients (P < 0.05). There were no significant differences between groups in other regions.

For [18F]FDG, the main effect for age was not significant (P = 0.37), but there was a main effect for region (P < 0.001). Furthermore, there was an interaction between age and region (P < 0.05), mainly driven by reduced parietal [18F]FDG uptake in younger patients with Alzheimer’s disease (Fig. 2B). The interaction between age and region lost significance after additional adjustment for gender, education, MMSE and APOE (P for interaction 0.15). When the analysis was repeated using age as continuous variable, results did not change. ANOVAs, adjusted for gender, revealed lower [18F]FDG standardized uptake value ratio in the parietal cortex of younger patients compared with older patients (P < 0.05). This finding was no longer significant after additional adjustment for education, MMSE and APOE. There were no significant differences between groups in other regions.

Linear regression analyses (adjusted for gender, education, MMSE and APOE) for the whole group and for younger and older patients with Alzheimer’s disease separately showed no correlation between [11C]PIB BPND and [18F]FDG standardized uptake value ratio in any of the cortical regions of interest.

### Table 2 Composite cognitive scores according to age

<table>
<thead>
<tr>
<th></th>
<th>Younger Alzheimer’s disease</th>
<th>Older Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.10 ± 0.13</td>
<td>−0.19 ± 0.13*</td>
</tr>
<tr>
<td>Visuo-spatial functions</td>
<td>−0.46 ± 0.19*</td>
<td>0.19 ± 0.11</td>
</tr>
<tr>
<td>Executive functions</td>
<td>−0.30 ± 0.15*</td>
<td>0.16 ± 0.11</td>
</tr>
<tr>
<td>Language</td>
<td>−0.10 ± 0.18</td>
<td>−0.09 ± 0.14</td>
</tr>
<tr>
<td>Attention</td>
<td>−0.27 ± 0.14*</td>
<td>0.20 ± 0.08</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard error. Composite scores were calculated by averaging z-scores for all tests within a cognitive domain. Neuropsychological data were available for 43 younger and 44 older patients with Alzheimer’s disease. Differences between groups were assessed using univariate ANOVA with adjustment for age and education in the first model and with additional adjustment for MMSE and APOE in the second model. *P < 0.05 and +P = 0.11 after adjustment for gender and education, P < 0.05 after additional adjustment for MMSE and APOE.

### Cognition and regional [11C]PIB binding potential and [18F]FDG standardized uptake value ratio

Linear regression analyses with adjustment for gender and education showed a negative association between visuo-spatial functioning composite scores and parietal [11C]PIB BPND for young patients with Alzheimer’s disease (P < 0.05) (Table 3 and Fig. 3A) and between visuo-spatial functioning composite scores and occipital [11C]PIB BPND for older patients with Alzheimer’s disease (P < 0.05; Fig. 3B). For [18F]FDG, linear regression showed associations between parietal standardized uptake value ratio with visuo-spatial (Fig. 3C), attention and executive functioning composite scores in younger patients with Alzheimer’s disease (all P < 0.05; Table 4). In older patients with Alzheimer’s disease, increased posterior cingulate standardized uptake value ratio was associated with worse memory (Fig. 3D) and language performance (P < 0.05). After additional adjustment for MMSE and APOE, only the correlation between posterior cingulate standardized uptake value ratio and language lost significance.

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**Figure 1** Global (A) [11C]PIB BPND, and (B) [18F]FDG standardized uptake value ratio (SUVr) in controls and in younger and older patients with Alzheimer’s disease (AD). Horizontal lines between symbols represent mean values. Differences between groups were assessed using ANOVA (*post hoc* Bonferroni tests: P < 0.001).
There were no other associations between regional \([11C]PIB\) BPND/\([18F]FDG\) standardized uptake value ratio and composite cognitive domain scores.

**Discussion**

The main findings of the present study are an increased amyloid burden and modest metabolic dysfunction in the parietal cortex of younger patients with Alzheimer’s disease. Parietal amyloid load was related to visuo-spatial functioning in younger patients, whilst metabolic impairment in the parietal cortex of these patients was related to visuo-spatial skills, executive functions and attention. In older patients, memory performance was associated with metabolic activity in the posterior cingulate. This suggests that clinical differences between younger and older patients with Alzheimer’s disease are related not only to topographical differentiation in downstream processes, but may originate from distinctive distributions of early upstream events.

The spatial relationship between amyloid deposition and its downstream effects in sporadic Alzheimer’s disease is not completely understood. Several studies have shown anatomical overlap between amyloid deposition and glucose metabolism in parieto-temporal, posterior cingulate and precuneus regions, indicating metabolic vulnerability in amyloid plaque enriched brain regions (Devanand et al., 2010; Forster et al., 2011). In contrast, amyloid deposition in the frontal cortex often coincides with relatively spared metabolism and, vice versa, low levels of fibrillary amyloid...
plaques in medial temporal regions are often accompanied by severe neurodegeneration. Previously, it has been found that patients with early-onset Alzheimer’s disease show differently distributed glucose hypometabolism in the absence of a regionally specific pattern of amyloid deposition (Rabinovici et al., 2010). This raised the question whether other pathological processes such as neurofibrillary tangle formation or neuroinflammation may account for this region-specific metabolic impairment. Based on the present study, however, it may be worthwhile to reconsider the possibility of an amyloidogenic predisposition for metabolic vulnerability, especially in the parietal cortex as this brain structure was most severely affected by both amyloid deposition and glucose hypometabolism in younger patients with Alzheimer’s disease. These findings are in line with current theories on the pathogenesis of Alzheimer’s disease proposing that amyloid-β initiates a cascade of neuropathological events that eventually lead to neuronal damage and cell death (Hardy and Selkoe, 2002). As such, disproportionate parietal amyloid-β accumulation may precede parietal metabolic brain dysfunction in patients with early-onset Alzheimer’s disease.

The finding of a different amyloid distribution in younger patients with Alzheimer’s disease is in contrast with two previous studies. In a recent study, increased global [11C]PIB retention without specific differences in distribution was shown in early-onset Alzheimer’s disease (Choo et al., 2011). Observed effects in that study, however, were mainly due to inclusion of a number of PIB-negative patients in the late-onset Alzheimer’s disease group in the absence of PIB-negative patients with early-onset Alzheimer’s disease. In contrast, we included only PIB-positive patients, thereby minimizing the possibility of misdiagnosis. In the first [11C]PIB study comparing early-onset with late-onset Alzheimer’s disease, however, no global or topographical differences in amyloid burden were reported (Rabinovici et al., 2010). Discrepancies with the present study may be due to differences in group characterization, sample sizes or the use of different methods for analysing the [11C]PIB PET data. Furthermore, Rabinovici et al. (2010) used an age cut-off of 65 years at time of disease onset to categorize early- and late-onset patients with Alzheimer’s disease. Patients in the present study were relatively young, leading to an age cut-off of 62 years at time of diagnosis.

Figure 3  Linear regression analyses showed correlations between parietal amyloid deposition (A) and glucose metabolism (C) with visuo-spatial function composite scores in younger patients with Alzheimer’s disease (standardized β [11C]PIB: −0.37; [18F]FDG: 0.55, both P < 0.05). In older patients with Alzheimer’s disease, there was a relationship between occipital [11C]PIB binding and visuo-spatial functioning (B) (standardized β: −0.39, P < 0.05). Furthermore, metabolic activity in the posterior cingulate was correlated with memory performance in older patients with Alzheimer’s disease (D) (standardized β: 0.41, P < 0.05). AD = Alzheimer’s disease; SUVr = standardized uptake value ratio.
This could suggest that the present findings may be driven by patients with Alzheimer’s disease with very early onset. Potentially, the marked increased parietal $[11C]$PIB binding is most prominent in very young patients, whilst $[^{18}F]$FDG uptake differs most between early- and late-onset patients with Alzheimer’s disease. This would fit a recently proposed hypothetical biomarker model (Jack et al., 2010) and possibly explains discrepant findings between this and a previous study (Rabinovici et al., 2010). Adding an even older Alzheimer’s disease group in a future study would be of major interest. An alternative explanation for the increased parietal $[11C]$PIB binding in younger patients with Alzheimer’s disease could be their clinical presentation. In the present study, younger and older patients had comparable MMSE scores, disease duration, level of education and APOE genotype. Yet, younger patients performed relatively worse on non-memory tasks, whilst older patients exhibited most severe impairment on memory tasks. These different phenotypes may be an ultimate expression of topographical differences as younger patients with Alzheimer’s disease showed an increased parietal amyloid burden. This notion was further supported by the association we found between parietal $[11C]$PIB binding and visuo-spatial functioning in young patients with Alzheimer’s disease. Distinct distributions of amyloid load, however, were not found in patients with focal variants of Alzheimer’s disease such as posterior cortical atrophy (characterized by impairment in vision and visuospatial skills; de Souza et al., 2011; Rosenbloom et al., 2011) or logopenic aphasia (characterized by word finding problems, anomia and difficulty in sentence repetition; Rabinovici et al., 2008; Leyton et al., 2011), when compared with patients with typical Alzheimer’s disease. Despite similar distributions of $[11C]$PIB retention in posterior cortical atrophy, these patients did show reduced $[^{18}F]$FDG uptake in occipito-temporal regions (Rosenbloom et al., 2011), suggesting that not amyloid plaque deposition but metabolic impairment drives the clinical presentation. Sample sizes in these studies were small, however, and further investigation is needed to unravel the pathways that eventually lead to distinct phenotypes of Alzheimer’s disease.

The origin of an apparent parietal predilection for both amyloid deposits and glucose hypometabolism in early-onset Alzheimer’s disease remains unknown. Early and subtle changes in brain network activity may play a role in this intriguing phenomenon. The parietal lobe is an important component of the default mode network that consists of a set of interconnected brain regions that typically activate during task-free imaging (Raichle et al., 2001). Basal neural network activity is highest in default mode network structures that are also vulnerable for amyloid deposition such as frontal cortex, posterior cingulate and parietal cortex. It has been hypothesized that amyloid plaques preferentially develop in brain areas susceptible to very early network changes (Buckner et al., 2005; Hedden et al., 2009). Due to unknown, possibly genetic or environmental factors, changes in default mode network integrity may be most pronounced in the parietal cortex in patients with early-onset Alzheimer’s disease, thereby anticipating parietal amyloid-$\beta$ accumulation and progressive metabolic impairment. Another possibility is that early- and late-onset patients with Alzheimer’s disease exhibit disruptions in different brain networks. Late-onset patients with Alzheimer’s disease may predominantly show default mode network and thus, hippocampal-cortical memory system disruptions, whilst patients with early-onset Alzheimer’s disease may more often exhibit reduced connectivity in the dorsal attention network (Corbetta and Shulman, 2002) or in the frontoparietal control system (Vincent et al., 2008). Whether age of onset is related to specific changes in functional connectivity in patients with Alzheimer’s disease remains to be investigated.

In early-onset Alzheimer’s disease, patients often present with cognitive deficits linked to parietal cortex such as acalculia, spatial disorientation and apraxia (Koss et al., 1996; Stopford et al., 2008; Koedam et al., 2010). Younger patients with Alzheimer’s disease in this study had most severe impairment in visuo-spatial skills, executive functions and attention, in addition to an
increased amyloid burden and modestly decreased glucose metabolism in the parietal lobe. We also showed a direct association between amyloid deposition in the parietal cortex and visuo-spatial functioning, and between parietal glucose metabolism and visuo-spatial abilities, executive functions and attention in these patients. These relationships were independent of gender, education, MMSE scores and APOE genotype. Data of the present study fit a hypothetical model in which disproportionate accumulation of amyloid-β precedes disproportional neuronal dysfunction in the parietal cortex of younger patients with Alzheimer’s disease, in turn leading to decline in cognitive functions that are typically associated with parietal brain structures. Older patients with Alzheimer’s disease showed a trend towards worse memory performance compared with younger patients. Memory performance was related strongly to reduced metabolic activity in the posterior cingulate, a critical brain region in sporadic Alzheimer’s disease. Furthermore, there was an association between amyloid deposition in the occipital cortex and visuo-spatial functioning. This effect is strongly driven by two patients with high [11C]PIB binding and low visuo-spatial composite scores (Fig. 3B). One of these older patients was diagnosed with posterior cortical atrophy, illustrating that an atypical presentation is not restricted to early-onset Alzheimer’s disease. Furthermore, our data suggest that dysfunction of the brain (i.e. reduced glucose metabolism) is more closely related to cognitive dysfunction in younger than in older patients with Alzheimer’s disease. It may be hypothesized that cognitive deficits in younger patients are a direct effect of Alzheimer’s disease pathology or its downstream effects, whilst in older patients other aging-related factors confound this relation.

Despite previously reported differences in extent and pattern of brain atrophy between early- and late-onset Alzheimer’s disease (Frisoni et al., 2007; Karas et al., 2007), PET data were not corrected for partial volume effects. Many uncertainties affect both accuracy and precision of (magnetic resonance-based) partial volume correction methods, such as coregistration and segmentation errors (Kloet et al., 2006). To date, there is no consensus on the best method for [11C]PIB and [18F]FDG data. It is possible that application of partial volume correction would have resulted in even higher [11C]PIB binding values in the parietal cortex of younger patients with Alzheimer’s disease. For [18F]FDG, however, lack of partial volume correction may have led to underestimation and could, therefore, have affected observed differences between younger and older patients with Alzheimer’s disease. This is not necessarily the case as partial volume correction did not make any difference in a previous study (Rabinovici et al., 2010). Another limitation of the present study is that patients with Alzheimer’s disease in the older group were relatively young (69 years on average at time of diagnosis). Amongst the strengths of this study is the large sample of patients with a clinical diagnosis of Alzheimer’s disease and in vivo evidence of amyloidosis. Furthermore, younger and older patients with Alzheimer’s disease were comparable in terms of gender, disease duration, education and disease severity, yet showed a clearly distinct cognitive profile, thereby providing sharp contrast between Alzheimer’s disease phenotypes according to age. Finally, an optimal quantitative parametric method (RPM2) was used for analyzing [11C]PIB data.

The present study provides in vivo evidence for a different topography of amyloid deposition and glucose hypometabolism in younger patients with Alzheimer’s disease compared to older patients. Increased amyloid burden, together with metabolic dysfunction, in the parietal cortex of younger patients with Alzheimer’s disease may explain the distinct cognitive profile in these patients. This study adds to the understanding of heterogeneity in terms of age at onset and clinical presentation and shows for the first time a more direct relationship between amyloid deposition and clinical signs.

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**References**


