Functional neuroinflammatory- and serotonergic imaging in Alzheimer's disease
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CHAPTER SIX
RADIOLABELLED PK11195 IN ALZHEIMER’S DISEASE
ABSTRACT

Objectives: Inflammation contributes to degeneration in Alzheimer's disease (AD), not simply as a secondary phenomenon, but primarily as a significant source of pathology. $^{\text{123}}$Iodo-PK11195 is a single photon emission computed tomography (SPECT) ligand for the peripheral benzodiazepine receptor, the latter being expressed on microglia (brain resident macrophages) and upregulated under inflammatory circumstances. The objectives were to assess AD inflammation by detecting $^{\text{123}}$Iodo-PK11195 uptake changes and investigate how uptake values relate with perfusion SPECT and neuropsychological findings. Methods: Ten AD and 9 control subjects were included. $^{\text{123}}$Iodo-PK11195 SPECT images were realigned into stereotactic space where binding indices, normalized on cerebellar uptake, were calculated. Results: The mean $^{\text{123}}$Iodo-PK11195 uptake was increased in AD compared to controls in nearly all neocortical regions, however, statistical significance was only reached in the frontal and right mesotemporal regions. Significant correlations were found between regional increased $^{\text{123}}$Iodo-PK11195 uptake and cognitive deficits. Conclusions: $^{\text{123}}$Iodo-PK11195 is a cellular disease activity marker and allows in vivo assessment of microglial inflammation in AD.
INTRODUCTION
Alzheimer’s disease (AD), accounting for about 70% of the dementia cases is neuropathologically characterized by dense and neuritic amyloid plaques and cerebral intraneuronal neurofibrillary tangles [1,2]. However, neither plaques nor tangles correlate strongly with the degree of dementia, loss of synapses and neurons, and abnormalities of the cytoskeleton [3,4]. Over the last few years, it has become clear that inflammatory mechanisms and more specifically activated microglia, i.e. the brain resident macrophages, may contribute to the AD neurodegenerative process, not only as a purely secondary phenomenon, but also as a possible primary source of its clinical pathology [5-8]. Epidemiologically, almost 20 retrospective studies have already shown the protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) in populations with a long history of NSAIDs consumption which would reduce the AD prevalence by 50% and delay its onset by 5 to 7 years [9-13]. This progression-retarding and neuroprotective effect of NSAIDs has up till now only been shown in one prospective, double-blind, placebo-controlled clinical trial of indomethacin where a significant decrease in the rate of mental deterioration in 28 AD patients was shown over a 6-months period [14]. On the other hand, other studies with diclofenac, hydroxychloroquine or nimesulide did not demonstrate this positive effect on AD progression, hence possibly indicating that influencing this neuroinflammation should be done in an early stage and maybe for a prolonged period of time [15-17].

Visualizing activated microglia and in this way inflammatory lesions in AD with positron emission tomography (PET) or single photon emission computed tomography (SPECT) would be of interest for clarifying the underlying pathophysiology, for selecting subgroups of patients that are more eligible for anti-inflammatory treatment, and, finally, for monitoring patients during trials with anti-inflammatory agents or ultimately during immunization treatment for monitoring the effective removal of amyloid deposits by activated microglia [18].

The peripheral benzodiazepine receptor (PBR) is structurally and pharmacologically distinct from the central benzodiazepine receptor (associated with GABA-regulated chloride channels), and earned his name based on his localization outside of the CNS and his high affinity for several 1,4-benzodiazepines. It is found in highest concentrations in kidneys, colon membranes, heart, steroid hormone producing cells of adrenal cortex, ovaries and testes, and several cell types of the immune system, such as mast cells and macrophages. It is also present in low concentrations throughout the brain, primarily associated with the choroid plexus, ependymal linings, and microglia [19]. Although the specific function of the PBR remains unknown, it is generally accepted to be involved in lipid metabolism and/or transport, steroid regulation, and cell proliferation [3]. The immunomodulatory role for this receptor includes the ability to modulate monocyte chemotaxis [20], cytokine expression, and to stimulate the formation of antibody-producing cells [7]. Interestingly, the PBR has the ability to reflect neuronal injury and inflammatory lesions without blood-brain barrier (BBB) damage, by an increased expression of the number of binding sites on proliferating and activated microglia, as previously indicated autoradiographically for AD [2,21].
PK11195 (1-(2-chlorophenyl)-N-(1-methyl-propyl)-3-isoquinoline carboxamide) is a specific and selective high affinity ligand for the PBR and can thus be used as a diagnostic marker for microglial activation, neuroinflammatory lesions, and finally neuronal damage. Moreover, the full transformation of microglia into parenchymal phagocytes, absent in areas with chronic or subtle brain pathology, is not necessary to reach maximal levels of PK11195 binding [22]. In vivo visualization of the human PBR, and in this way of cellular inflammatory infiltration, by means of radiolabelled PK11195 has previously been done with $^{11}$C radiolabelled PK11195 for PET in various diseases like glial neoplasms, ischemic stroke, multiple sclerosis (MS), Rasmussen’s encephalitis, hepatic encephalopathy, cerebral vasculitis, and herpes encephalitis [23-27]. Recently, $^{11}$C-PK11195 has also been applied in early and mild dementia patients revealing an increased regional binding in the entorhinal, temporoparietal, and cingulate cortex. Moreover, serial volumetric MRI scans revealed that areas with high $^{11}$C-PK11195 binding subsequently showed the highest rate of atrophy up to 12-24 months later indicating that the presence of a local immune response in cortical areas did indeed reflect an active disease process associated with tissue loss. Also, measurement of cerebral glucose metabolism revealed that areas with high $^{11}$C-PK11195 binding were also characterized by decreased regional glucose use. Finally, in one patient with isolated memory impairment without dementia, the pattern of atrophy as seen by volumetric MRI imaging was predicted by the initial distribution of increased $^{11}$C-PK11195 binding [28].

The application of this ligand, however, is restricted to institutions with a PET system and an in-house cyclotron that have access to these short-lived positron emitters. Therefore, the availability of a radiolabelled SPECT ligand for the study of the PBR would allow wider clinical application on a larger scale. Recently, we therefore assessed the biodistribution and dosimetry of $^{123}$I radiolabelled PK11195 [29]. It was concluded that $[^{123}]$iodo-PK11195 is a suitable and safe agent for the assessment of the PBR with a high enough specific activity required for quantitative studies [30]. The objectives of the present study were to visualize inflammation in vivo in AD patients by detecting $[^{123}]$iodo-PK11195 uptake changes compared to controls and to investigate whether $[^{123}]$iodo-PK11195 SPECT relates with findings obtained from perfusion SPECT and neuropsychological testing, both sensitive markers of functional brain integrity in AD [31,32,32].
PATIENTS AND METHODS

Patients

The study was approved by the medical ethics committee of the Ghent University Hospital and all patients gave informed (proxy-)consent. Ten patients suffering from probable AD (4 men; mean age 77 ± 10.7 yrs (SD); range 55 to 87 yrs) according to the NINCDS-ADRDA criteria were included [33]. All had a cerebral MRI scan negative for focal lesions. As a control group, 9 normal subjects (6 men; mean age 67 ± 8.6 yrs; range 53 to 76 yrs) were included. This control group formed part of a perfusion SPECT normal database consisting of nearly 100 healthy controls, which all underwent thorough medical screening including high-resolution MRI, a complete history and physical examination, blood and urine tests, and full clinical neurological, neuropsychological, and psychiatric examination. Detailed exclusion criteria for the healthy controls are described elsewhere [34]. For ethical reasons, the AD patients' current treatment was continued during this study. Only the use of anti-inflammatory medication in general and more specifically NSAIDs for the last six months by patients and controls was an exclusion criterium for this study. Age, sex, MMSE-score, neuropsychological profile and significant perfusion defects for the AD patients are given in table 1.

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Sex</th>
<th>MMSE</th>
<th>Major neuropsychological dysfunction</th>
<th>Perfusion defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.2</td>
<td>F</td>
<td>18</td>
<td>memory, executive, visuospatial, verbal</td>
<td>/</td>
</tr>
<tr>
<td>79.2</td>
<td>F</td>
<td>23</td>
<td></td>
<td>right frontal, right parietal</td>
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<tr>
<td>80.1</td>
<td>F</td>
<td>23</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>84.5</td>
<td>F</td>
<td>9</td>
<td>(visual) memory, executive, visuospatial</td>
<td>bilateral frontal, right lateral temporal, bilateral caudate head</td>
</tr>
<tr>
<td>86.5</td>
<td>F</td>
<td>14</td>
<td></td>
<td>left prefrontal, lateral frontal</td>
</tr>
<tr>
<td>87.3</td>
<td>F</td>
<td>25</td>
<td>visual</td>
<td>-</td>
</tr>
<tr>
<td>55.4</td>
<td>M</td>
<td>20</td>
<td>visuospatial</td>
<td>right lateral temporal, right parietal</td>
</tr>
<tr>
<td>73.3</td>
<td>M</td>
<td>23</td>
<td>visuospatial</td>
<td>left frontal</td>
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<td>75.7</td>
<td>M</td>
<td>22</td>
<td>executive, visuospatial</td>
<td>left lateral temporal, left parietal, right frontal</td>
</tr>
<tr>
<td>85.3</td>
<td>M</td>
<td>10</td>
<td>memory, executive, visuospatial, verbal</td>
<td>right frontal, left striatum, right caudate head</td>
</tr>
</tbody>
</table>

Table 1 Age, sex, MMSE-score, neuropsychological profile and perfusion defects for the AD patients

Methods

\[^{123}\text{I} \text{IODO-PK11195 SPECT scan}\]

Radionuclide synthesis and injection

\[^{123}\text{I} \text{was purchased from Dupont (Dupont Pharmaceuticals Ltd., Brussels, Belgium) and PK11195 (1-(2-chlorophenyl)-N-(1-methyl-propyl)-3-isooquinoline carboxamide) was obtained from RBI (Natick, Massachusetts, USA). \;}^{123}\text{I} \text{labeled PK11195 (}^{123}\text{I} \text{jodo-PK11195) was synthesized according to the method described previously [35], using a direct displacement of aromatic chlorine under solid-state conditions. The specific activity of the}\

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labelled compound was 6.7–17.6 GBq/µmol (180–475 mCi/µmol). The total labelling yield was 50–60% and the radiochemical purity of the final product, as assessed with high performance liquid chromatography (HPLC), was more than 99%. Thyroid was blocked with Lugol’s solution for all subjects (5% iodine and 10% potassium iodide; one-day protocol of 20 drops one hr before radioligand injection). The mean dose administered was 185 MBq.

**Imaging and reconstruction**

All subjects were scanned on a triple-headed gamma camera (Toshiba GCA-9300A, Dutoit Medical, Wijnegem, Belgium) equipped with low energy, super-high-resolution lead fan-beam collimators (measured resolution 8.1 mm) and 153Gd transmission rod sources allowing transmission before emission scanning, enabling image coregistration [36]. Imaging was performed one hour after injection since stable [11C]PK11195 uptake ratios were noticed as early as 20 minutes after injection reflecting pseudo-equilibrium [37]. Emission images were acquired during 20 min in a 128×128 matrix with 90 projections. After triple-energy window scatter correction and uniform attenuation correction (µ=0.09), images were processed by means of filtered backprojection and a Butterworth postfilter (order 8; cut-off 0.07) [38].

**Estimation of binding index**

After image registration into Talairach co-ordinates using a 9-parameter rigid transformation, a predefined volume of interest (VOI) analysis was performed consisting of 26 cortical, 6 subcortical, and 2 cerebellar 3D-volumes of interest for each patient (Brass, Nuclear Diagnostics, Hägersted, Sweden) [36]. Every registration with the subsequent VOI analysis was carefully checked for errors where in some cases, a manual adjustment was made when the lower cerebellar slices were not completely imaged due to subject positioning on the camera (at least five cerebellar slices had to be visualized for final inclusion). A binding index for every VOI was calculated by normalization to the cerebellum i.e. dividing the counts per volume unit in a given VOI through the counts per volume unit in the cerebellum, the latter being free of pathophysiological involvement. Comparison of binding index between patients and controls was assessed by means of a one-tailed Mann-Whitney U test since, out of neuropathological data, an increased binding index was expected for AD patients [21].

**Neuropsychological testing**

All patients underwent the Mini-Mental State Examination (MMSE) and a screening battery for cognitive impairment (Amsterdam dementia screening test, ADS6) containing the following subtests: picture recognition (n=8), orientation (n=8), drawing alternating sequences (n=7), verbal fluency (n=8), copying geometric figures (n=8), and free recall (n=8) [39]. Not every (sub)test could be performed in all patients due to non-compliance.

**99mTc-ECD perfusion SPECT scan**

All patients, except for one, underwent a 99mTc-ECD perfusion SPECT scan. On average 30 minutes after the injection of 925 MBq 99mTc-ECD (ethyl cysteinate dimer; Dupont Pharmaceuticals Ltd., Brussels, Belgium). Images were acquired in a 128×128 matrix with 90 projections and a frame time of 40 seconds. After triple-energy window scatter correction and uniform attenuation correction, images were processed by means of filtered backprojection and a Butterworth postfilter (order 8; cut-off 0.12). Perfusion SPECT images were automatically fitted and realigned into Talairach co-ordinates where a similar VOI analysis was performed using the same predefined VOI-map (normalization on cerebellar uptake). All patient perfusion data were averaged to assess a global group perfusion deficit. Comparison was done to 20 healthy controls (mean age 70.5 ± 6.2 yrs) [34]. For the individual patient, a hypoperfusion in a specific region was considered as significant when the uptake was less than the averaged uptake for the group of healthy volunteers minus two times the standard deviation for that specific region.
### RESULTS

**[¹²³I]iodo-PK11195 SPECT scan**

No effect of age was found on radiolabelled PK11195 uptake for cortical regions in controls. Grouped mean [¹²³I]iodo-PK11195 uptake values for patients and controls are shown in Table 2.

<table>
<thead>
<tr>
<th>Region</th>
<th>AD patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>133.8</td>
<td>60.6</td>
<td>99.2</td>
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<tr>
<td>Right</td>
<td>141.9</td>
<td>68.6</td>
<td>112.8</td>
</tr>
<tr>
<td>Prefrontal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td>143.9</td>
<td>55.8</td>
<td>100.8</td>
</tr>
<tr>
<td>Right</td>
<td>139.4</td>
<td>62.6</td>
<td>102.0</td>
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<tr>
<td>Lateral frontal</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>126.7</td>
<td>32.6</td>
<td>101.1</td>
</tr>
<tr>
<td>Right</td>
<td>125.7</td>
<td>42.9</td>
<td>97.7</td>
</tr>
<tr>
<td>Superior frontal</td>
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<tr>
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<td>115.5</td>
<td>32.0</td>
<td>97.4</td>
</tr>
<tr>
<td>Right</td>
<td>110.1</td>
<td>32.8</td>
<td>92.2</td>
</tr>
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<td>Cingulate gyri</td>
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<td>Anterior</td>
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<td>94.0</td>
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<tr>
<td>Posterior</td>
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<td>10.7</td>
<td>101.0</td>
</tr>
<tr>
<td>Sensorimotor</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
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<td>41.5</td>
<td>106.1</td>
</tr>
<tr>
<td>Right</td>
<td>94.4</td>
<td>30.4</td>
<td>100.6</td>
</tr>
<tr>
<td>Temporal anterior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>123.5</td>
<td>61.7</td>
<td>109.8</td>
</tr>
<tr>
<td>Right</td>
<td>146.4</td>
<td>80.8</td>
<td>110.8</td>
</tr>
<tr>
<td>Temporal superior</td>
<td></td>
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<tr>
<td>Left</td>
<td>97.7</td>
<td>9.0</td>
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<tr>
<td>Right</td>
<td>93.8</td>
<td>12.1</td>
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<tr>
<td>Temporal medial inferior</td>
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<td>Left</td>
<td>106.2</td>
<td>15.7</td>
<td>99.6</td>
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<tr>
<td>Right</td>
<td>103.6</td>
<td>28.9</td>
<td>92.8</td>
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<tr>
<td>Mesotemporal</td>
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<tr>
<td>Right</td>
<td>117.7</td>
<td>31.6</td>
<td>98.5</td>
</tr>
<tr>
<td>Parietal inferior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>115.9</td>
<td>34.8</td>
<td>102.8</td>
</tr>
<tr>
<td>Right</td>
<td>93.6</td>
<td>31.8</td>
<td>97.6</td>
</tr>
<tr>
<td>Parietal superior</td>
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</tr>
<tr>
<td>Left</td>
<td>118.8</td>
<td>60.3</td>
<td>102.3</td>
</tr>
<tr>
<td>Right</td>
<td>119.3</td>
<td>54.7</td>
<td>104.6</td>
</tr>
<tr>
<td>Occipital</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>16.4</td>
<td>103.5</td>
</tr>
<tr>
<td>Right</td>
<td>102.3</td>
<td>12.1</td>
<td>99.9</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>77.4</td>
<td>11.7</td>
<td>88.7</td>
</tr>
</tbody>
</table>

*p-values indicating significantly raised uptake values

Table 2. [¹²³I]iodo-PK11195 regional uptake values and standard deviation for AD patients compared to controls.
Elevated mean uptake values for AD patients were found in all frontal regions, temporal anterior, temporal medial inferior and mesotemporal region, left parietal inferior and parietal superior region, left sensorimotor cortex, and the right occipital region. Grouped mean $^{[125]}$Iodo-PK11195 uptake values for AD patients and controls are displayed in figure 1. Significantly increased uptake values were reached in the left orbitofrontal, bilateral prefrontal and lateral frontal region, and the right mesotemporal region (one-tailed Mann-Whitney $U$ test). Figure 2 shows the $^{[125]}$Iodo-PK11195 uptake values for the left prefrontal and the right mesotemporal area.

Figure 1. Grouped mean (+/- standard error of the mean) $^{[125]}$Iodo-PK11195 uptake values

\[\Delta\text{controls}; \bullet\text{AD patients}\]

Figure 2. Boxplot of the $^{[125]}$Iodo-PK11195 uptake values for the left prefrontal (left) and the right mesotemporal area (right)
Neuropsychological testing and correlation with $^{[123]}$Iodo-PK11195 uptake values

The mean MMSE score of the AD patients was 19 ± 6 (range 9-25). Results from the picture recognition task correlated inversely with the $^{[123]}$Iodo-PK11195 uptake value in the right superior frontal region (two-tailed Spearman’s correlation coefficient, p=0.005). Results of the orientation task correlated inversely with the left lateral frontal, right superior frontal and the left parietal (figure 3, left) $^{[123]}$Iodo-PK11195 uptake values (two-tailed Spearman’s correlation coefficient, p=0.03, 0.04, and 0.006 respectively). Verbal fluency results correlated inversely with the left parietal inferior $^{[123]}$Iodo-PK11195 uptake value (two-tailed Spearman’s correlation coefficient, p=0.007). Results of the free recall task correlated inversely with $^{[123]}$Iodo-PK11195 uptake values in the left and right frontal (figure 3, right), left temporal, and the left parietal superior region (two-tailed Pearson correlation coefficient, p=0.02, 0.03, 0.03, and 0.01 respectively). No correlations were found between $^{[123]}$Iodo-PK11195 uptake values and the neuropsychological test results of the controls.

Inverse correlation between results of the orientation task with the left parietal $^{[123]}$Iodo-PK11195 uptake value (left, Spearman’s correlation coefficient -0.896, p=0.006) and the free recall test with the left orbitofrontal $^{[123]}$Iodo-PK11195 uptake value (right, Pearson correlation coefficient -0.742; p=0.03)

$^{99m}$Tc-ECD SPECT scan

Group perfusion defects were found in the bilateral frontal, temporal and parietal inferior regions, basal ganglia and the cingulate gyri (Independent samples t-test, p < 0.01, < 0.03, < 0.02, < 0.01, and 0.001 respectively).
DISCUSSION

The present study describes the in vivo assessment of activated microglia in AD using radiolabelled PK11195 and SPECT. As such, this is the first SPECT study to show inflammatory lesions in AD and hence may be a potential parameter for investigational studies or therapeutic trials aiming for the inflammatory component. A previous PET study did not show an increased $^{11}$C PK11195 uptake in a series of 8 AD patients [40]. However, the use of only one normal elderly subject together with glioma patients as controls could have hampered this analysis. On the other hand, the present findings are in line with more recent findings with PET and $^{11}$C-PK11195 in early and mild dementia patients revealing increased regional binding in the entorhinal, temporoparietal, and cingulate cortex [28]. The discrepancy between these two studies however could be due the use of $^{123}$I in the present study with its higher lipophilicity facilitating brain uptake influencing both specific binding and tracer kinetics [41].

With regard to regional uptake values, the fact that mean $^{123}$I jodo-PK11195 uptake values are increased in various regions probably indicates a widespread and diffuse inflammatory process. Likewise, increased $^{11}$C PK11195 signals were found well beyond focal lesions in multiple sclerosis patients, supporting the notion that additional mechanisms apart from the focal macrophage accumulations found in the areas of BBB leakage must contribute to disease progression [25]. Moreover, the concordance between raised $^{123}$I jodo-PK11195 uptake values and perfusion deficits in frontal regions together with the significant inverse correlation between $^{123}$I jodo-PK11195 uptake values and several neuropsychological test results support the bystander lysis theory where activated microglia contribute to neuronal lysis by direct cytotoxic actions of some of their mediators.

Although mean uptake values were increased in various neocortical regions pathognomonically compromised in AD, significance was particularly reached in frontal neocortical regions. Although somewhat unexpected, this is in concordance with a very recent study where an intense immunoreactivity for the immune and inflammatory mediator CD40L, expressed on microglia and involved in microglia-dependent neuron death, was found throughout the frontal cortex of AD patients [8,42]. Also, this frontal increase in $^{123}$I jodo-PK11195 uptake could possibly indicate the progression together with the spreading of active inflammation towards more frontal regions in patients already at an advanced stage of the disease, although the mean MMSE score in the present study was still at a moderate level of 19. This advanced neuropathological stage is in concordance with the frontal perfusion deficits observed in the present study, typically seen later in the course of the disease [43]. Concerning this progression towards more frontal regions, also recent biopsy results showed that the progressive neurological impairment in AD is accompanied by a significant increase in senile plaques, neurofibrillary tangles and microglial cell activation in the frontal cortex [44]. However, group analyses should be carefully interpreted since there is a marked heterogeneity in AD patients concerning stage of the disease, progression pattern, predominant topographical lesion and cognitive subtype, with a substantial overlap between AD and other neurodegenerative conditions [43,45,46]. This heterogeneity, to which we actually contributed due to the rather large range of MMSE-score for the included AD patients, is also reflected in the larger standard deviations of $^{123}$I jodo-PK11195 uptake...
values in AD patients compared to controls. Concerning this heterogeneity, behavioural as well as
cognitive variability has been correlated with PET and SPECT findings [47]. Two subgroups with
distinct progression rates were already distinguished segregated by neuropsychological and cerebral
metabolic profiles where one rapidly deteriorating group had a significantly greater impairment in
executive functions attributed to the frontal lobe and a concomitant greater frontal hypometabolism
revealed by PET scanning [48].

Where the age difference between AD patients and controls could explain at least some of the
perfusion SPECT findings, it cannot explain the increased [\(^{123}\)I]iodo-PK11195 uptake in AD patients
since age-related increases in \(^{11}\)C PK11195 uptake only have been described in the thalamus and no
age-related effect at all was found in the present study [49]. Moreover, this age discrepancy between
AD patients and controls probably made us underestimate the actual [\(^{123}\)I]iodo-PK11195 uptake due to
the fact that for the current measurement no atrophy correction was performed while atrophy will be
more present in the older AD group (next to the atrophy already present pathognomonically), giving
rise to a loss of signal. This can be seen for example on one hand in the decreased basal ganglia
radioligand uptake but also on the other hand in the lack a significantly increased radioligand uptake in
the left mesotemporal region since this area, encompassing the hippocampus, is known for its
substantial atrophy in AD [50].

In the present study, a semiquantitative analysis was performed with a regional normalization and the
cerebellum as reference region and thus normalization factor. A regional rather than a global
normalization (with whole brain as normalization factor) was preferred since a region-specific
normalization is known to be more sensitive for diseases with various regions pathophysiologically
involved, like AD [51]. Although some reports described the pathological involvement of the
cerebellum in AD [52], this region was chosen as the normalization region since its taken together low
pathologic susceptibility and the absence or at least minimal presence of upregulated inflammatory
mediators in the cerebellum [53]. A previous study concluded already that the cerebellum is the more
appropriate choice of reference region in the quantification of perfusion SPECT in primary
degenerative dementia [54]. With regard to perfusion SPECT imaging, the cerebellum was shown to
be scintigraphically uninvolved [55].

In conclusion, [\(^{123}\)I]iodo-PK11195 provides a cellular marker of disease activity (progression), able to
indicate inflammatory pathology in AD patients. Interestingly, the combination of perfusion defects
and increased [\(^{123}\)I]iodo-PK11195 uptake values could be able to discriminate AD patients from
controls or other dementia patients, although for diagnostic purposes additional information
concerning for example the test-retest reliability of [\(^{123}\)I]iodo-PK11195 SPECT scanning should be
assessed. Also, the marked heterogeneity in regional increased uptake values and the concomitant
large standard deviations for the different neocortical regions could probably hamper the (diagnostic)
use of the present radioligand for individual patient studies. Finally, it is at present not known whether
[\(^{123}\)I]iodo-PK11195 SPECT would be able to detect pathological changes in a preclinical or a very early
stage of the disease. Worthy of note is the fact that, since the PBR also has an immunomodulatory role and, moreover, PK11195 appears to possess anti-inflammatory properties [56-58], the PBR may be itself a target for therapeutic intervention. This broadens the applicability of this radioligand for the monitoring of anti-inflammatory drug treatment trials in neurodegenerative diseases.
REFERENCES


