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**In vivo imaging of astrocytosis in Alzheimer's disease: an (11)C-L: -deuteriodeprenyl and PIB PET study.**

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**Title**

In vivo imaging of astrocytosis in Alzheimer´s disesase: a ^{11}C-L-deuteriodeprenyl and PIB PET study


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## Abstract

Astrocytosis is an important feature of the neuropathology of Alzheimer's disease (AD), yet there is currently no way of detecting this phenomenon *in vivo*. In this study we examine the retention of the PET tracer ^{11}C-L-deuteriodeprenyl (DED), thought to bind activated astrocytes, in 9 patients with moderate to severe AD compared with 11 healthy controls. As a measure of amyloid load, ^{11}C labelled Pittsburgh Compound B (PIB) retention was determined. Results show a significantly higher ^{11}C-L-deuteriodeprenyl retention in the frontal (35.1% increase, p=0.001), parietal (35.2%, p=0.001), temporal (30.9%, p =0.0001) and medial temporal lobes (22.3%, p=0.001) in AD compared to healthy controls after blood flow correction. DED retention in the sensorimotor and occipital cortices, and in white matter and subcortical structures, did not differ between gruops. There was a moderate but statistically significant (r=0.492, p = 0.01) correlation between DED and PIB retention values. Our conclusion is that DED may serve as an *in vivo* marker for astrocytosis in Alzheimer's disease, providing a window into intermediate processes between amyloidosis and neuronal loss and a mean of monitoring immunotherapy.

## Keywords

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## Introduction

Glial cells are believed to play a central role in the pathogenesis of Alzheimer's disease (AD) [1]. For this reason, effort has been made to visualize glia, particularly microglia, in AD patients in vivo [2, 3]. Astrocytes are the single most numerous glia cells, distributed in white and grey matter, where they play a central role in local microenvironment homeostasis, and are part of the neuroinflammatory process [1]. In AD there is proliferation and activation of astrocytes (astrocytosis, or astrocytic gliosis), which is mainly but not exclusively restricted to neuritic (senile) plaques, out of which 70-90% contain astrocytes [4, 5, 6]. The exact contribution of astrocytes in

AD is not known. Probably, the role of the astrocytes is variable depending on their exact relation to the amyloid plaque, their location in the cortical structure and the timing in the disease process [7]. Initially, they seem to act as beta amyloid (Aβ) scavengers, supporting neuronal cells in Aβ clearance [7]. In amyloid plaque evolution, after diffuse plaques are formed, dystrophic neurites and astrocytes appear inside and around the plaque, by definition creating a neuritic plaque. Hence, in the initial stages the contribution of astrocytes seems beneficial, but their effects in the later stages are under debate [1]. When astrocytes become activated (as customly defined by their greatly enhanced glial fibrillary acidic protein [GFAP] binding) in AD they express high levels of monoamine oxidase B (MAO-B) [4, 5, 8]. Monoamine oxidases are enzymes participating in the degradation of amines, MAO-B being the main isoform in the brain, where it is mainly found in glia and aminergic neurons [9]. In the healthy subject, the highest concentrations of MAO-B are found subcortically (thalami, basal ganglia), less in cerebral and cerebellar cortex and white matter [10-13]. The reason for the overexpression of MAO-B in activated astrocytes in AD is unknown, but the consequence is thought to be free radical production and cytotoxicity. Hence it is a potential drug target in AD [14]. MAO-B levels can be estimated using L-deprenyl [10,11], a selective irreversible MAO-B antagonist, which has been developed as a Positron Emission Tomography (PET) tracer, ^{11}C-L-deprenyl [15]. The deuterium substituted compound ^{11}C-L-deprenyl-D2, or ^{11}C-deuteriodeprenyl (DED) has kinetic advantages as a PET tracer [16]. DED has been used to visualise astrocytosis in  Amyotrophic Lateral Sclerosis, [17] and Creutzfeldt Jakob`s disease [18], where the findings have been in consistence with what is known about astrocytosis in these conditions. [11]C labelled Pittsburgh Compound B (PIB) is a PET tracer [19] used for in vivo measurements of amyloid depositions in neurodegenerative diseases, particularly AD. It is thought to bind insoluble amyloid, and thus to amyloid plaques regardless of morphology [20]. In AD, PIB retention is largely independent of disease stage (Mild Cognitive Impairment, mild to moderate AD) [21, 22].  The aim of his paper was to study DED and PIB distribution as measurement of astrocytosis and amyloid deposition respectively in AD patients and healthy volunteers.

**Material and methods**

**Subjects**

Ten patients (eight women and two men) with a median age of 82 (range 71-85) at PET examination, (*Table 1*) were recruited from the Memory Clinic at the Department of Geriatrics, Uppsala University Hospital. Nine had a diagnosis for probable Alzheimer´s disease according to the NINCDS-ADRDA and the Diagnostic and Statistical Manual IV criteria, and one (Patient ID nr 8) fulfilled the criteria for mixed dementia [23]. The diagnostic work-up included a thorough clinical examination with close informant interview, routine laboratory tests and CT scan (*Table 1*). In four patients cerebrospinal fluid was analysed, showing decreased concentrations of Aβ42 (4/4), and increased levels of total tau (4/4) and phosphorylated tau (3/4) adding support to the AD diagnosis. At the time of PET examination the severity of dementia, as measured with the Mini Mental Status Examination [24] ranged from moderate to severe (range 10 to 16, median 15), and the median time since diagnosis was 15 months (range 2 to 38). All patients except two were on medication when undergoing PET with choline esterase inhibitors and/or memantine. No one was treated with MAO inhibitors. On clinical follow up 3 months after PET examination one patient (Patient ID nr 2) developed spontaneous parkinsonism and hallucinations, fulfilling criteria of dementia with Lewy bodies [25], a diagnosis later confirmed at autopsy. Because of AD-like PIB retention values (Table 1) and plaque burden at neuropathological examination, this patient was retained in the analysis. Patients were scheduled to undergo both DED and PIB PET scan, whereas healthy controls only underwent DED scan. One patient was excluded from all further analysis because of movement during scans, in one (Patient ID nr 9) the DED but not the PIB was performed because of movements during the latter scan. For comparison 11 neurologically and psychiatrically healthy controls (8 women and 3 men) with no history of cognitive impairment were recruited. Their median age was 67 years (range 60-71 years), which is significantly younger than the patients (Mann Whitney, p below 0.05). All patients and healthy controls were non-smokers.

**Radiotracer synthesis**

Production of PIB and DED was carried out according to the standard good manufacturing process at Uppsala Imanet. Synthesis of N-methyl [11C] 2-(40-methylaminophenyl)-6-hydroxy-benzothiazole (PIB) was performed by means of the method described previously [19, 21, 26]. Synthesis of ^{11}C-L deprenyl was prepared as described previously [27-29].

**PET procedure**

PET was performed in either of two Siemens ECATHR cameras with an axial field of view of 155 mm, providing 63 contiguous 2.46 mm slices with a 5.6 mm transaxial and a 5.4 mm axial resolution. The orbitomeatal line was used to center the head of the subjects. The data were acquired in three- dimensional mode. Mean DED dose was 249,2 MBq and of PIB was 251,9 MBq. The scanner protocol for transmissions, emissions and reconstructions were the same as reported in the literature [18, 19].

**Image quantification**

Regions and volumes of interest (ROI and VOI) were used for image quantification. ROI were delineated on the PIB and DED scans using a standardised pattern previously applied [18,19, 21]. Eight ROI/VOI were a priori selected for analysis based on previous experience [18,19, 21]. Since no arterial sampling for input function correction was performed, simplified methods for quantitative analysis were applied. For PIB, standardised uptake values (SUV) in late time interval (40-60 min) were normalised to cerebellar uptake [19,21,22,30] and for DED, a modified Patlak analysis [18,29] was used. In this modified Patlak procedure, the cerebellar time-activity curve is the input function, which is modified by an exponential factor in order to neutralize a possible MAO-B activity in the reference region. The slope of the resulting Patlak model is assumed to represent tracer binding, whereas the intercept is used as an estimation of blood flow [18, 29]. Similarly, the PIB late frames summation divided by the cerebellum has been used as a measure of PIB retention. A 6 minutes summation of early frames divided by the retention in cerebellum was used as a measure of blood flow as proposed by Blomquist [31] and more recently by Rostomian [32]. Because regional blood flow can be decreased in patients with Alzheimer's disease tracer binding was corrected for regional blood

flow using the slope/intercept ratio for DED, and the late (40-60 min)/early (6 min)
frame ratio for PIB retention.

**Histopathology**

A neuropathological examination was performed in one patient (Patient ID nr 2, Table
1). Macroscopically hippocampal atrophy and enlargement of the lateral ventricles
was noted. Microscopic examination showed plenty of agyrophilic and kongophilic
neuritic plaques in the hippocampi, and generally in the cerebral cortex. In the
hippocampi neurofibrillary inclusions were abundant, but not in the cerebral cortex. In
the hippocampi Hirano bodies were seen, and Lewy bodies were found in the
substantia nigra, locus coerulus, hippocampi and transenthorhinal cortex. With GFAP
staining mild astrogliosis in the pyramid cell layer and in the subiculum was seen.
Expressed in neuropathological scales the Alzheimer pathology reached Braak IV-V,
plaque score was C according to Consortium to Establish a Registry for Alzheimer's
disease (CERAD), and "moderate likehood" according to National Institute on Aging
and Reagan Institute (NIA-RI). Neuropathological diagnosis was set to Dementia with
Lewy Bodies.

**Statistical analysis**

DED binding was compared between patients and controls for each ROI with a Mann
Whitney, two sided test, at the significance set to 0.00625 after Bonferroni correction
for eight ROIs (0.05/8).  Analyses were made with both uncorrected values (slope
values) and corrected (slope/intercept) for blood flow. Pearson correlation between
regional DED (only slope/intercept values) and PIB (both late frames and late/early
frames values) was examined using all ROIs in the 8 patients who underwent both
DED and PIB examination (64 ROIs), with significance set to 0.05. For each
individual region, correlation between DED (only slope/intercept values) and PIB
(both late frames and late/early frames values) was calculated using Spearman`s rank
correlation, with p corrected for 8 regions to 0.00625.

**Results**

Using DED slope values (uncorrected for blood flow) only non significant minor
differences between patients and controls were noted.  When using the slope/intercept
ratio, which represents a correction for blood flow, significantly higher DED ratio was

seen in frontal (35.1% increase, p=0.001), parietal (35.2% p=0.001), temporal (30.9% p=0.001 ) and the medial temporal lobes (MTL, 22.3%, p=0.001) in AD patients compared with controls, but not in sensorimotor or occipital cortex, nor in white matter or in the subcortical ROI (Table 2). Eight of the nine patients were PIB positive defined as late SUV/cerebellum ratio over 1,65 as threshold in frontal and/or parietal cortex [33, 34] (Table 1). The slope/intercept DED ratios did not correlate with the late frames PIB retention (r=0.013, p=0.916), but with the late/early frame PIB ratio (r=0.492, p=0.001). Of the individual regions, the only region with a significant correlation between DED and PIB (late/early frames ratio) after correction for multiple comparisons, was the occipital cortex ($r_s$= 0.833, p= 0.005).

**Discussion**

In this study, we found a substantial difference in cerebral DED binding between healthy subjects and patients with moderate to severe AD, thought to reflect the astrocyte activation in AD. Methodologically the significantly younger control population (67 vs 82 in median) is a potential confounder in our study, since other studies have shown an age dependent increase in cerebral MAO-B. In post mortem studies this increase has been localised subcortically and in limbic cortices, and not in the neocortex [12]. In contrast, a study examining DED PET retention as a function of age found higher retention also in the cerebral cortex, with a rise of 5.7%/decade (over 20-80 years) [35], which is less than the differences noted in our study. In our sample, there was negative or very week correlation between DED slope/intercept values and age in our control group, examined in the four cortical regions which showed statistically significant increase in DED binding between patients and controls (Pearson correlation: frontal cortex r=-0.050 p=0,88, parietal cortex r=0.067 p=0,85, temporal cortex r=0.092, p=0,79, MTL r=0.081 p=0,81). The DED binding is thought to indirectly, by binding to MAO-B, detect the increase in astrocyte density and activity (astrocytosis) in AD. When activated, astrocytes display considerably higher MAO-B expression than when not. DED is highly specific for MAO-B and other sources of DED binding seem improbable. Other sources of MAO-B in cortex than activated astrocytes and the physiological (age augmented) background activity, is another, however unlikely possibility.

The pattern of DED binding is well in accordance with what is expected from neuropathological findings.  Elevated DED levels were found only in cortex, the main

area of neuritic plaque deposition at neuropathological examination [36]. Also cortical regions affected by high neuritic plaque deposition, i.e. the frontal, parietal, temporal, and medial temporal lobes [37], showed more DED binding than for example the sensorimotor cortex.

In our moderate to severe AD patients, correlation between DED and PIB was only moderate (r=0.492, p=0.001), and examining single regions, significance was found only in the occipital cortex ($r_s$=0.833, p=0.005). There are several possible explanations for this. We suggest that the relative binding of DED and the PIB retention reflect a complex relation between different types of plaques, in different stages of their evolution. Elevated PIB retention is an early event in AD probably reflecting the presence of fibrillary amyloid rather than a specific morphological type of plaque since PIB levels tend to be stable during disease [20,21]. An explanation of our findings could be that the amount of amyloid contained in neuritic plaques is less than the total amyloid, or that less neuritic plaques than expected from neuropathology (70-90%) [4] do contain astrocytes. Also, non-plaque associated astrocytosis, as a result of neuronal cell death per se, could in our moderately to severely affected patients, be considerable.

The cortical region with the weakest correlation between DED binding and PIB retention was the MTL ($r_s$= 0.190, p=0.651). DED retention in this region of our AD patients was similar to that observed in other cortical areas, whereas the PIB retention was similar to that observed in the reference region (Figure 1). The MTL is affected late by amyloid deposits in the course of the disease, so moderate to severe AD patients should have amyloid deposition in this region [32]. The weak correlation is probably not produced by a reduction of the blood flow in the MTL as suggested by PIB early frames and DED intercept values. In the patient (Patient ID nr 2, Table 1) who underwent autopsy (Pat 2, Figure 1), histopathology showed high density of argyrophilic and kongophilic neuritic plaques containing amyloid cores in the hippocampi and generally in the cerebral cortex and mild astrocytosis. That the MTL display "negative" PIB but "positive" DED could have several explanations, one being that the accumulated atrophy, gliosis and detritus in the MTL of our moderate to severe patients, somehow interferes with PIB binding.

Imaging astrocytes adds another dimension of traditional amyloid imaging by PIB PET. It is well known that amyloid accumulation can precede symptoms and neuronal

cell death by years, even decades, and methods elucidating the intermediate processes taking place between amyloid accumulation and neurodegeneration are needed. Also, while association between the total amyloid load (estimated post-mortem or with PIB) and dementia severity is generally low or absent, there is an association between neuritic plaque density and dementia severity [38]. Our findings are restricted to moderate-severe disease and studies investigating other pathologies (Mild Cognitive Impairment, mild AD dementia) will be required.

In conclusion: using PET, we demonstrate higher cerebral DED binding corrected to blood flow in patients with moderate- severe Alzheimer´s disease compared with controls. This is thought to reflect ongoing astrocytosis around amyloid plaques. Visualising astrocytosis in the living human brain provides an entirely new *in vivo* window into the pathophysiology of Alzheimer´s disease and may, in particular settings, be useful for prognosis, monitoring of disease activity and therapeutic efforts.

**Conflict of interests**

The authors declare that they have no conflict of interests

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**Table title and legend**

**Table 1** Clinical and demographic characteristics of patients

ID nr: Patient ID nr. M: male, F: female. AD: Alzheimer's disease, LBD: Dementia with Lewy Bodies, VaD: vascular dementia. Age (in years) and MMSE (Mini Mental Status Examination) at PET examination. Medication: relevant medication at examination. PIB: PIB retention status, see "Results". NA: patient nr 9 moved during PIB scan, which could not be used for evaluation.

**Table 2** $^{11}$C-L-deprenyl-D2, (DED) binding in patients and healthy controls

Whm: cerebral white matter. Front: frontal cortex. Par: parietal cortex. Occ: occipital cortex. SM ctx: sensorimotor cortex. Tmp: temporal cortex. MTL: medial temporal lobe. DED[s]: mean difference in DED slope values between patients and controls, in percent. DED [s/i] HC: median DED slope/intercept value of healthy controls, with range, DED [s/i] P corresponding values of patients. DED[s/i]: mean difference in DED slope/intercept values between patient and controls, in percent. P-values: Mann Whitney, two sided test. *significant at p= 0.00625
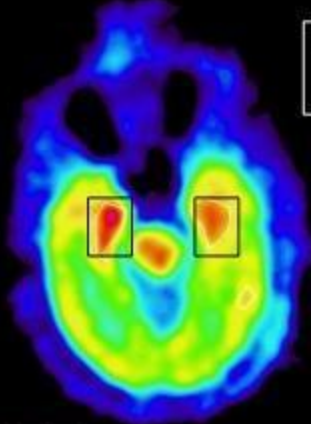
**Figure caption**

**Fig 1** $^{11}$C-L-deuteriodeprenyl (DED), and $^{11}$C labelled Pittsburgh Compound B (PIB) scans of two patients. Numbering refers to Table 1. (Pat 1: Pat ID nr 1, Pat 2: Pat ID nr 2). Scale is a percentage of maximum uptake. Boxes illustrate the medial temporal lobes (see Discussion)
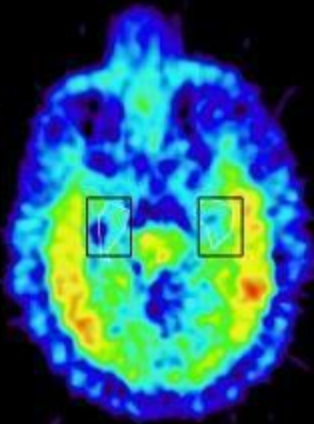
| Patient ID | Sex | Diagnosis | Age | MMSE score | PIB |
|---|---|---|---|---|---|
| 1 | M | AD | 83 | 16 | positive |
| 2 | F | LBD | 82 | 13 | positive |
| 3 | M | AD | 85 | 16 | positive |
| 4 | F | AD | 85 | 15 | positive |
| 5 | F | AD | 71 | 15 | positive |
| 6 | F | AD | 81 | 13 | positive |
| 7 | F | AD | 83 | 16 | positive |
| 8 | F | AD+ VaD | 83 | 16 | negative |
| 9 | F | AD | 80 | 10 | NA |

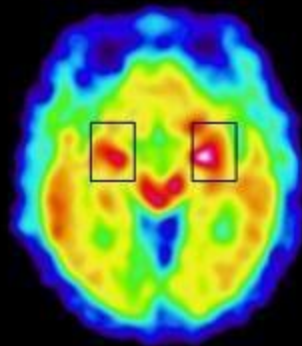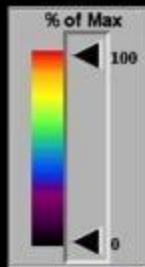| Region | DED[s] | p-value | DED [s/i] HC | DED[s/i] P | DED[s/i] | p-value |
|---|---|---|---|---|---|---|
| Whm | 18,0% | 0,059 | 0,05229 (0,03136-0,06403) | 0,06474 (0,04207-0,1089) | 23,4% | 0,044 |
| Front | 11,0% | 0,434 | 0,03707 (0,02328-0,04110) | 0,04789 (0,03901-0,05435) | 35,1% | 0,001* |
| Par | 9,0% | 0,67 | 0,03497 (0,02217-0,04129) | 0,04637 (0,03928-0,05770) | 35,2% | 0,001* |
| Occ | 12,0% | 0,943 | 0,03212 (0,01914-0,03729) | 0,03771 (0,03203-0,04669) | 25,9% | 0,014 |
| SM ctx | 10,0% | 0,394 | 0,03445 (0,02118-0,03811) | 0,03832 (0,03227-0,04281) | 15,8% | 0,053 |
| Thalami | -3,0% | 0,155 | 0,05050 (0,02960-0,05567) | 0,04981 (0,04493-0,06285) | 9,8% | 0,676 |
| Tmp | 3,0% | 0,887 | 0,04325 (0,02739-0,05038) | 0,05334 (0,05039-0,06616) | 30,9% | 0,0001* |
| MTL | 1,0% | 1 | 0,05182 (0,03294-0,05866) | 0,05975 (0,05046-0,06909) | 22,3% | 0,001* |

Pat 1

DED

PIB

% of Max

100

0

Pat 2