Astrocytosis measured by ^{11}C-deprenyl PET correlates with decrease in gray matter density in the parahippocampus of prodromal Alzheimer patients

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Keywords: Mild Cognitive Impairment, Astrocytosis, amyloid deposition, gray matter density, parahippocampus, Multi-tracer PET imaging, Alzheimer's disease

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Responses to Reviewers' comments

We sincerely thank the reviewers for their valuable comments and suggestion and we have revised the manuscript according to their suggestions.

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The author shows in vivo that parahippocampal astrocytosis, assessed by 11C-DED PET, is related with reduced GM density measured by MRI in PIB positive MCI patients and with 11C-PIB PET in the parahippocampus of AD patients. The paper is interesting, but difficult to read due to the number of correlations (MRI, PET imaging, CSF study) in 20 patients put together in 6 overlapping subgroups. In order to clarify the paper, data from FDG PET and CSF analysis could be removed or moved to supplementary data as well as the number of subgroups analysed (limited to 3: 4 PIB -ve MCI, 9 PIB +ve MIC and 13 AD rather than 5 by removing the MCI and the PIB +ve MCI subgroups.

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I am also somewhat surprise that no correction for multiple comparisons has been applied. Answer: Regarding no correction for multiple comparisons, we describe our hypothesis in the last paragraph of introduction in the revised version of the manuscript.

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Answer: As can be observed in Supplementary Figure 1(C) and (D) in the revised version of the manuscript there is regarding the correlation between 11C-DED slope values and PIB retention there was one PIB+ve MCI patient outlier, which might explain that the lack of significant correlation in the PIB+ve MCI/AD group.

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	parahippocampus could have been interesting. Answer: We agree with the reviewer that it would be very interesting to perform a more extensive study regarding CSF and imaging biomarkers and different brain regions in AD and MCI patients. Since the regional increase in amyoloid plaque load and astrocytosis as well as brain volume changes seem to occur in somewhat different brain regions we decided in the present manuscript mainly focus in the parahippocampus on astrocytosis and volume changes since both these pathological processes seem to be strongly present in this brain region although amyloid plaque load and impairment in cerebral glucose metabolism are more present in cortical brain regions. We have in earlier published studies (Forsberg et al., Curr Alzheimer Res 2010) applying SPM analysis for studying correlations between 11C-PIB retention and CSF biomarkers, showed a significant negative correlations between CSF Aß42 and 11C-PIB retention in the temporal, parietal, and frontal cortex for both AD and MCI patients as well as MCI patients. Furthermore regarding correlations between 11C-PIB retention and cerebral glucose metabolism measured by 18F-FDG, as also mentioned in the discussion of the revised version of the manuscript, we and others have reported a negative correlations the parietal and temporal cortex for AD and MCI patients (Engler et al. 2006).

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Abstract

Purpose: The Alzheimer disease (AD) pathology is characterized by deposition of fibrillar amyloid, neurofibrillary tangles as well as activation of astrocytosis, microglia activation, atrophy, dysfunctional synapse and cognitive impairments. The aim of this study was to test the hypothesis whether astrocytosis is related with reduced gray matter density in prodromal AD.

Methods: Twenty patients with AD or mild cognitive impairment (MCI) underwent multi-tracer PET studies with ^{11}C-Pittsburgh compound B (^{11}C-PIB), ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) and ^{11}C-deuterium-L-deprenyl (^{11}C-DED) PET imaging as well as MRI scanning, CSF biomarker analysis and neuropsychological assessments. The parahippocampus was selected as region of interest and each value was calculated for four different imaging modalities. Correlation analysis was applied between DED slope values and gray matter (GM) densities by MRI. To further explore possible relationships, correlation analyses were performed between the different variables including CSF biomarker.

Results: A significant negative correlation was obtained between DED slope values and GM density in the parahippocampus in PIB positive (PIB+ve) MCI patients ($p = 0.025$)(prodromal AD). Furthermore, in exploratory analyses, a positive correlation was observed between PIB-PET retention and DED binding in AD patients ($p = 0.014$) and a negative correlation was observed between PIB retention and CSF Aβ42 levels in MCI patients ($p = 0.021$), while the GM density and CSF total tau levels negatively correlated in both PIB+ve MCI ($p = 0.002$) and MCI patients ($p = 0.001$). No significant correlation was observed with FDG-PET and any with any of the other PET, MRI or CSF biomarkers.

Conclusions: High astrocytosis in the parahippocampus of PIB+ve MCI (prodromal AD) patients suggest an early preclinical influence on cellular tissue loss. The lack of correlation between astrocytosis and CSF tau levels but a positive correlation between

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1. Introduction

The classical pathologic hallmarks of Alzheimer's disease (AD) are the presence of amyloid plaques and neurofibrillary tangles but other processes as inflammation (astrocytosis, microgliosis) are known as possible pathophysiologic events of AD [1].

The brain astrocyte which are reactive in the brain against infection and injury has been proposed to exert an important role in AD when activated through neuroinflammation [2]. The enzyme monoamine oxidase B (MAO-B) exists on the outer mitochondrial membrane, predominantly in astrocytes [3-5]. L-deprenyl is an irreversible MAO-B inhibitor and the Positron emission tomography (PET) tracer 11C-deuterium-L-deprenyl (^{11}C-DED) has high affinity and specificity for MAO-B [6]. Three studies have been published using ^{11}C-DED PET in AD patients [7-9] and one of these studies demonstrated an increased 11C-DED binding especially in patients with mild cognitive impairment (MCI) suggest that inflammation is an early phenomenon of AD pathology [7].

The biomarker-based new diagnostic criteria have been proposed to enhance the clinical detection of AD in early prodromal stages of the disease. Biomarkers recommended by these criteria include amyloid tracer uptake and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) using PET, medial temporal lobe atrophy as assessed by structural MRI, and cerebrospinal fluid (CSF) biomarkers including Aβ1-42, total tau (tTau), and phosphorylated tau (pTau) [10, 11].

In addition to these biomarkers, ^{11}C-DED PET imaging of astrocytosis (neuroinflammation) may help to further understand the AD pathophysiology. Several previous studies have tried to explore relationships between suggested biomarkers, most of them used a combination of two or three biomarkers [12-19]. In one CSF study a relationship was reported between cerebral brain volumes and CSF tau in AD patients and Aβ42 in cognitively normal subjects respectively [17]. Several studies have evaluated correlations between amyloid accumulation and cerebral glucose metabolism in AD, MCI or cognitively normal elderly [14-16, 18, 19], while others examined the relationships

between amyloid and cerebral volume in cognitively normal, subjective cognitive impairment, mild cognitive impairment, or AD [12, 13].

In this study, we hypothesised that in the parahippocampus which is known as a region showing early destructive tau pathology processes [20] and structural changes [21] during AD progression, neuronal astrocytosis is correlated with the reduced gray matter density in prodromal AD. To test this hypothesis, we examined the relationship between astrocytosis using ^{11}C-DED and gray matter density with MRI in MCI and AD patients. In addition we also explored possible relationships between amyloid plaque load, regional glucose metabolism, astrocytosis using ^{11}C-PIB/^{11}C-DED/^{18}F-FDG PET, gray matter density with MRI and CSF biomarkers.

2. Materials and methods

2.1. Subjects

Twenty patients (thirteen MCI and seven AD patients) were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. The patients had undergone clinical memory assessment after been referred from the primary care centers in the community for investigation of suspected cognitive disorders. The patients underwent comprehensive clinical examination, electroencephalogram, MRI, CSF and blood analysis including APOE genotype, and neuropsychological testing. The diagnosis of MCI followed the clinical criteria as defined by Petersen et al.[22]: memory complaint, objective memory impairment (1.5 SD below age matched controls) [23], normal general cognitive function, intact daily living, not fulfilling the DSM-IV criteria for dementia (American Psychiatric Association, 1994). AD met the clinical criteria of the DSM-IV criteria for dementia and the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association (NINCSD-ADRDA) criteria for AD [24]. All patients underwent multi-tracer PET

studies with 11C-DED, 11C-PIB and 18F-FDG. All patients and their caregivers provided written informed consent to participate in the study, which was conducted according to the declaration of Helsinki and subsequent revisions. Ethical approval was obtained from the regional human ethics committee of Stockholm and the Faculty of Medicine and Radiation, Protection Committee of Uppsala University Hospital, Sweden.

2.2. PET Data

All subjects underwent PET examinations with ^{11}C-DED/^{11}C-PIB/^{18}F-FDG at Uppsala PET Centre, Academical Hospital, Uppsala, Sweden. The tracers were produced according to good manufacturing standards at Uppsala PET centre. The PET scans were performed by a Siemens ECAT EXACT HR+ scanner (CTI PET systems Inc.) with a field of view of 155 mm, providing 63 contiguous 2.46 mm slices with 5.6mm transaxial and 5.4mm axial resolution. Images were reconstructed from the data and corrected for tissue attenuation of 511-keV gamma radiation photons by employing an external 68Ge source. The ^{11}C-DED acquisitions consisted of 19 time frames (4 × 30, 8 × 60, 4 × 300, and 3 × 600s), with a total duration of 60 min. The ^{11}C-PIB acquisitions consisted of 24 frames (4 × 30, 9 × 60, 3 × 180, and 8 × 300s) over 60 min. The late 40- to 60-min ^{11}C-PIB sum image was created and used for subsequent image analysis. For each ^{18}F-FDG acquisition, 21 frames (4 × 30, 9 × 60, 3 × 180, and 5 × 300s) were acquired over 45 min. A late 25- to 45-min ^{18}F-FDG sum image was created and used for subsequent analysis. Patients fasted for 4 h preceding the ^{18}F-FDG scan. The mean injected doses for each tracer were 211 ± 66 MBq for ^{11}C-DED, 228 ± 70 MBq for ^{11}C-PIB, and 229 ± 49 MBq for ^{18}F-FDG.

2.3. Image Processing

^{11}C-PIB/^{11}C-DED/^{18}F-FDG PET images were co-registered and re-sliced to their individual T1 reference image. All T1 reference images were segmented into gray matter (GM) and

white matter tissue classes using the unified segmentation algorithm of SPM8. The resultant probabilistic GM density map for each participant had a threshold of 0.5 applied to it, and a binary GM mask was created (0, no tissue, and 1, tissue with a > 50% probability belonging to GM). The inverse nonlinear transformation parameter file from SPM's segmentation algorithm was used to warp a simplified digital probabilistic atlas [25], consisting of 26 cortical and subcortical regions, into each individual's native T1 space. These atlases were multiplied by the corresponding binary GM mask, which generated a GM-specific digital atlas for each participant. Raw co-registered and re-sliced PET and MRI data for each patient were sampled using the same individual digital atlases previously created. Mean PET uptake and MRI gray matter density were measured for each atlas region using this method. Regional metabolic rate of glucose were created for ^{18}F-FDG PET and each atlas region by dividing by the respective mean pontine glucose metabolic rate. For ^{11}C-PIB/^{11}C-DED PET, regional amyloid binding or ^{11}C-DED slope value ratios were acquired by dividing each atlas region by the respective mean cerebellar values.

2.4. Cerebrospinal Fluid Biomarker measurements

Cerebrospinal fluid (CSF) was obtained by lumbar puncture performed in non-fasting subjects between 8 - 11 am at the Memory clinic, Karolinska University Hospital. CSF samples with more than 500 erythrocytes/µl were excluded. All samples were centrifuged for 10 minutes at 3000 xg and 4 ºC immediately after collection. The supernatant was aliquoted after careful mixing to avoid gradient effects, and were stored at -80 ºC until analysis. Measurement of total tau (tTau), phosphorylated tau (pTau) and amyloid-β1-42 (Aβ1-42) in CSF was performed using a sandwich enzyme-linked immunosorbent assays (ELISA) (INNO-BIA AlzBio3 assay, Innogenetics, Ghent, Belgium) [26-28].

2.5. Neuropsychological Assessments

An experienced neuropsychologist performed cognitive assessments. These neuropsychological tests assess specific domains such as verbal abilities (Similarities and Information), visuospatial abilities (Block Design and Rey-Osterrieth copy), episodic memory (Rey Auditory Verbal Learning and Retention after 30min; Rey-Osterrieth Retention after 30min) and attention and executive function (Trail Making Test A and B). Detailed information regarding the above-mentioned tests has been described previously [29]. All cognitive raw scores were z-transformed by using reference data from healthy adults at the Geriatric Clinic, Karolinska University Hospital Huddinge [30].

2.6. Statistical Analysis

The MCI subjects were categorized due to 11C-PIB retention data into PIB negative (PIB-ve) and PIB positive (PIB+ve) groups, which were defined with a cut-off value of 1.41 as described in our earlier European multi-center study in 11C-PIB [7]. To explore multimodal correlations in AD continuum, subjects were divided to six groups: PIB-ve MCI; PIB+ve MCI; those who include both PIB-ve MCI and PIB+ve MCI groups (MCI); those who include PIB positive subjects of MCI and AD patients (PIB+ve MCI/AD); those who were diagnosed as AD (AD); those all who recruited as MCI and AD (MCI+AD) (Figure 1). Comparing characteristics of defined PIB-ve MCI, PIB+ve MCI, and AD groups, ANOVA for age, education, and MMSE; chi-square tests for gender and APOE ε4 allele numbers; Kruskal-Wallis test for values of 4 imaging modalities, CSF biomarkers of Aβ1-42, tTau and pTau were applied. For the region of interest (ROI) of parahippocampus, mean values of DED binding slope, PIB retention ratio, glucose metabolic rate, and GM density were acquired from 4 different imaging modalities of ^{11}C-DED/^{11}C-PIB/^{18}F-FDG PET and MRI. Correlation analyses of Spearman using SPSS version 18 were done. To test our hypothesis, statistical significance was defined as $p < 0.05$ for correlation between DED

binding slope values and GM density in parahippocampus. For additional correlation analyses between DED binding slope values and PIB retention ratio; glucose metabolic rate; CSF biomarkers of Aβ1-42 and tTau, having aim of exploration, we applied significance level also as $p < 0.05$ without correction of multiple comparisons.

3. Results

3.1. Characteristics of PIB-ve MCI, PIB+ve MCI and AD patients

Demography and clinical data of patients are summarized in Table 1. No significant difference was observed in age, gender, education, APOE ε4 allele numbers and Mini Mental State Examination (MMSE) score between the groups. The PIB-ve MCI and PIB+ve MCI groups demonstrated comparable mean MMSE score values, whereas the MMSE score was lower for the AD group but did not reached statistical significance. Group differences were observed for mean parahippocampal gray matter density/PIB retention ratio and CSF Aβ1-42 (Kruskal-Wallis; $p < 0.05$).There was no significant difference in mean parahippocampal DED slope values/Glucose metabolic rate and CSF tTau/pTau between 3 groups. Neuropsychological test results among groups are presented in Supplementary Table 1.

3.2. Correlation between ^{11}C-Deprenyl binding slope values and Gray Matter Density in the parahippocampus

A significant negative correlation between DED binding slope values and GM density was found only in the PIB+ve MCI group ($p = -0.733$, $p = 0.025$) (Table 2, Figure 2), while significant correlation was not observed in the other patients groups.

3.3. Exploratory Correlations between ^{11}C-Deprenyl regional binding slope (DED), Gray Matter Density (MRI), ^{11}C-Pittsburgh Compound-B binding (PIB) retention, and ^{18}F-Fluorodeoxyglucose metabolism (FDG) in the parahippocampus

Table 2 summarizes the observed correlation between the 4 different imaging modalities of ^{11}C-DED/^{11}C-PIB/^{18}F-FDG PET and MRI respectively. A significant correlation was observed between DED and PIB in AD (ρ = 0.857, p = 0.014) and MCI + AD group (ρ = 0.468, p = 0.038) (Supplementary Figure 1C).

3.4. Exploratory Correlations between CSF biomarkers and four different imaging modalities in the parahippocampus

Table 3 summarizes the correlation for CSF and imaging biomarkers. A significant negative correlation was observed between MRI gray matter density and CSF total tau levels in MCI (ρ= -0.797, p = 0.001), PIB+ve MCI (ρ = -0.883, p = 0.002), and MCI + AD group (ρ = -0.474, p = 0.035) respectively (Supplementary Figure 2, A and B). A significant negative correlation between PIB and CSF Aβ1-42 was found in MCI (ρ = -0.632, p = 0.021) and MCI + AD (ρ = -0.624, p = 0.003) patients respectively (Supplementary Figure 2, C and D). The AD patients showed a significant negative correlation between PIB retention and CSF total tau levels (ρ = -0.893, p = 0.007).

4. Discussion

The rapid development of PET molecular imaging techniques provides important possibilities to understand the time course of complex pathophysiological processes in AD. In the present study deposition of amyloid plaque, astrocytosis and cerebral glucose metabolism were measured in relation to gray matter density measured by MRI.

Hippocampus is well known from pathological studies to be characterized by high astrocytosis, tau phosphorylation while the amyloid plaque load is low and much higher in cortical brain regions of AD brains. In a recent study we performed in vitro autoradiography studies using [3H]-PIB and [3H]-deprenyl in order to measure laminar distribution of amyloid plaques and astrocytes in AD postmortem brain tissue we observed by in vitro autoradiography studies a clear laminar pattern with high [3H]-PIB binding in all layers and [3H]-deprenyl in only the superficial layers of the frontal cortex while [3H]-PIB showed low binding to fibrillar Aβ, but [3H]-deprenyl high binding to activated astrocytes throughout the hippocampus [31]. The present study demonstrates in vivo that parahippocampal astrocytosis assessed by ^{11}C-DED PET is related with reduced GM density measured by MRI in PIB positive MCI patients (prodromal AD) . Moreover, we also explored that clinical demented AD patients showed a positive correlation between astrocytosis and PIB accumulation by ^{11}C-PIB PET in the parahippocampus.

The significant negative correlation between astrocytosis and GM density in PIB+ve MCI may suggest that parahippocampal inflammation may influence/be influenced by gray matter cell loss in prodromal AD patients, while in clinical demented AD patients less active astrocytosis exist [7]. The positive correlation we observed in the parahippocampus between ^{11}C-DED binding and ^{11}C-PIB retention is most probably due to the fact that despite low ^{11}C-PIB retention in the hippocampus of AD patients, there is an increasing deposition of amyloid plaques in the hippocampus in clinical AD compared to MCI as measured by 11C-PIB [32].

We observed a significant negative correlation between the GM density of the parahippocampus and CSF tTau levels in PIB+ve MCI patients. This finding is consistent with previous studies reporting that neurofibrillary tangles are responsible for cerebral

atrophy, especially in medial temporal lobe [33-35]. Interestingly we observed no relationship between astrocytosis (^{11}C-DED binding) and CSF tTau levels suggesting that in the parahippocampus of clinically demented AD patients the astrocytosis are related to amyloid pathology rather than tau, which is in line with previous studies suggesting that dysregulation of Aβ clearance by astrocytes may be responsible for its accumulation in AD [36-38].

Taken together, our findings suggest that, in prodromal AD the parahippocampus, astrocytosis might influence gray matter cell loss, but in clinically demented AD, astrocytosis is less related to cerebral cell loss but some pathological causility with amyloid processes.

In our current analysis, we did not observe any significant relationships between cerebral glucose metabolism in the parahippocampus and other measured parameters. Impairment in cerebral glucose metabolism has generally been described as a later phenomenon in the time course of AD in comparison to astrocytosis, amyloid brain deposition and changes in CSF biomarkers [39, 40]. A negative correlation between amyloid plaque deposition and decline in cerebral glucose metabolism has been reported in the temporal or parietal cortex for AD and MCI patients [14-16, 18]. Recently a significant negative relationship between atrophy and cerebral glucose metabolism was demonstrated in the hippocampus and precuneus of AD patients [19]. Significant correlation study between amyloid plaque load and atrophy measured by PET has solely been demonstrated in the temporo-parietal cortex of subjects of subjective cognitive impairment [13]. There has so far until now as far as we know not been any study demonstrating significant correlations between the three imaging modalities in the parahippocampus.

To our knowledge, the present study is the first to explore multi-modal biomarker profile in the parahippocampus at different stages of AD. Our study suggests that during AD pathology processes, the astrocytosis may influence neuronal cell structure and tissue loss, especially in prodromal AD but when the amyloid pathology is less prominent in the parahippocampus as it is in more advanced clinical AD. PET imaging of astrocytosis might in the future be possible targets for early detection and prevention trials of disease-modifying therapies.

Disclosure statement

None of the authors have any actual or potential conflicts of interest.

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Table 1. Patient demographic data

	PIB-ve MCI	PIB+ve MCI	AD
Number	4	9	7
Age, yr	62.6 (7.3)	63.3 (7.3)	65.1 (6.3)
Sex			
Male	3	5	3
Female	1	4	4
Education, yr	12.8 (2.5)	12.9 (2.1)	10.4 (1.8)
APOE ε4	1	7	5
MMSE score	27.3 (2.1)	28.0 (2.0)	24.4 (5.7)
Parahippocampus			
DED slope values (1/min)	0.013 (0.001)	0.014 (0.002)	0.013 (0.002)
Gray matter density	0.87 (0.001)	0.88 (0.025)	0.85 (0.022)[a]
Glucose metabolic rate (ratio to pons)	1.11 (0.061)	1.12 (0.114)	1.07 (0.089)
PIB retention ratio (ratio to cerebellum)	1.05 (0.217)	1.38 (0.103)[b]	1.39 (0.207)[c]
CSF biomarkers pmol/l			
Aβ1-42	885.0 (290.9)	501.8 (140.0)[c]	470.0 (131.4)[c]
tTau	291.5 (48.3)	356.0 (135.1)	523.7 (230.9)
pTau	65.8 (14.2)	65.6 (17.1)	85.7 (24.8)

MCI = Mild cognitive impairment subjects; AD = Alzheimer disease patients; DED = 11C-deuterium-L-deprenyl; PIB = 11C-Pittsburg Compound-B; PIB-ve = PIB negative which has low PIB retention ratio; PIB+ve = PIB positive which has high PIB retention ratio; APOE ε4 = number of subjects carrying at least one Apolipoprotein ε4 allele; tTau = total tau; pTau = phosphorylated tau; Aβ1-42 = amyloid β1-42; values are mean (SD) except number/sex/APOE ε4; [a]Significant different from PIB+ve MCI ($p < 0.05$); [b]Significantly different from PIB-ve MCI ($p < 0.001$); [c]Significantly different from PIB-ve MCI ($p < 0.05$)

Table 2. Correlations between DED, PIB and FDG imaging and MRI gray matter density in the Parahippocampus of MCI and AD patients

Patient group	Number	DED vs. MRI	DED vs. PIB	DED vs. FDG	PIB vs. FDG	PIB vs. MRI	FDG vs. MRI
PIB-ve MCI	4	-0.400 (0.600)	-0.200 (0.800)	0.400 (0.600)	0.000 (1.000)	0.800 (0.200)	0.400 (0.600)
PIB+ve MCI	9	**-0.733 (0.025)**	0.283 (0.460)	-0.183 (0.637)	0.583 (0.099)	-0.067 (0.865)	0.050 (0.898)
AD	7	0.107 (0.819)	**0.857 (0.014)**	0.071 (0.879)	0.179 (0.702)	-0.357 (0.432)	0.000 (1.000)

Values are correlation coefficients of Spearman's rho and p values in parenthesis. Bold values are $p < 0.05$. MCI = Mild cognitive impairment subjects; AD = Alzheimer disease patients; PIB = 11C-Pittsburg Compound-B retention ratio; PIB-ve = PIB negative which has low PIB retention ratio; PIB+ve = PIB positive which has high PIB retention ratio; DED = 11C-Deprenyl regional binding slope; MRI = Regional gray matter density; FDG = Regional 18F- Fluorodeoxyglucose metabolism

Table 3. Correlation between DED/MRI/PIB imaging and CSF biomarkers in the Parahippocampus of MCI and AD patients

Patient group	Number	DED vs. tTau	DED vs. Aβ1-42	MRI vs. tTau	MRI vs. Aβ1-42	PIB vs. tTau	PIB vs. Aβ1-42
PIB-ve MCI	4	-0.800 (0.200)	0.600 (0.400)	0.000 (1.000)	-0.400 (0.600)	-0.400 (0.600)	0.200 (0.800)
PIB+ve MCI	9	0.500 (0.170)	0.250 (0.516)	**-0.883 (0.002)**	-0.483 (0.187)	-0.017 (0.966)	-0.450 (0.224)
AD	7	-0.750 (0.052)	-0.750 (0.052)	0.500 (0.253)	0.143 (0.760)	**-0.893 (0.007)**	-0.607 (0.148)

Values are correlation coefficients of Spearman's rho and p values in parenthesis. Bold values are $p < 0.05$. MCI = Mild cognitive impairment subjects; AD = Alzheimer disease patients; PIB = 11C-Pittsburg Compound-B retention ratio; PIB-ve = PIB negative which has low PIB retention ratio; PIB+ve = PIB positive which has high PIB retention ratio; DED = 11C-Deprenyl regional binding slope; MRI = Regional gray matter density; FDG = Regional 18F- Fluorodeoxyglucose metabolism; CSF = Cerebrospinal fluid biomarkers such as total tau (tTau) or amyloid β1-42 (Aβ1-42)

Figure legends

Figure 1. Diagram showing the Alzheimer's disease (AD) continuum subjects groups categorized as Mild Cognitive Impairment (MCI), PIB+ve MCI, PIB+ve MCI/AD, AD and MCI + AD. PIB+ve indicate subjects having high Pittsburgh Compound B (PIB) retention values (in relation to cerebellum) above cut off score of 1.41.

Figure 2. Representative correlation plot between gray matter density by MRI and ^{11}C-DED slope values in the parahippocampus of PIB positive (PIB+ve) MCI patients. White bold arrows of upper figure indicate bilateral parahippocampus of Hammers atlas.

Supplementary Figure 1. Correlation analysis between mean gray matter and 11C-DED slope values in the parahippocampus (A) for MCI and AD patients, (B) for MCI patients, including PIB positive (PIB+ve) and PIB negative (PIB-ve) groups and 11-PIB retention ratio and 11C-DED slope value (C) for MCI and AD patients, (D) for MCI patients. * indicates $p < 0.05$ by correlation analyses.

Supplementary Figure 2. Correlation analyses between CSF total tau values and mean parahippocampal gray matter density (A) for MCI and AD patients, (B) for MCI patients, including PIB positive (PIB+ve) and PIB negative (PIB-ve) groups, between CSF Aβ1-42 values and parahippocampal 11C-PIB retention ratio (C) for MCI and AD patients, (B) for MCI patients. * indicates $p < 0.05$ by correlation analyses.

Figure 1.

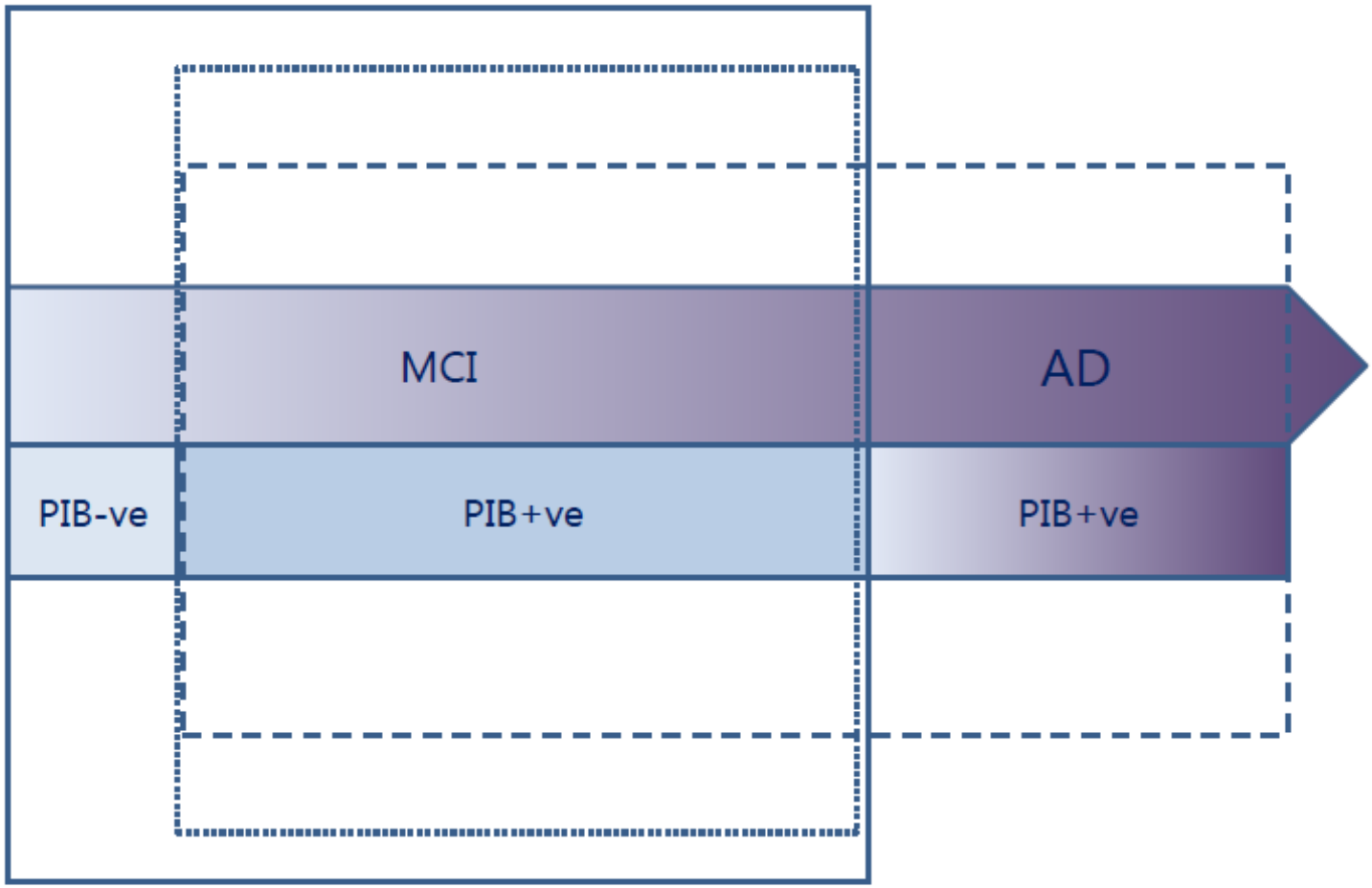
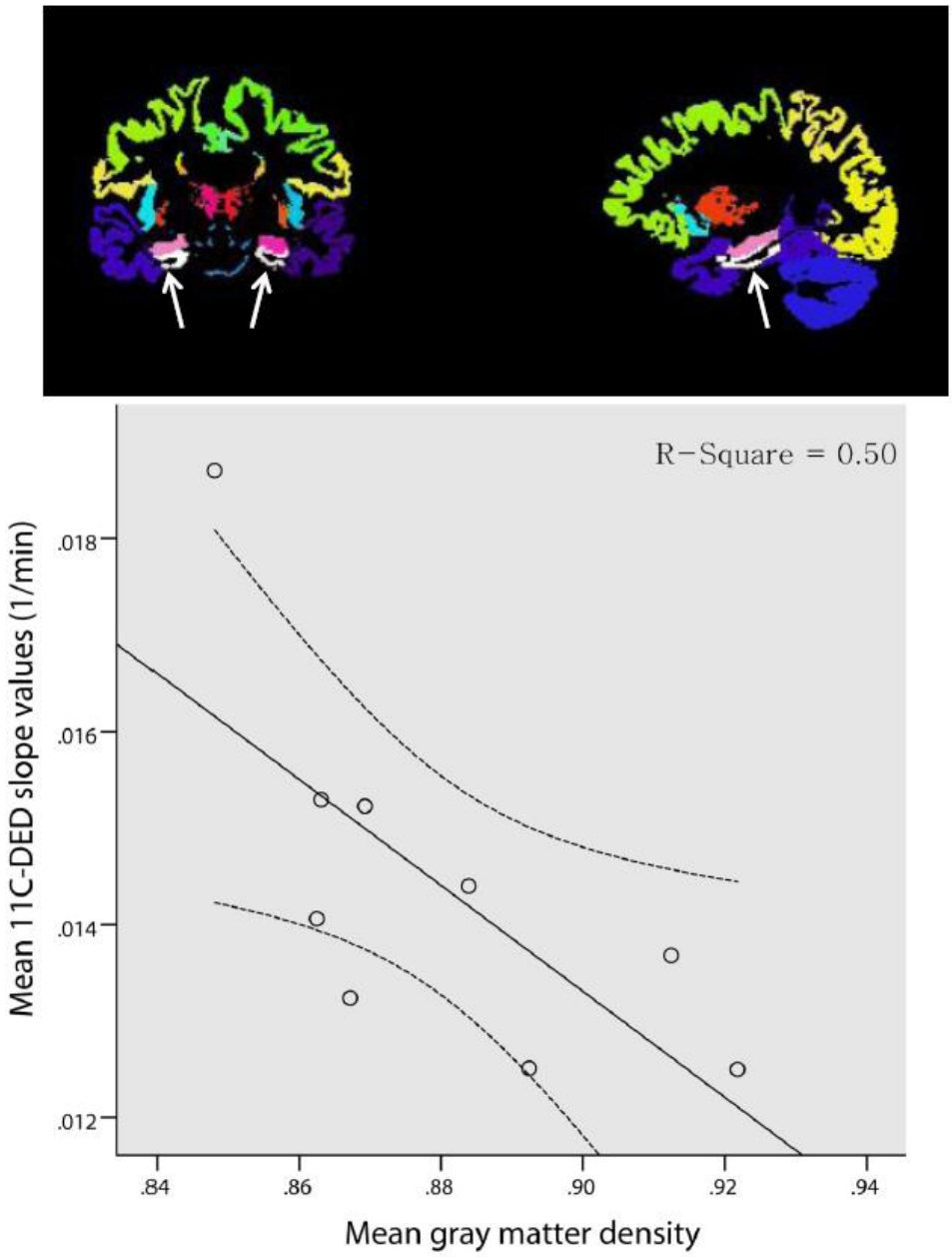


Figure 2.


R−Square = 0.50
Mean 11C-DED slope values (1/min)
.018
.016
.014
.012
.84
.86
.88
.90
.92
.94
Mean gray matter density

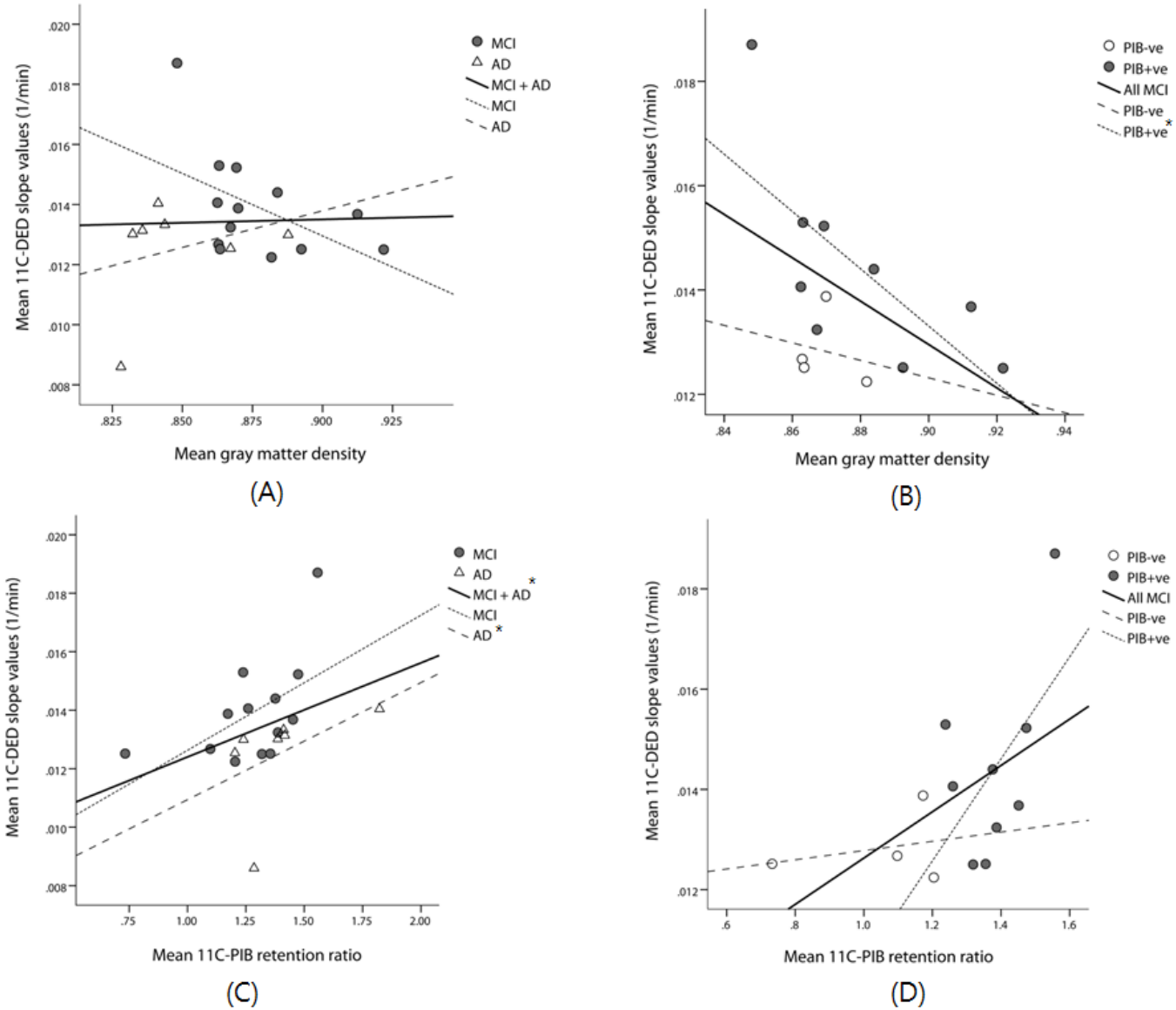
Supplementary Table 1

Supplementary Table 1. Neuropsychological Test Results (z Scores)

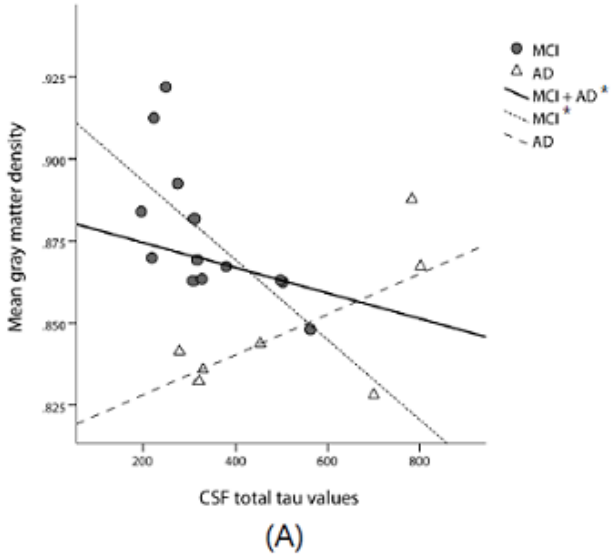
	PIB-ve MCI	PIB+ve MCI	AD
Similarities	0.67 (0.79)	-0.57 (1.13)	-2.06 (1.92)*
Information	-0.91 (0.91)	-0.84 (0.62)	-1.97 (2.27)
Block Design	0.05 (1.73)	-0.82 (1.09)	-1.87 (1.12)
Rey Complex Figure Test copy	-0.28 (0.87)	-0.34 (0.53)	-2.13 (3.80)
Rey Complex Figure Test delay	-0.72 (1.17)	-1.20 (0.84)	-2.13 (3.80)
Rey Auditory Verbal Learning Test	-0.60 (0.73)	-1.21 (0.89)	-2.02 (1.04)
Rey Auditory Verbal Retention Test	-1.46 (0.83)	-1.58 (0.73)	-2.23 (0.95)
Trail Making Test A time	-0.61 (0.64)	-1.03 (1.54)	-2.98 (6.37)
Trail Making Test B time	-0.42 (1.04)	-0.73 (1.29)	-1.66 (1.66)

All values are mean (SD); MCI = Mild cognitive impairment subjects; AD = Alzheimer disease patients; PIB = Regional 11C-Pittsburg Compound-B binding; PIB-ve = PIB negative which has low PIB retention ratio; PIB+ve = PIB positive which has high PIB binding; *Significantly different from PIB-ve MCI ($p < 0.05$)

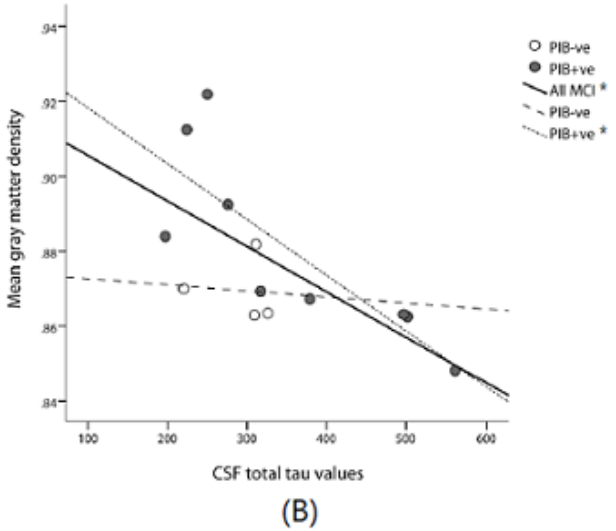
Supplementary Figure 1.



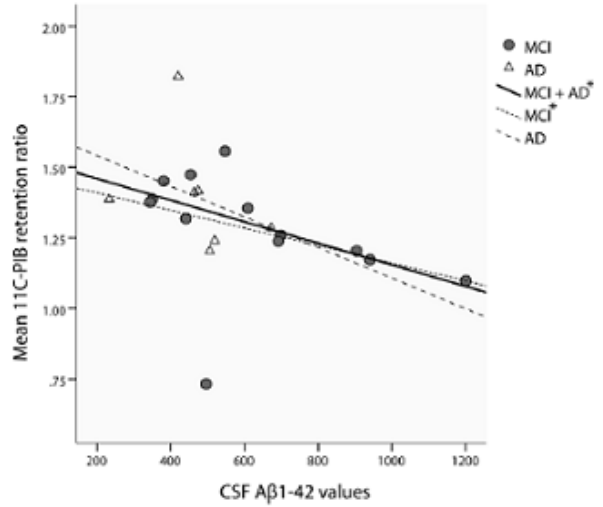
Supplementary Figure 2.


Mean gray matter density
CSF total tau values
MCI
AD
MCI + AD *
MCI *
AD

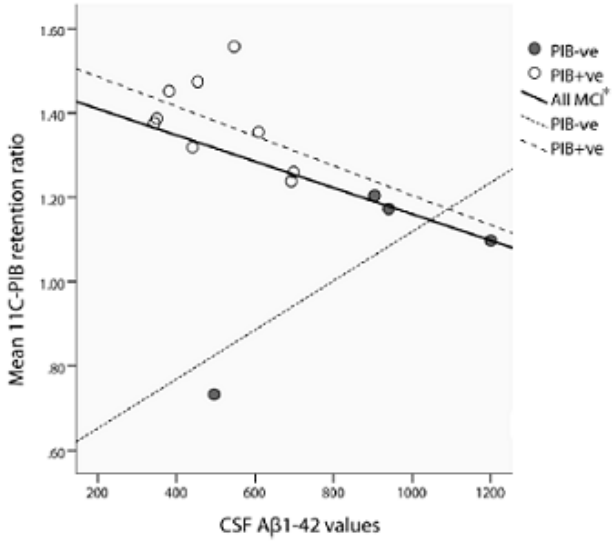
(A)


Mean gray matter density
CSF total tau values
PIB-ve
PIB+ve
All MCI *
PIB-ve
PIB+ve *

(B)


Mean 11C-PIB retention ratio
CSF Aβ1-42 values
MCI
AD
MCI + AD*
MCI*
AD

(C)


Mean 11C-PIB retention ratio
CSF Aβ1-42 values
PIB-ve
PIB+ve
All MCI*
PIB-ve
PIB+ve

(D)

Supplementary Material Fig 1A

Click here to download Supplementary Material: 20140130_Supplementary Figure 1_A_DED_MR.tif

Supplementary Material Fig 1B

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Supplementary Material Fig 1C

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Supplementary Material Fig 1D

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Supplementary Material Fig 2A

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Supplmentary Material Fig 2B

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Supplementary Material Fig 2C

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Supplementary Material Fig 2D

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