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Neurobiology of Aging 29 (2008) 1456–1465

NEUROBIOLOGY OF AGING

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PET imaging of amyloid deposition in patients with mild cognitive impairment

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Received 8 January 2007; received in revised form 25 March 2007; accepted 30 March 2007
Available online 11 May 2007

Abstract

It is of great clinical value to identify subjects at a high risk of developing AD. We previously found that the amyloid positron emission tomography (PET) tracer PIB showed a robust difference in retention in the brain between AD patients and healthy controls (HC). Twenty-one patients diagnosed with MCI (mean age 63.3 ± 7.8 (S.D.) years) underwent PET studies with ^{11}C-PIB, and ^{18}F-fluoro-deoxy-glucose (FDG) to measure cerebral glucose metabolism, as well as assessment of cognitive function and CSF sampling. Reference group data from 27 AD patients and 6 healthy controls, respectively, were used for comparison. The mean cortical PIB retention for the MCI patients was intermediate compared to HC and AD. Seven MCI patients that later at clinical follow-up converted to AD (8.1 ± 6.0 (S.D.) months) showed significant higher PIB retention compared to non-converting MCI patients and HC, respectively ($ps < 0.01$). The PIB retention in MCI converters was comparable to AD patients ($p > 0.01$). Correlations were observed in the MCI patients between PIB retention and CSF $A\beta_{1\text{-}42}$, total Tau and episodic memory, respectively.

Keywords: Mild cognitive impairment; Converters; Amyloid; PET; PIB; FDG; CSF biomarkers

1. Introduction

Mild cognitive impairment (MCI) represents a transitional phase between normal ageing and dementia disorders, especially Alzheimer's disease (AD). Patients with MCI have an increased risk of developing AD (Petersen et al., 1999). At present there is great interest in finding diagnostic tools for detection of an increased risk of developing AD. The diagnostic accuracy of current and commonly used MCI criteria is low to moderate (Visser et al., 2005). Both structural and functional neuroimaging have shown promising results in improving MCI diagnosis. Results suggest that changes in glucose metabolism, measured by means of [^{18}F]-2-deoxy-d-glucose (FDG) positron emission tomography (PET), might have a predictive value in the detection of MCI patients at a high risk of developing AD (Arnaiz et al., 2001; Chetelat et al., 2003; Drzezga et al., 2003). Similarly, magnetic resonance imaging (MRI) used in the assessment of brain atrophy and deterioration in the hippocampus, and entorhinal and temporal neocortical volumes, has been used to discriminate MCI patients at a risk of developing AD (Chetelat and Baron, 2003; Kordower et al., 2001). Cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$ and Tau have been studied as potential biomarkers in MCI. They have shown prognostic value in discriminating

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0197-4580/$ – see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.neurobiolaging.2007.03.029

MCI patients that will develop AD (Blennow and Hampel, 2003; Buerger et al., 2005; Hansson et al., 2006; Herukka et al., 2005). Longitudinal studies involving MRI and CSF measurements might provide synergistic and improved sensitivity and specificity in prognostic studies of conversion from MCI to AD (de Leon et al., 2006). Recently, various PET ligands used in amyloid imaging *in vivo* have been developed (Klunk et al., 2001; Shoghi-Jadid et al., 2002; Verhoeff et al., 2004). Promising results have been obtained with *N*-methyl [^{11}C] 2-(4′-methylaminophenyl)-6-hydroxy-benzothiazole (PIB), which was found to discriminate successfully between AD patients and age-matched healthy controls (Klunk et al., 2004). Since then several studies have been performed studying AD patients with PIB-PET. We have evaluated the longitudinal changes of PIB retention and found PIB showing quite stable PIB binding in AD patients despite progression in cerebral glucose metabolism and cognition (Engler et al., 2006). The use of voxel-based methods for studying amyloid depositions has also been implemented complementing earlier region of interest based analysis (Kemppainen et al., 2006; Ziolko et al., 2006). One recent study showed an interaction between the PIB binding and the rate of grey matter atrophy (Archer et al., 2006). The link between PIB binding, glucose metabolism and cognitive status has been studied previously (Edison et al., 2006; Engler et al., 2006; Klunk et al., 2004). Amyloid imaging in healthy elderly subjects using PIB showed high PIB in 4 out of 41 non-demented subjects (Mintun et al., 2006). Recently, Small et al. using the amyloid ligand FDDNP presented a study of MCI patients that showed intermediate levels of binding compared to healthy volunteers and AD patients (Small et al., 2006). The separation of healthy versus demented subjects measured with FDDNP seems to be somewhat lower than with PIB (Small et al., 2006), although future studies comparing these tracers would be advisable.

The aim of this study was to measure (by PET) PIB retention in the brains of MCI patients and analyse its relationship with cerebral glucose metabolism, cognitive function and CSF biomarkers and conversion to AD.

2. Methods

2.1. MCI patients

Twenty-one MCI patients (mean age 63.3 ± 7.8 (S.D.) years) were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. The patients had been referred from the primary care centres in the community for investigation of suspected dementia development. All patients were examined at the clinic according to the same comprehensive procedure, which included physical examination, evaluation of neurological and psychiatric status, blood (including apolipoprotein E (ApoE) genotyping), serum and urine analysis, electroencephalography (EEG), MRI, single photon computed tomography (SPECT), cerebrospinal fluid (CSF) analysis, mini-mental-state examination (MMSE) and neuropsychological assessment performed by an experienced neuropsychologist. All subjects lived independently in the community and a majority of the subjects below 65 years of age had still a professional job. In most cases a close informant was interviewed in order to obtain information about the functional status. The diagnosis for MCI followed clinical criteria defined by Petersen et al. (Petersen et al., 1999; Winblad et al., 2004). The criteria were used during a consensus meeting where a clinically experienced geriatrician, neurologist, neuropsychologist and nurse met to discuss the outcome of the assessments of the patient and make the established diagnosis. For the diagnosis of MCI the patients met the following criteria: memory complaint, preferable corroborated by a close informant, objective memory impairment, normal general cognitive function, intact daily living, not fulfilling the DSM-IV criteria for dementia (American Psychiatric Association, 1994). All patients enrolled in the study gave written consent to participate. The Ethics Committees of the Karolinska Institute, Stockholm and Uppsala University, Uppsala, and the Isotope Committee at the Uppsala Academic Hospital, Uppsala, Sweden, approved the study.

After the PET studies were performed the MCI patients have been clinically followed includig neuropsychological examination. Some MCI patients have experienced cognitive decline and after clinical examinations have been considered to fulfil the diagnosis of AD. The analysis of MCI converters and non-converters will be described below.

2.2. Alzheimer patients and healthy subjects

As reference group's data from 27 AD patients (13 males and 14 females; mean age 66.2 ± 9.2 (S.D.) (range 51–80) years; MMSE 22.4 ± 5.2 (S.D.); 17/27 ApoE ε4 carriers) and 6 healthy controls (HCs) 67.3 ± 8.8 (S.D.) (range 57–77) were utilized for comparison. The AD patients were recruited from the Department of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden. They had underwent a comprehensive clinical examination including medical history, neurological and psychiatric examination, electroencephalography, computed tomography or magnetic resonance imaging, single photon emission computed tomography scan, cerebrospinal fluid analysis, blood analysis including ApoE genotyping and neuropsychological testing. All fulfilled the diagnosis of probable AD according to the criteria of the National Institute of Neurological and Communication Disorders, Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). The HCs were spouses to AD patients and were evaluated with neuropsychological and clinical assessments that assured their status as healthy controls.

2.3. Neuropsychological assessments

The neuropsychological tests that routinely are used in the assessment of the patients with memory problems at the Department of Geriatric Medicine and used in the present study covered seven domains, namely: (1) intelligence (global cognitive function) (MMSE), (2) language (vocabulary, similarities, FAS word fluency), (3) spatial (reasoning, block design, Rey Osterrieth copy), (4) immediate memory (digit span, Corsi Block span), (5) episodic memory (RAVL learning, RAVL retention, Rey Osterrieth retention), (6) attention/cognitive speed (digit symbol, Trail making test A), (7) executive function (Trail making test B). Twelve out of 21 MCI patients showed neuropsychological test results that were below −1.5 S.D. in episodic memory, four patients showed poor memory compared to what would be expected due to age and education but the test results were not below −1.5 S.D. in any test. Five MCI patients showed test results below −1.5 S.D. in some test(s) but not in memory. According to these results 12 out of 21 MCI patients were considered as amnestic MCI.

The time between neuropsychological tests and PET scans was 3.1 ± 2.8 (S.D.) months. For comparison with the PET data mini-mental-state examination (MMSE) (Folstein et al., 1975) was used as a measurements of global cognitive status and three tests of episodic memory were used: Rey Auditory Verbal Learning and Retention as well as Rey Osterrieth retention (Lezak, 1995). *Z*-scores were generated for each episodic memory test, based on the raw scores, by comparing the data to a reference data set, comprised of reference material in a data base used at Karolinska University Hospital Huddinge, Stockholm (Bergman et al., 2007). The mean *Z*-score of the three episodic memory tests was then calculated and used for statistical analysis. MMSE data was available for all 21 MCI patients and all 27 AD patients. A mean *Z*-score of episodic memory performance was available for all 21 MCI patients.

2.4. Cerebrospinal fluid measurements

Cerebrospinal fluid was obtained by lumbar puncture from 18 of the 21 MCI patients (2 patients preferred to abstain from CSF sampling and in one MCI subject lumbar puncture was contraindicated due to anti-coagulant treatment). The lumbar puncture was performed in non-fasting subjects normally between 8 and 11 a.m. Ten milliliter was collected where the first 0.5 ml was discarded and the rest of the sample centrifuged at 1500 × *g* (3000–4000 rpm) at +4 °C for 10 min. The CSF samples were frozen and stored at −80 °C in portions of 1 ml until analyses were performed. Measurement of total Tau (tTau) was performed using a sandwich enzyme-linked immunosorbent assay (ELISA) (Blennow et al., 1995). Phosphorylated Tau (pTau; P-Thr181) was assayed by sandwich ELISA, with monoclonal antibody (MAb) HT7 as capturing antibody and biotinylated MAb AT270 as detection antibody (Vanmechelen et al., 2000). Amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) was analysed using a sandwich ELISA specific for $A\beta_{1\text{-}42}$, as described in detail elsewhere (Andreasen et al., 1999). For the MCI patients, CSF $A\beta_{1\text{-}42}$ values were obtained from 16 subjects, pTau values from 15 subjects and tTau values from 18 subjects. Based on comparison with clinical reference values used in assessment of dementia at Karolinska University Hospital Huddinge, the levels of CSF analyses are considered pathological at the following thresholds: $A\beta_{1\text{-}42} < 450$ pg/ml, tTau > 400 pg/ml and pTau > 60 pg/ml.

2.5. Positron emission tomography (PET)

The patients underwent two PET examinations, which were normally performed at the same day. The PET examinations with PIB and FDG were performed at Uppsala PET centre/Uppsala Imanet AB in Uppsala, Sweden. Production of FDG and PIB was carried out according to good manufacturing standards at Uppsala Imanet, and the synthesis of PIB was performed using a method previously described (Klunk et al., 2004; Mathis et al., 2003). The PIB and FDG examinations were performed using Siemens ECAT EXACT HR+ scanners (CTI PET-systems Inc.), 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 patients were scanned after fasting for 4 h under resting conditions in a dimmed room. The orbito-meatal line was used to centre the heads of the subjects, and the data were acquired in three-dimensional mode. The tracer doses of PIB and FDG, and the scanner protocol for transmissions, emissions and reconstructions has been described in detail previously (Klunk et al., 2004).

The set of regions of interest (ROIs) used in statistical analysis has previously been described in detail (Engler et al., 2003; Klunk et al., 2004). Based on previous results in AD patients (Engler et al., 2006; Klunk et al., 2004) the following areas were included in the analysis: the frontal, parietal and temporal cortices, posterior cingulum, subcortical white matter. The reference region for calculating the late scan ratio of the PIB data was drawn as follows. An early summation image was created. This image gave a good anatomical representation of the cortical areas due to the fact that the early frames show the flow component of the tracer. On top of the early summation image a late summation image was placed showing the non-specific binding in whiter matter. The reference region was then drawn in the cortical area outside the whiter matter seen in the late summation image.

A computerized reorientation procedure was used to align consecutive PET data for accurate intra-individual comparisons (Andersson and Thurfjell, 1997). For each patient the PIB images were realigned to the respective FDG image, using the FDG images as templates.

For the FDG examinations, parametric maps of cerebral glucose metabolism (CMRglc) were generated by means of the Patlak method using the time course of the tracer from arterialized-venous plasma samples as an input function (Patlak et al., 1983). The frames from 20 to 60 min and

Table 1
Demographic and clinical data of the 21 MCI patients as a total group and divided into MCI converters and non-converters

	MCI total	MCI converters	MCI non-converters
N	21	7	14
Age (years)	63.3 ± 7.8	63.4 ± 7.9	62.6 ± 8.4
Gender M/F	8/13	1/6	7/7
Education (years)	12.7 ± 3.8	13.0 ± 3.7	12.0 ± 4.2
APOE ε4 carriers	14	6	8
MMSE	28.2 ± 1.4	27.0 ± 1.3**	28.9 ± 0.9
EpMem	−0.60 ± 0.92	−1.52 ± 0.48***	−0.13 ± 0.72
$A\beta_{1\text{-}42}$ (pg/ml)	551 ± 180	447 ± 56*	614 ± 201
tTau (pg/ml)	382 ± 200	488 ± 183	329 ± 193
pTau (pg/ml)	65 ± 31	76 ± 32	58 ± 29

Data shown as mean ± S.D.; MMSE, mini-mental-state examination; EpMem, episodic memory (mean *Z*-score); $A\beta_{1\text{-}42}$, amyloid-$\beta_{1\text{-}42}$; tTau, total Tau protein; pTau, phosphorylated Tau protein. Significant difference between MCI converters and MCI non-converters ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$), Student's *t*-test, two-tailed, unequal variance.

a lumped constant of 0.418 were used to generate the parametric maps of CMRglc. To account for global differences between patients the CMRglc data was normalized to the pons (ROI/ref). The data on glucose metabolism will be referred to as rCMRglc. No data on glucose metabolism was available for one of the patients as a result of technical problems.

For PIB the mean uptake values of the ROIs obtained in a late time interval (40–60 min) were normalized to the corresponding uptake in a reference region (ROI/ref). These late reference ratio data on PIB retention will be referred to as late scan ratio. The choice of method was based on previous results indicating that the late scan reference ratio renders stable and reliable data (Lopresti et al., 2005). The cerebellar cortex was chosen as reference region because of its previously reported lack of Congo red- and thioflavin-S-positive plaques (Mirra et al., 1994; Yamaguchi et al., 1989).

2.6. Statistical analysis

The statistical analysis used to compare the MCI patients with the reference groups (healthy controls and AD patients) were performed by using two-sample, unequal variance, two-tailed Student's *t*-tests. Based on the sub-division of converted MCI patients and non-converted MCI patients the groups were compared using two-sample, unequal variance, two-tailed Student's *t*-tests. The data was controlled for multiple comparisons using Bonferroni correction yielding a significance level of 0.01 (0.05/5 (number of regions analysed)).

The analysis of correlation between PIB retention, CSF data, rCMRglc, MMSE, *Z*-score of episodic memory, was conducted using Spearman rank order correlation coefficient *R*. The correlations between PIB-PET data and CSF data was corrected for multiple comparisons using Bonferroni correction yielding a significance level of 0.0042 (0.05/12 (number of correlations performed)). No statistical corrections for multiple comparisons were performed for additional correlation analysis due to the explorative nature of the study. This implies some caution when evaluating these results.

3. Results

3.1. MCI patients

The demographic information regarding the MCI patients is seen in Table 1. During clinical follow-up of the MCI patients after the performed PET scans seven of the MCI patients converted to AD after 8.1 ± 6.0 months (S.D.) after their respective PET scans. The diagnosis of AD was based on comprehensive clinical examination as mentioned in Section 2 and according to the criteria of NINCDS-ADRDA (McKhann et al., 1984). These seven MCI patients will below be considered as MCI converters and the remaining 14 MCI patients will be considered as MCI non-converters. It is important to observe that the seven MCI converters did not fulfil the criteria for AD when they underwent the PET studies. As shown in Table 1 there was no significant difference in age between the MCI converters compared to non-converters. There were a higher proportion of ApoE ε4 carriers in the MCI converter group (85%) compared to the non-converter MCI group (57%). The MMSE test score was significant lower in converters compared to non-converters. The MCI converters showed impaired cognitive function compared to MCI non-converters, which reached statistical significance for the mean *Z*-score of episodic memory ($p < 0.001$) (Table 1).

Mean levels of CSF $A\beta_{1\text{-}42}$, tTau and pTau in the MCI patients are shown in Table 1. As regards $A\beta_{1\text{-}42}$ and tTau no difference from normal was observed in the total MCI group, while the mean level of pTau was above the pathological threshold in total MCI group. The MCI group showed significantly higher levels of $A\beta_{1\text{-}42}$ and significantly lower level of tTau compared to AD ($ps < 0.01$). Three MCI patients showed pathological levels of $A\beta_{1\text{-}42}$ and seven showed increased tTau and six pathological pTau values, respectively. The MCI converters showed significantly lower levels of CSF $A\beta_{1\text{-}42}$ compared with the MCI non-converters group ($p < 0.05$) (Table 1). Within the group of seven MCI patients that converted to AD, three subjects had pathological levels of $A\beta_{1\text{-}42}$ and four showed pathological levels of tTau and pTau

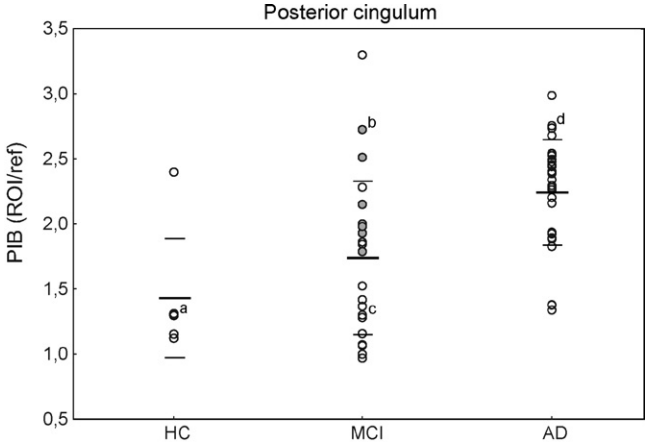

Fig. 1. PIB retention (ROI/ref) in posterior cingulum in MCI patients compared with healthy controls (HCs) ($n=6$) and AD patients ($n=27$). Long horizontal lines indicate mean, short horizontal lines indicate standard deviation (S.D.). Filled circles indicate MCI patients that later after the PET scans converted to AD. The small letters indicate the patients shown in Fig. 2: a, HC; b, MCI converter; c, MCI non-converter; d, AD. One healthy control 77 years of age with normal cognitive function had high PIB retention as earlier reported at baseline and 2 year follow-up studies (Klunk et al., 2004; Engler et al., 2006).

(data was available for six of the MCI subjects that converted to AD).

3.2. PIB retention

The individual data of PIB retention in the posterior cingulum for the MCI patients AD patients and healthy controls are presented in Fig. 1. The mean value for the MCI patients is between the corresponding PIB retention for the HC and AD groups. The PIB retention data for the seven MCI patients that later have converted to AD are all above the mean value (filled circles). The MCI patient in Fig. 1 with highest PIB retention is still a MCI patient after 25 months follow-up but has strong hereditary dispostion for dementia. Example of images from one MCI converter and one MCI non-converter is shown in Fig. 2, together with 1 healthy control and one AD patient. The mean values and statistical analysis between the groups are shown in Table 2. Statistical analysis revealed significantly lower PIB retention in the MCI patients in the frontal, parietal and temporal cortices and the posterior cingulum compared with that in the AD group ($p<0.01$). The total MCI group showed no significant difference compared to the HCs ($p>0.01$). Analysis of PIB retention in the subgroup MCI converters revealed high retention in cortical brain regions in all seven subjects. Compared with the HC group, the MCI converters showed significantly higher PIB retention in the frontal, parietal and temporal cortices ($p<0.01$). There were no significant difference between the MCI converters and the AD patients in any region ($p>0.01$). The MCI converters revealed significantly higher PIB retention in the posterior cingulum ($p<0.01$) compared with the non-converters. There was no significant difference between HC and MCI non-converters ($p>0.01$) in any cortical brain region. The MCI non-converters had significantly lower PIB retention in cortical brain regions compared to the AD group ($p<0.01$).

3.3. Cerebral glucose metabolism

The results from statistical analysis of rCMRglc are shown in Table 3. There was no significant difference in rCMRglc between MCI patients and healthy controls in any cortical brain region ($p>0.01$). The MCI patients, in comparison to

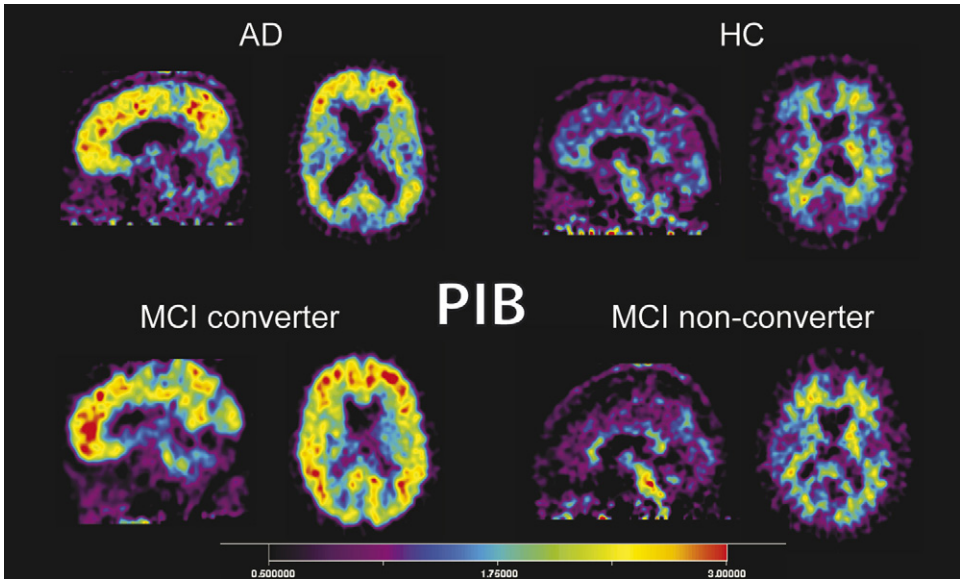

Fig. 2. PIB retention in one MCI converter, one MCI non-converter, one AD patient, and one healthy control. The PET scans show PIB retention at a sagittal and longitudinal section at the level of the basal ganglia. Red indicates high, yellow medium and blue low PIB retention. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 2
PIB retention in AD patients, MCI patients and the two subgroups MCI non-converters (MCI-nc) and MCI converter (MCI-c) and healthy controls (HC)

	Fr ctx	Par ctx	Tmp ctx	Cing post	WhM
AD	2.3 ± 0.5	2.2 ± 0.4	1.8 ± 0.3	2.2 ± 0.4	1.8 ± 0.2
MCI	1.6 ± 0.6*	1.7 ± 0.5*	1.5 ± 0.3*	1.7 ± 0.6*	1.8 ± 0.3
MCI-c	2.0 ± 0.4#	2.0 ± 0.4#	1.6 ± 0.2#	2.2 ± 0.3¥	1.8 ± 0.3
MCI-nc	1.4 ± 0.5*	1.6 ± 0.6*	1.4 ± 0.3*	1.5 ± 0.6*	1.8 ± 0.3
HC	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.1	1.4 ± 0.5	1.9 ± 0.1

Fr, frontal; Par, parietal; Tmp, temporal; Cing post, posterior cingulum; WhM, subcortical white matter.
* Statistical significance between MCI and MCI non-converters compared to AD patients ($p < 0.01$).
# Statistical significance between MCI converters compared to healthy controls ($p < 0.01$).
¥ Statistical significance between MCI converters compared to MCI non-converters ($p < 0.01$). Analysis performed with Student's *t*-test, two-tailed, unequal variance and corrected for multiple comparisons with Bonferroni correction.

Table 3
rCMRglc values in AD patients, MCI patients and the two subgroups MCI non-converters (MCI-nc)and MCI converters (MCI-c) and healthy controls (HC)

	Fr ctx	Par ctx	Tmp ctx	Cing post	WhM
AD	1.4 ± 0.2	1.1 ± 0.2	1.1 ± 0.1	1.1 ± 0.2	0.8 ± 0.2
MCI	1.7 ± 0.2*	1.7 ± 0.3*	1.3 ± 0.2*	1.7 ± 0.3*	0.9 ± 0.2
MCI-c	1.6 ± 0.3	1.5 ± 0.5	1.2 ± 0.2	1.5 ± 0.5	0.9 ± 0.2
MCI-nc	1.8 ± 0.2*	1.7 ± 0.2*	1.3 ± 0.1*	1.7 ± 0.2*	0.9 ± 0.2
HC	1.5 ± 0.3	1.5 ± 03	1.2 ± 0.3	1.5 ± 0.3	0.8 ± 0.1

Fr, frontal; Par, parietal; Tmp, temporal; Cing post, posterior cingulum; WhM, subcortical white matter. Values are normalized to the pons (ROI/ref)
* Statistical significance between MCI and MCI non-converters compared to AD patients ($p < 0.01$, corrected for multiple comparisons with Bonferroni correction), Student's *t*-test, two-tailed, unequal variance.

AD patients, showed significantly higher rCMRglc in the cortical brain areas studied ($p < 0.01$). Neither the MCI converters nor the MCI non-converters did show any significant difference in rCMRglc compared to the healthy controls. The MCI non-converters showed significantly higher rCMRglc in the cortical areas compared to the AD patients ($p < 0.01$), while the MCI converters did not show any significant difference compared to AD ($p > 0.01$).

3.4. Correlation analysis

Significant correlations were observed between CSF $A\beta_{1\text{-}42}$ versus PIB retention in the frontal cortex and posterior cingulum (Table 4) ($p < 0.0042$, corrected for multiple comparisons). Correlations were also observed between cortical PIB retention versus tTau (Table 4), but they did not survive threshold after correction for multiple comparisons. Correlations between PIB retention in the posterior cingulum and CSF biomarkers are presented in Fig. 3A–C.

A significant negative correlation was observed between mean *Z*-score of episodic memory and PIB retention in the posterior cingulum ($p = 0.043$), frontal cortex ($p = 0.034$) and temporal cortex ($p = 0.0064$) (not corrected for multiple comparisons). Correlations between episodic memory and PIB retention in the posterior cingulum is presented in Fig. 3D. There were no significant correlations between glucose metabolism and PIB retention in any of the brain regions analysed (data not shown; $p > 0.05$), and no correlation between mean *Z*-score of episodic memory and glucose metabolism in any of the brain regions analysed (data not shown; $ps > 0.05$).

4. Discussion

MCI is considered as a transitional stage between normal aging and dementia, especially early AD. There are problems and limitations of the clinical diagnosis of MCI. In this study we describe the measurement of PIB retention by means of PET imaging in a group of MCI patients from an academic medical centre where the subjects were recruited among clinical patients referred to the geriatric

Table 4
Correlation between PIB vs. $A\beta_{1\text{-}42}$, tTau and pTau in MCI patients showing Spearman rank order correlation *R* $A\beta_{1\text{-}42}$: $n = 16$; tTau: $n = 18$; pTau: $n = 15$)

ROI	PIB vs. $A\beta_{1\text{-}42}$	PIB vs. tTau	PIB vs. pTau
Fr ctx	−0.74*	0.64#	0.52
Par ctx	−0.64#	0.61#	0.52
Tmp ctx	−0.66#	0.51	0.48
Cing post	−0.70*	0.52	0.48

n, number of subjects; ROI, region of interest; rCMRglc, relative cerebral metabolic rate of glucose; $A\beta_{1\text{-}42}$, amyloid-$A\beta_{1\text{-}42}$; tTau, total Tau protein; pTau, phosphorylated Tau protein; Fr, frontal; Par, parietal; Tmp, temporal; Cing post, posterior cingulum; Statistical significance indicated as.
* $p < 0.0042$, corrected for multiple comparisons with Bonferroni correction.
# $p < 0.01$, not corrected for multiple comparisons.

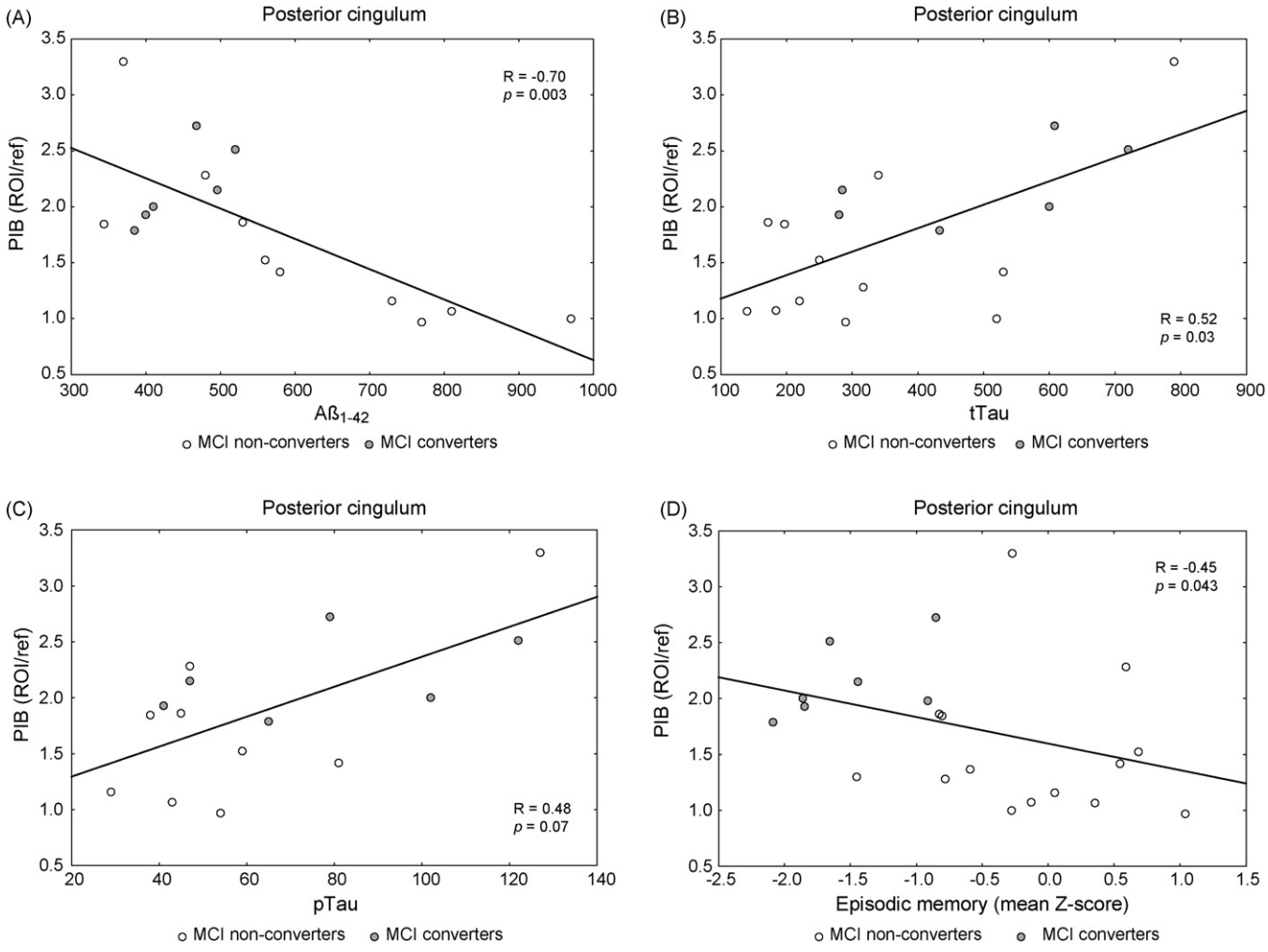

Fig. 3. (A–D) Correlation between PIB retention in posterior cingulum and $A\beta_{1\text{-}42}$ (A), respectively, total Tau (tTau) (B), phosphorylated Tau (pTau) (C) and episodic memory (mean *Z*-score (D). MCI patients who converted to AD are indicated with filled circles, non-converted MCI patients are indicated as open circles. Pathological CSF levels of $A\beta_{1\text{-}42}$ is <450 pg/ml, tTau is >400 pg/ml, and pTau is >60 pg/ml. *R* = Spearman rank order correlation *R*.

department by primary care physicians in the Stockholm area. It is known that MCI may have a multitude of causes, including AD and other forms of dementia as well as depression and various physical disorders. Since MCI is a common syndrome there is a great need to establish methods for predicting progression to AD (Galvin et al., 2005; Morris et al., 2001; Petersen, 2004; Storandt et al., 2002). This is of special interest when new treatment strategies are established where a prerequisite for successful treatment will be early detection of the disease. The MCI patients in this study were fairly young (mean age 63.3 ± 7.8) compared with those in an earlier report from our clinic where, in which 133 subjects (mean age 69.5 ± 5.8) from Karolinska University Hospital Huddinge were compared with 170 subjects (mean age 78.5 ± 8.4) from the Mayo Clinic (Arnaiz et al., 2004). The global cognitive function was in the very mild range.

The results in the present study show higher mean PIB retention among the MCI patients than in age-matched healthy controls, but lower mean PIB retention than in AD patients. Seven of the 21 MCI patients converted at later clinical follow-ups to AD during 2–16 months after their respective PET scan (8.1 ± 6.0 S.D. months). These seven converting MCI patients differed as a group significantly from the non-converts with respect to higher proportion of ApoE $\varepsilon 4$ carriers, impairment in episodic memory, lower CSF $A\beta_{1\text{-}42}$ and higher PIB retention. It is quite apparent from what is presented in Fig. 1 that MCI patients can show high or low PIB retention as also recently reported (Lopresti et al., 2005). In the present study 11 out of 21 the MCI patients showed high retention in the frontal, parietal, and temporal cortices, comparable to data in a previous study on AD patients (Klunk et al., 2004). Nine of the MCI patients with high PIB retention were considered of amnestic type (Winblad et al., 2004). Three of the MCI patients with low PIB retention compared to HC were considered of amnestic type. The seven MCI patients with high PIB retention who converted to AD at follow-up retention were all MCI of amnestic type. Since the neuropathological feature of AD is probably present very early (Morris et al., 2001) the high PIB retention in a subgroup

underline the heterogeneity and difficulty in an accurate diagnosis but highlights also the possibility to discriminate early by amyloid imaging.

Heterogeneity in changes of cerebral glucose metabolism has been suggested in MCI patients (Anchisi et al., 2005). However, in this study we did not detect generally a decreased glucose metabolism in cortical brain areas as earlier reported in MCI patients (Anchisi et al., 2005; Chetelat and Baron, 2003; Drzezga et al., 2003). Nevertheless, in some individual MCI patients, decreased rCMRglc was found in areas, such as the parietal and temporal cortices. More interestingly is that higher cerebral glucose metabolism in the MCI group compared to AD patients and controls might be a sign for possible ongoing compensatory mechanisms. There might be deterioration of rCMRglc at an early stage in the progression to AD although the amyloid deposition is probably an earlier event in the AD pathology than changes in cerebral glucose metabolism. The negative correlation between rCMRglc and PIB retention that we earlier observed in patients with mild AD (Klunk et al., 2004) was not present in the MCI group. This finding suggests that there is a difference in the time courses of amyloid deposition and deterioration of rCMRglc in MCI. The observation is supported by the results of our recent study, in which AD patients were rescanned with PIB and FDG after 2 years. The retention of PIB was found to be unchanged at 2-year follow-up while rCMRglc and cognition had deteriorated (Engler et al., 2006).

A relatively large inter-individual variation was revealed in cognitive function between the MCI patients where the seven patients that later converted to AD showed a decrease in episodic memory as MCI patients. We also observed a negative correlation between episodic memory and PIB in the MCI patients in contrast to the lack of correlation between global cognitive function and PIB retention. These results were not corrected for multiple comparisons due to the exploratory nature of the study implicating caution in interpreting the results. The strongest correlation was found between episodic memory and PIB retention in temporal cortex, a part of the brain known to be involved in memory processes ($R = -0.58$; $p = 0.006$). The lack of correlation between rCMRglc and the analysed cognitive tests are somewhat surprising due to the fact that several studies show decrease in glucose metabolism already in MCI patients (Chetelat et al., 2003; Drzezga et al., 2003). One plausible explanation is the heterogeneity of the MCI group.

Cerebrospinal fluid biomarkers, such as $A\beta_{1\text{-}42}$, tTau and pTau might be useful when identifying MCI patients at risk of developing AD (Blennow and Hampel, 2003; Buerger et al., 2005; Herukka et al., 2005). In a recent 4-year follow-up study it was shown that a combination of $A\beta_{1\text{-}42}$ and tTau yielded a sensitivity of 95% and a specificity of 83% in detecting MCI patients that developed AD (Hansson et al., 2006). Interestingly, we detected significant correlations between CSF $A\beta_{1\text{-}42}$ and tTau versus PIB retention in the brain for the 18 patients in which CSF was available. It can be observed from Fig. 3A that 11 MCI patients showed high PIB retention (1 S.D. above the mean for HC) but only 5 of these patients showed pathological levels of $A\beta_{1\text{-}42}$, 7 showed pathological levels of tTau and 6 showed pathological levels of pTau. All seven of the MCI patients that converted to AD showed high PIB retention and from the CSF data (available from six of the patients) pathological levels of $A\beta_{1\text{-}42}$ was observed in three patients and pathological levels of pTau in four patients. It thus seems as if PIB imaging might be more effective than CSF biomarkers in the discrimination of prodromal AD patients. A larger study of MCI patients with PIB scans and CSF measurements is needed. An inverse relationship between PIB retention and $A\beta_{1\text{-}42}$ in humans was recently suggested by Fagan et al. (2006), while they found no correlation between PIB retention versus tTau or pTau (Fagan et al., 2006). A possible explanation for the lack of correlation might be the low number of AD patients (Fagan et al., 2006). Although our findings in the present study with PIB are promising, further studies are needed to evaluate the predictive value of PIB-PET studies in a larger population of MCI patients.

In this study we demonstrate that PIB retention in MCI patients is intermediate between healthy controls and AD patients. There are MCI patients with high or low PIB retention. The seven MCI patients that later, at follow-up, converted to AD all showed significant high levels of amyloid in the brain compared to MCI non-converters and healthy controls. Interestingly in this clinical material of MCI patients there is a subgroup of patients with PIB retention in the range of healthy controls. A significant correlation was observed between PIB retention and CSF $A\beta_{1\text{-}42}$, tTau and episodic memory, respectively. Amyloid neuroimaging might be a promising diagnostic tool for detection of subjects at risk of developing AD, as well as for evaluating new anti-amyloid therapy.

Conflicts of interest

A.W., A.R., B.L. are employed by Uppsala Imanet GE HealthCare, Uppsala, Sweden. The dementia program within Imanet which this manuscript is a part of has been driven since the start as an academic program and the employees have no financial benefit of the work. None of the other authors have any conflict of interest.

Acknowledgements

Financial support from the Swedish Research Council (project 05817, A.N.), the foundation for Old Servants (A.N.), Stohne's foundation (A.N.), the KI foundations (A.N.), the Alzheimer Foundation in Sweden (A.N.), Swedish Brain Power (A.N., B.L.), the EC-FP5-projec tNCI-MCI and the EC-FP6-project DiMI, LSHB-CT-2005-512146, QLK6-CT-2000-00502 (A.N.) is gratefully acknowledged.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, forth ed. American Psychiatric Association, Washington, DC.

Anchisi, D., Borroni, B., Franceschi, M., Kerrouche, N., Kalbe, E., Beuthien-Beumann, B., Cappa, S., Lenz, O., Ludecke, S., Marcone, A., Mielke, R., Ortelli, P., Padovani, A., Pelati, O., Pupi, A., Scarpini, E., Weisenbach, S., Herholz, K., Salmon, E., Holthoff, V., Sorbi, S., Fazio, F., Perani, D., 2005. Heterogeneity of brain glucose metabolism in mild cognitive impairment and clinical progression to Alzheimer disease. Arch. Neurol. 62 (11), 1728–1733.

Andersson, J.L., Thurfjell, L., 1997. Implementation and validation of a fully automatic system for intra- and interindividual registration of PET brain scans. J. Comput. Assist. Tomogr. 21 (1), 136–144.

Andreasen, N., Hesse, C., Davidsson, P., Minthon, L., Wallin, A., Winblad, B., Vanderstichele, H., Vanmechelen, E., Blennow, K., 1999. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease. Arch. Neurol. 56 (6), 673–680.

Archer, H.A., Edison, P., Brooks, D.J., Barnes, J., Frost, C., Yeatman, T., Fox, N.C., Rossor, M.N., 2006. Amyloid load and cerebral atrophy in Alzheimer's disease: an 11C-PIB positron emission tomography study. Ann. Neurol. 60 (1), 145–147.

Arnaiz, E., Almkvist, O., Ivnik, R.J., Tangalos, E.G., Wahlund, L.O., Winblad, B., Petersen, R.C., 2004. Mild cognitive impairment: a cross-national comparison. J. Neurol. Neurosurg. Psychiatry 75 (9), 1275–1280.

Arnaiz, E., Jelic, V., Almkvist, O., Wahlund, L.O., Winblad, B., Valind, S., Nordberg, A., 2001. Impaired cerebral glucose metabolism and cognitive functioning predict deterioration in mild cognitive impairment. Neuroreport 12 (4), 851–855.

Bergman, I., Blomberg, M., Almkvist, O., 2007. The importance of impaired physical health and age in normal cognitive aging. Scand. J. Psychol. 48, 115–125.

Blennow, K., Hampel, H., 2003. CSF markers for incipient Alzheimer's disease. Lancet Neurol. 2 (10), 605–613.

Blennow, K., Wallin, A., Agren, H., Spenger, C., Siegfried, J., Vanmechelen, E., 1995. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? Mol. Chem. Neuropathol. 26 (3), 231–245.

Buerger, K., Teipel, S.J., Zinkowski, R., Sunderland, T., Andreasen, N., Blennow, K., Ewers, M., Debernardis, J., Shen, Y., Kerkman, D., Du, Y., Hampel, H., 2005. Increased levels of CSF phosphorylated tau in apolipoprotein E varepsilon4 carriers with mild cognitive impairment. Neurosci. Lett..

Chetelat, G., Baron, J.C., 2003. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. Neuroimage 18 (2), 525–541.

Chetelat, G., Desgranges, B., De La Sayette, V., Viader, F., Eustache, F., Baron, J.C., 2003. Mild cognitive impairment: can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology 60 (8), 1374–1377.

de Leon, M.J., DeSanti, S., Zinkowski, R., Mehta, P.D., Pratico, D., Segal, S., Rusinek, H., Li, J., Tsui, W., Saint Louis, L.A., Clark, C.M., Tarshish, C., Li, Y., Lair, L., Javier, E., Rich, K., Lesbre, P., Mosconi, L., Reisberg, B., Sadowski, M., DeBernadis, J.F., Kerkman, D.J., Hampel, H., Wahlund, L.O., Davies, P., 2006. Longitudinal CSF and MRI biomarkers improve the diagnosis of mild cognitive impairment. Neurobiol. Aging 27 (3), 394–401.

Drzezga, A., Lautenschlager, N., Siebner, H., Riemenschneider, M., Willoch, F., Minoshima, S., Schwaiger, M., Kurz, A., 2003. Cerebral metabolic changes accompanying conversion of mild cognitive impairment into Alzheimer's disease: a PET follow-up study. Eur. J. Nucl. Med. Mol. Imaging 30 (8), 1104–1113.

Edison, P., Archer, H.A., Hinz, R., Hammers, A., Pavese, N., Tai, Y.F., Hotton, G., Cutler, D., Fox, N., Kennedy, A., Rossor, M., Brooks, D.J., 2006. Amyloid hypometabolism, and cognition in Alzheimer disease. An [11C]PIB and [18F]FDGPET study. Neurology.

Engler, H., Forsberg, A., Almkvist, O., Blomquist, G., Larsson, E., Savitcheva, I., Wall, A., Ringheim, A., Langstrom, B., Nordberg, A., 2006. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 129 (Pt. 11), 2856–2866.

Engler, H., Lundberg, P.O., Ekbom, K., Nennesmo, I., Nilsson, A., Bergstrom, M., Tsukada, H., Hartvig, P., Langstrom, B., 2003. Multitracer study with positron emission tomography in Creutzfeldt-Jakob disease. Eur. J. Nucl. Med. Mol. Imaging 30 (1), 85–95.

Fagan, A.M., Mintun, M.A., Mach, R.H., Lee, S.Y., Dence, C.S., Shah, A.R., Larossa, G.N., Spinner, M.L., Klunk, W.E., Mathis, C.A., Dekosky, S.T., Morris, J.C., Holtzman, D.M., 2006. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta(42) in humans. Ann. Neurol. 59 (3), 512–519.

Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J. Psychiatry Res. 12 (3), 189–198.

Galvin, J.E., Powlishta, K.K., Wilkins, K., McKeel Jr., D.W., Xiong, C., Grant, E., Storandt, M., Morris, J.C., 2005. Predictors of preclinical Alzheimer disease and dementia: a clinicopathologic study. Arch. Neurol. 62 (5), 758–765.

Hansson, O., Zetterberg, H., Buchhave, P., Londos, E., Blennow, K., Minthon, L., 2006. Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. Lancet Neurol. 5 (3), 228–234.

Herukka, S.K., Hallikainen, M., Soininen, H., Pirttila, T., 2005. CSF Abeta42 and tau or phosphorylated tau and prediction of progressive mild cognitive impairment. Neurology 64 (7), 1294–1297.

Kemppainen, N.M., Aalto, S., Wilson, I.A., Nagren, K., Helin, S., Bruck, A., Oikonen, V., Kailajarvi, M., Scheinin, M., Viitanen, M., Parkkola, R., Rinne, J.O., 2006. Voxel-based analysis of PET amyloid ligand [11C]PIB uptake in Alzheimer disease. Neurology 67 (9), 1575–1580.

Klunk, W.E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D.P., Bergstrom, M., Savitcheva, I., Huang, G.F., Estrada, S., Ausen, B., Debnath, M.L., Barletta, J., Price, J.C., Sandell, J., Lopresti, B.J., Wall, A., Koivisto, P., Antoni, G., Mathis, C.A., Langstrom, B., 2004. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 55 (3), 306–319.

Klunk, W.E., Wang, Y., Huang, G.F., Debnath, M.L., Holt, D.P., Mathis, C.A., 2001. Uncharged thioflavin-T derivatives bind to amyloid-beta protein with high affinity and readily enter the brain. Life Sci. 69 (13), 1471–1484.

Kordower, J.H., Chu, Y., Stebbins, G.T., DeKosky, S.T., Cochran, E.J., Bennett, D., Mufson, E.J., 2001. Loss and atrophy of layer II entorhinal cortex neurons in elderly people with mild cognitive impairment. Ann. Neurol. 49 (2), 202–213.

Lezak, M.D., 1995. Neuropsychological Assessment, third ed. Oxford Univ. Press, New York, pp. 1026.

Lopresti, B.J., Klunk, W.E., Mathis, C.A., Hoge, J.A., Ziolko, S.K., Lu, X., Meltzer, C.C., Schimmel, K., Tsopelas, N.D., Dekosky, S.T., Price, J.C., 2005. Simplified quantification of Pittsburgh compound B amyloid imaging PET studies: a comparative analysis. J. Nucl. Med. 46 (12), 1959–1972.

Mathis, C.A., Wang, Y., Holt, D.P., Huang, G.F., Debnath, M.L., Klunk, W.E., 2003. Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J. Med. Chem. 46 (13), 2740–2754.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34 (7), 939–944.

Mintun, M.A., Larossa, G.N., Sheline, Y.I., Dence, C.S., Lee, S.Y., Mach, R.H., Klunk, W.E., Mathis, C.A., DeKosky, S.T., Morris, J.C., 2006. [11C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology 67 (3), 446–452.

Mirra, S.S., Gearing, M., McKeel Jr., D.W., Crain, B.J., Hughes, J.P., van Belle, G., Heyman, A., 1994. Interlaboratory comparison of neuropathology assessments in Alzheimer's disease: a study of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). J. Neuropathol. Exp. Neurol. 53 (3), 303–315.

Morris, J.C., Storandt, M., Miller, J.P., McKeel, D.W., Price, J.L., Rubin, E.H., Berg, L., 2001. Mild cognitive impairment represents early-stage Alzheimer disease. Arch. Neurol. 58 (3), 397–405.

Patlak, C.S., Blasberg, R.G., Fenstermacher, J.D., 1983. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J. Cereb. Blood Flow Metab. 3 (1), 1–7.

Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. J. Intern. Med. 256 (3), 183–194.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch. Neurol. 56 (3), 303–308.

Shoghi-Jadid, K., Small, G.W., Agdeppa, E.D., Kepe, V., Ercoli, L.M., Siddarth, P., Read, S., Satyamurthy, N., Petric, A., Huang, S.C., Barrio, J.R., 2002. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am. J. Geriatr. Psychiatry 10 (1), 24–35.

Small, G.W., Kepe, V., Ercoli, L.M., Siddarth, P., Bookheimer, S.Y., Miller, K.J., Lavretsky, H., Burggren, A.C., Cole, G.M., Vinters, H.V., Thompson, P.M., Huang, S.C., Satyamurthy, N., Phelps, M.E., Barrio, J.R., 2006. PET of brain amyloid and tau in mild cognitive impairment. N. Engl. J. Med. 355 (25), 2652–2663.

Storandt, M., Grant, E.A., Miller, J.P., Morris, J.C., 2002. Rates of progression in mild cognitive impairment and early Alzheimer's disease. Neurology 59 (7), 1034–1041.

Vanmechelen, E., Vanderstichele, H., Davidsson, P., Van Kerschaver, E., Van Der Perre, B., Sjogren, M., Andreasen, N., Blennow, K., 2000. Quantification of tau phosphorylated at threonine 181 in human cerebrospinal fluid: a sandwich ELISA with a synthetic phosphopeptide for standardization. Neurosci. Lett. 285 (1), 49–52.

Verhoeff, N.P., Wilson, A.A., Takeshita, S., Trop, L., Hussey, D., Singh, K., Kung, H.F., Kung, M.P., Houle, S., 2004. In-vivo imaging of Alzheimer disease beta-amyloid with [11C]SB-13 PET. Am. J. Geriatr. Psychiatry 12 (6), 584–595.

Visser, P.J., Scheltens, P., Verhey, F.R., 2005. Do MCI criteria in drug trials accurately identify subjects with predementia Alzheimer's disease? J. Neurol. Neurosurg. Psychiatry 76 (10), 1348–1354.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Backman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., van Duijn, C., Visser, P., Petersen, R.C., 2004. Mild cognitive impairment-bey ond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J. Intern. Med. 256 (3), 240–246.

Yamaguchi, H., Hirai, S., Morimatsu, M., Shoji, M., Nakazato, Y., 1989. Diffuse type of senile plaques in the cerebellum of Alzheimer-type dementia demonstrated by beta protein immunostain. Acta Neuropathol. (Berl.) 77 (3), 314–319.

Ziolko, S.K., Weissfeld, L.A., Klunk, W.E., Mathis, C.A., Hoge, J.A., Lopresti, B.J., DeKosky, S.T., Price, J.C., 2006. Evaluation of voxel-based methods for the statistical analysis of PIB PET amyloid imaging studies in Alzheimer's disease. Neuroimage 33 (1), 94–102.