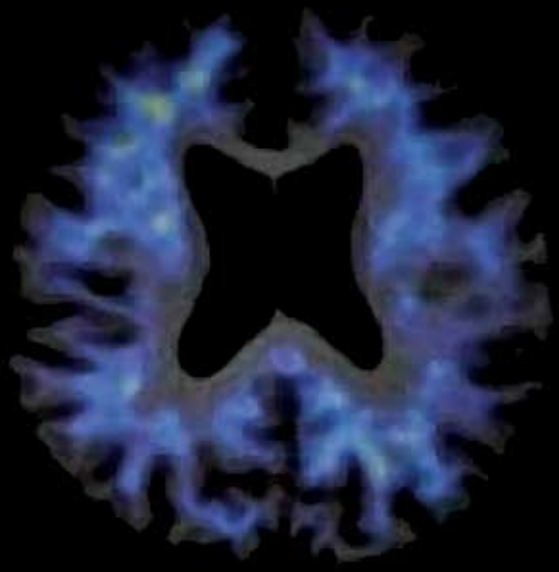

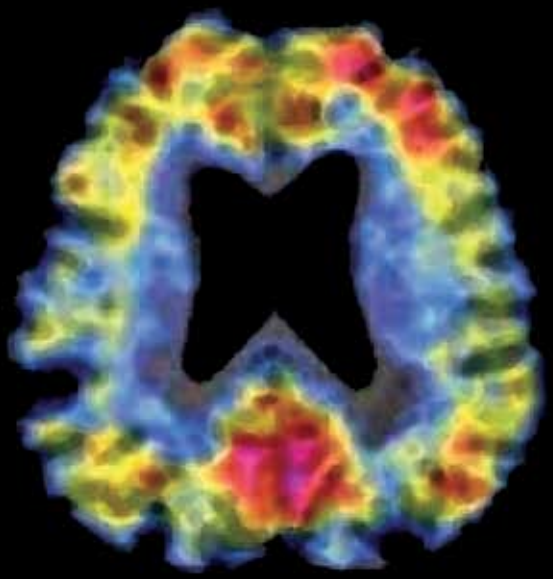

Human Amyloid Imaging

Chicago 2008

Friday, April 11th 2008

Chicago Marriott Downtown Hotel

Schedule & Abstract Book

Schedule - Human Amyloid Imaging, Chicago, 2008

07:30 – 08:00 **Continental breakfast**

08:00 – 08:15 **Introduction**

08:15 – 09:30 **Session 1: Keith Johnson, Agneta Nordberg (Chairs)**

8:15 – 8:30 Classification of amyloid-positivity in controls: comparison of objective approaches to visual reads
WE Klunk, University of Pittsburgh, PA, USA

8:30 – 8:45 Fibrillar β-amyloid burden in cognitively normal persons homozygous for the apolipoprotein E ε4 allele
EM Reiman, Banner Alzheimer's Institute, University of Arizona, AZ, USA

8:45 – 9:00 Patterns of [^{11}C]PIB uptake in non-demented subjects
MA Mintun, Washington University, MO, USA

9:00 – 9:15 Assessment of β amyloid in frontal cortical brain biopsy and by PET with [^{11}C]PIB
JO Rinne, University of Turku, Finland

9:15 – 9:30 Identification of "AD-like" normal elderly controls using PIB-PET imaging
EC Mormino, University of California at Berkeley, CA, USA

09:30 – 10:00 **General discussion**

10:00 – 10:15 **Morning break**

10:15 – 11:30 **Session 2: William Jagust, William Klunk (Chairs)**

10:15 – 10:30 Initial report of ADNI PIB-PET imaging studies
CA Mathis, Departments of Radiology, Psychiatry, and Neurology, University of Pittsburgh, PA, USA

10:30 – 10:45 [^{11}C]PIB longitudinal assessment of amyloid deposition in Alzheimer's disease and mild cognitive impairment
A Okello, Imperial College London, UK

10:45 – 11:00 Plaque and tangle PET imaging with FDDNP-PET
GW Small, University of California, LA, USA

11:00 – 11:15 *In vivo* assessment of β-amyloid deposition: a longitudinal study
VL Villemagne, Austin Health, Melbourne, Australia

11:15 – 11:30 Amyloid imaging in Japan
K Ishii, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

11:30 – 12:15	**Keynote presentation by David M Holtzman, Andrew B and Gretchen P Jones Professor and Chairman, Department of Neurology, Washington University School of Medicine, St Louis, MO, USA**
12:15 – 14:00	**Lunch and poster session**
14:00 – 14:45	**Keynote presentation by David A Bennett, Director, Rush Alzheimer's Disease Center, and Robert C Borwell, Professor of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA**
14:45 – 16:15	**Session 3: Christopher Rowe, Chester Mathis (Chairs)**
14:45 – 15:00	Amyloid deposition is associated locally with cortical thinning *KA Johnson, Harvard Medical School, Boston, MA, USA*
15:00 – 15:15	The local and global impact of amyloid burden on glucose metabolism in Alzheimer's disease: evidence from [^{11}C]PIB and [^{18}F]FDG PET imaging *AJ Furst, University of California at Berkeley, CA, USA*
15:15 – 15:30	[^{11}C]PIB retention is not associated with brain volume trajectories in clinically normal elderly: preliminary findings from the Baltimore Longitudinal Study of Aging (BLSA) *I Driscoll, National Institute on Aging, NIH, MD, USA*
15:30 – 15:45	Cortical amyloid deposition associated with impaired default network activity in non-demented older individuals *RA Sperling, Harvard Medical School, Boston, MA, USA*
15:45 – 16:00	Correlations between psychometric performance, [^{11}C]PIB, and MRI in cognitively normal, amnestic MCI, and AD subjects *CR Jack Jr, Mayo Clinic and Foundation, Rochester, MN, USA*
16:00 – 16:15	Amyloid deposition is an early event in AD and shows a complex relationship with functional characteristics *A Forsberg, Karolinska Institute, Stockholm, Sweden*
16:15 – 16:30	**General discussion**

Classification of amyloid-positivity in controls: comparison of objective approaches to visual reads

WE Klunk, AD Cohen, JC Price, CA Mathis, DA Wolk, JM Mountz, LA Weissfeld, SK Ziolko, RD Nebes, HJ Aizenstein, JA Saxton, B Snitz, P Houck, E Halligan, ST DeKosky

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Background: Amyloid deposition in Alzheimer's disease (AD) can be detected with PET amyloid imaging using Pittsburgh Compound-B (PIB). Amyloid deposition also is present in 20–25% of cognitively normal elderly control subjects. Therefore, it becomes important to develop a reliable objective method to distinguish amyloid-positive controls from amyloid-negative controls.

Objective: To develop an objective method for the classification of amyloid-positivity at the earliest stages of amyloid deposition and compare this to visual readings by experienced clinical researchers.

Methods: Sixty cognitively normal controls (52 with average age of 73 ± 7 years; range 56–89; and 8 that were 35–55 years old) were screened for normal cognition with a neuropsychological test battery developed to detect mild cognitive impairment (MCI) and AD. They underwent PIB PET scanning (90 min) and Logan distribution volume ratios to the cerebellum (DVR or V_T/V_{ND}) were calculated and corrected for atrophy using co-registered MRIs. One objective method used two iterations to remove "mild" outliers (values above the upper-inner fence) to identify a residual amyloid-negative group. A second objective method identified a "discontinuity" in the distribution of a parameter calculated from the magnitude and variability of PIB retention across key brain regions to identify amyloid-negative subjects. These methods were compared to each other and to visual reads of the PIB PET scans by five experienced readers trained to use a common criterion for amyloid-positivity.

Results: Both objective methods identified a nearly identical set of 16 of the 60 subjects (27%) as amyloid-positive — each identifying one subject as amyloid-positive not identified by the other. No controls under age 56 were classified as amyloid-positive by any method. Comparing the consensus of the readers to the discontinuity approach, showed agreement in 15/16 (94%) of the amyloid-positive cases and in 40/44 (91%) amyloid-negative cases. One subject who was consistently identified as amyloid-positive by both objective measures, but questionably positive by the readers, became clearly amyloid-positive on a follow-up scan performed 4 years after the index scan.

Conclusions: We conclude that it is possible to identify an objective and generalizable method for the identification of amyloid-positivity in early stages of amyloid pathology.

Fibrillar amyloid-β burden in cognitively normal persons homozygous for the apolipoprotein E ε4 allele

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Background: Although fibrillar amyloid-beta (Aβ) is observed in some older persons who are cognitively normal, it is not yet known whether preclinical fibrillar β amyloid is related to a predisposition to Alzheimer's disease (AD).

Objective: To compare fibrillar Aβ burden in cognitively normal apolipoprotein E (APOE) ε4 homozygotes (HM), who are at especially high risk of late-onset AD, and ε4 non-carriers (NC) in their 50s and 60s using positron emission tomography (PET) and [^{11}C]-labeled Pittsburgh Compound-B (PIB).

Methods: PIB, 90 min dynamic PET scans, the Logan method and an automatically labeled cerebellar region-of-interest were used to compute parametric brain images of the PIB Distribution Volume Ratio (DVR), a measure of fibrillar Aβ burden, in 5 APOE ε4 homozygotes (HM) and 5 ε4 non-carriers (NC) who were 56–68 years of age, cognitively normal and enrolled in an ongoing longitudinal study. Statistical parametric mapping (SPM5) was used to generate t-score maps of between-group differences in PIB DVR.

Results: The HM and NC groups did not differ significantly in their age, Mini-Mental State Examination or memory test scores, gender distribution, or educational level. The HM group had higher PIB DVR than the NC group bilaterally in anterior and middle cingulate, frontal, temporal and parietal cortex, precuneus, medial temporal lobe, and basal ganglia ($p = 0.05$ to $6x10^{-6}$, uncorrected). There were no cerebral voxels in which the NC group had higher PIB DVR than the HM group ($p \leq 0.05$, uncorrected).

Conclusions: This preliminary study supports the relationship between preclinical fibrillar Aβ burden and the genetic predisposition to AD. It provides a foundation to track rates of fibrillar Aβ deposition in cognitively normal persons at differential risk of late-onset AD, determine the extent to which this information predicts rates of conversion to mild cognitive impairment (MCI) and AD, and use PIB DVR as a surrogate endpoint in primary prevention trials.

Patterns of [^{11}C]PIB uptake in non-demented subjects

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Introduction: Alzheimer's disease likely has a long preclinical phase in which the abnormalities in β-amyloid production, clearance and deposition play a critical role. As part of a longitudinal study at the Washington University ARDC we have been using PET [^{11}C]PIB to image older non-demented subjects and determine the frequency of abnormal PIB uptake in non-demented individuals and whether any pattern is predictive of ultimate development of dementia.

Methods: Subjects receiving a Clinical Dementia Rating of 0 after evaluation at the Washington University ADRC studied with ~12 mCi [^{11}C]PIB i.v. and 60 min of dynamic PET scanning. Regions-of-interest were used to extract time-activity curves and Binding Potential values (BPs) were calculated using Logan graphical analysis with a cerebellar input function. Four regions with the highest BP values (prefrontal, temporal, precuneus and gyrus rectus) seen in a separate set of subjects with dementia of the Alzheimer's type (DAT) were averaged to create the Mean Cortical Binding Potential (MCBP). PIB images from non-demented subjects who had elevated MCBP values were averaged after transformation to standard atlas space.

Results: In a group of 119 non-demented subjects (ages 32 to 88 years) we used a threshold of MCBP > 0.18 for determining abnormal uptake (Fagan *et al*., 2006) and found a mean of 17.6% non-demented subjects with elevated PIB uptake. Average PIB images of these non-demented subjects showed particularly elevated uptake in the precuneus and the pregenual anterior cingulate. There was a clear age-dependence: 0% pos in 32–49 years; 3% pos in 50–59 years; 20% pos in 60–69 years; and 31.1% pos 70+ years. These results are consistent with the hypothesis that β-amyloid deposits substantially precede onset of dementia.

Assessment of β amyloid in frontal cortical brain biopsy and by PET with [^{11}C]PIB

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Department of Neurosurgery, Kuopio University Hospital, Kuopio Unit of Pathology and Neurology, Department of Clinical Medicine, University of Kuopio, Kuopio, Turku PET Centre, University of Turku, Turku, Unit of Neurology, Institute of Clinical Medicine, University of Kuopio, Kuopio, Department of Neurology, Kuopio University Hospital, Kuopio, Finland.

Background: Aggregates of β amyloid (Aβ) together with hyperphosphorylated tau (HPτ) in post-mortem human brains are considered as diagnostic lesions of Alzheimer's disease (AD). These lesions can be seen in surgical biopsies, a method seldom used in the AD diagnostics. Pittsburgh Compound-B (PIB) PET seems a promising method for non-invasive imaging of Aβ in the brain. To our knowledge, there are no systematic assessments of [^{11}C]PIB PET in patients with AD-lesions in surgical brain biopsies.

Objective: To compare [^{11}C]PIB PET in patients with/without AD-lesions in the frontal cortical biopsy.

Patients: Ten patients who underwent intraventricular pressure monitoring with a frontal cortical biopsy (evaluated for Aβ and HPτ) for suspected normal pressure hydrocephalus.

Methods: [^{11}C]PIB PET and evaluation for cognitive impairment using a battery of neuropsychological tests. Immunohistochemical evaluation for Aβ and HPτ in frontal cortical biopsy.

Results: In six patients with Aβ in the frontal cortical biopsy, PET imaging revealed higher [^{11}C]PIB uptake ($p < 0.05$) in the frontal, parietal and lateral temporal cortices, and in the striatum as compared to the four patients without frontal Aβ deposits.

Conclusions: Our study supports the use of the non-invasive [^{11}C]PIB PET in the assessment of Aβ deposition in the brain. The results show that [^{11}C]PIB uptake correlates with the presence of Aβ deposits in cortical brain biopsy.

Identification of “AD-like” normal elderly controls using PIB-PET imaging

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Objective: To compare different quantitative approaches to defining cases as with Alzheimer’s disease (AD) and normal controls (NC) using PIB-PET.

Methods: We compared PIB-PET data from 8 AD patients (AD, age = 67.0 ± 7.1, MMSE = 19.4 ± 9.1) and 16 NC subjects (age = 71.6 ± 6.4, MMSE = 29.8 ± 0.6). We used PIB data from 50–70 min normalized to cerebellum and template based regions of interest (ROIs) to extract PIB counts from three cortical regions: gyrus rectus, lateral temporal and precuneus. Three ROI methods were contrasted using receiver-operator characteristic (ROC) curves. (1) ROI approach: mean PIB value from a single ROI. (2) Cortical index approach: average of the 3 ROI means extracted in method one. (3) Highest ROI approach: the highest mean from the ROIs used in method one. Values showing the greatest discrimination ability were then used to select a cut off value, and this cut off was applied to an independent sample of AD and NC PIB scans analyzed in the same way, from the Alzheimer’s Disease Neuroimaging Initiative database (ADNI; AD = 11, age = 73.2 ± 10.5, MMSE = 23.6 ± 2.0; NC = 12, age = 78.7 ± 6.2, MMSE = 28.4 ± 1.6).

Results: All quantitative measures showed good separation between AD and NC, with overlap between the groups restricted to a few cases. Discrimination ability was assessed by comparing the area beneath the ROC curves: gyrus rectus ROI (0.91), lateral temporal ROI (0.87), precuneus ROI (0.99), cortical index (0.98), highest ROI (0.97). Optimal cut offs were selected from the precuneus ROI (PIB = 1.3) and PIB Index (PIB = 1.26) methods and applied to the ADNI sample. With both these cut offs, 5/12 controls were AD-like in the ADNI cohort.

Conclusions: Quantitative approaches can be used to classify subjects as having AD or normal PIB uptake. These methods may identify NC subjects at high risk for AD.

Initial report of ADNI PIB-PET imaging studies

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Background: PIB-PET imaging was added to the Alzheimer's Disease Neuroimaging Initiative (ADNI) study in 2007. ADNI PIB-PET studies in 24 controls, 48 mild cognitive impairment (MCI), and 24 AD subjects with 2–3 years of follow-up scans are approved at 16 PET sites in the US and Canada to provide a publically accessible, imaging biomarker database for use in clinical trials of anti-amyloid therapies as well as for other academic studies.

Objective: To summarize the ADNI PIB-PET baseline data collected at multiple sites, with particular emphasis on the prevalence of individuals who showed evidence of amyloid deposition.

Methods: As of late February 2008, 78 baseline PIB-PET studies from 12 ADNI sites had been collected and posted on the UCLA Laboratory of NeuroImaging (LONI) website after completion of requisite quality control and pre-processing steps by the University of Michigan, which included summing over 50–70 min post-injection, co-registration to Talaraich space, re-orientation along AC-PC axis, standardization to a uniform voxel size and resolution, and normalization to cerebellar grey matter. The ADNI LONI database included PIB-PET studies in 17 controls (MMSE range 24–30, mean 29 ± 1; Age: 79 ± 5 years), 46 MCI (MMSE range 18–30, 27 ± 2; Age: 74 ± 8 years), and 15 AD (MMSE range 15–26, 22 ± 3; Age: 73 ± 9 years) subjects. A preliminary assessment of the data involved a single-plane sampling of the anterior cingulate (ACG) and precuneus (PRC) regions, using anatomical landmarks as guidelines. Positive amyloid deposition (PIB+) was defined when the ACG SUVR (standardized uptake value ratio in region relative to the cerebellum) or PRC SUVR exceeded 1.60.

Conclusions: Using this cut-off value, a large percentage of the elderly control (56%) and MCI (74%) subjects were PIB+, while 2 clinically diagnosed AD subjects were clearly PIB- with PRC SUVR values of 1.08 and 1.20.

[^{11}C]PIB longitudinal assessment of amyloid deposition in Alzheimer's disease and mild cognitive impairment

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Objective: The positron emission tomography (PET) radiotracer Pittsburgh Compound-B (PIB) allows the *in vivo* visualization of cerebral amyloid, the neuropathological hallmark of Alzheimer's disease (AD). Using [^{11}C]PIB PET, we sought to assess progression of amyloid deposition in AD and mild cognitive impairment (MCI) patients followed up longitudinally.

Methods: 11 AD (66.7 ± 5.5 years) and 8 amnestic MCI subjects (66.1 ± 7.8) who had baseline MRI and [^{11}C]PIB PET had repeat scans (phase I follow-up) at 17 months (range 12–22). Of these, 4 AD and 3 MCIs had a third [^{11}C]PIB PET scan (phase II follow-up) at 31 months (range 27–36). Parametric 60–90 minute ratio images of PIB retention were generated using a cerebellar reference region. Regions of interest were defined using a probabilistic atlas in MNI space.

Results: AD patients showed increased PIB retention ratios in regions including posterior cingulate (2.23), frontal (2.06), parietal (2.04) and temporal (1.91) cortex. Two of 11 AD patients had normal PIB binding at baseline. PIB retention in AD patients remained unchanged during both phases I and II of follow-up, apart from one AD patient with normal baseline PIB binding who demonstrated 20–30% increases in PIB retention (cingulate, frontal and parietal) at phase II compared to baseline. Baseline [^{11}C]PIB binding was increased in 4 of 8 MCI patients (50%). PIB retention in MCIs remained largely unchanged at phase I follow-up (mean increases 6–8% in ROIs). However, the 2 PIB positive MCI subjects at baseline who have reached phase II follow-up, have shown 20% increases in cortical PIB retention at 27 and 31 months.

Conclusions: These findings in MCI and AD suggest that amyloid deposition occurs early in these conditions and although it appears to have stabilized in most AD patients, may continue to increase in certain MCI patients. Further follow-up will be essential in confirming these initial findings.

Plaque and tangle PET imaging with FDDNP-PET

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Before the development of neuroimaging technologies that could measure amyloid plaques and tau tangles, these protein deposits could only be observed at autopsy, or rarely, at biopsy. Several small molecule probes for use with positron emission tomography (PET) imaging have been developed to provide *in vivo* measures of amyloid plaques, and this presentation will provide an update on clinical studies of a compound that provides a measure of both tau tangles and amyloid plaques, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP). FDDNP and its non-fluorinated analogue, DDNP, are fluorescent and provide clear *in vitro* visualizations of plaques and tangles in Alzheimer's disease (AD) brain specimens examined under confocal fluorescent microscopy. Neuropathological studies performed at autopsy of patients with AD who previously received FDDNP-PET scans show close matching of *in vitro* brain sections concentrated with plaques and tangles and brain regions showing increased *in vivo* FDDNP-PET signals. FDDNP-PET scanning differentiates patients with AD from those with mild cognitive impairment and cognitively intact controls, and initial 5-year longitudinal follow up shows that FDDNP binding values increase as cognitive symptoms progress. In studies of Down's syndrome, which has been proposed as a model for the study of AD, age and behavioral symptoms are associated with increased FDDNP signals, which is consistent with previous studies demonstrating indifference and other behavioral symptoms in people with Down's syndrome who show neuropathological signs of AD at autopsy. Impaired cognitive status, older age, and apolipoprotein E-4 carrier status are associated with increased brain FDDNP-PET binding in non-demented persons, consistent with previous clinical and post-mortem studies associating these risk factors with amyloid plaque and tau tangle accumulation. Three-dimensional cortical surface projection images of FDDNP-PET show patterns remarkably similar to those expected from autopsy studies demonstrating regional brain accumulation patterns of plaques and tangles.

In vivo assessment of β-amyloid deposition: a longitudinal study

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Background: *In vivo* amyloid imaging with PET is allowing new insights into β-amyloid (Aβ) deposition in the brain. Longitudinal studies enable researchers to more clearly define the role of Aβ deposition in the development of dementias where Aβ may play a role.

Methods: Fifty one subjects — 15 with Alzheimer's disease (AD), 8 with mild cognitive impairment (MCI) and 28 age-matched healthy controls (HC) — were re-assessed 21 ± 5 months after their first [^{11}C]PIB-PET scan. Aβ burden was quantified using SUVR employing the cerebellar cortex as reference region. Every participant underwent a comprehensive neuropsychological examination within 2 weeks from each PET scan. Composite episodic memory and non-memory scores were calculated using 53 PIB negative healthy controls as reference.

Results: Cortical PIB binding was markedly elevated in every AD subject. In the MCI group, PIB binding was either "AD-like" (50%) or "HC-like". At baseline, 8 out of the 28 HC (29%) showed cortical binding, predominantly in the prefrontal and posterior cingulate/precuneus regions, though to a lesser degree than AD patients. Though no significant difference in PIB binding was attained between baseline and follow-up in the groups examined, 12 out of 15 AD showed an increase ranging from 3% to 18% (mean 9.5%). Furthermore, 3/8 PIB positive (38%) HC and 4/4 (100%) PIB positive MCI declined at follow-up and their clinical classification was changed to either MCI or AD at the repeat visit. Only one PIB negative HC showed decline to MCI. There was a strong correlation between episodic memory and Aβ burden in non-demented participants.

Conclusions: PIB binding changed little over 2 years, though there was a slight increase in the AD group. The presence of Aβ deposits in the brain, even at presymptomatic stages, seems to be a strong predictor of cognitive decline and conversion.

Amyloid imaging in Japan

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The Alzheimer's Disease Neuroimaging Initiative in Japan (J-ADNI) project was launched last year. Thirty-three clinical sites were nominated to register and follow up a total of 600 subjects: 300 mild cognitive impairement (MCI), 150 Alzheimer's disease (AD) patients, and 150 healthy controls. Half of the subjects are expected to participate in FDG-PET study and a quarter in amyloid PET. The study protocol was designed to be compatible with that of US-ADNI. Two amyloid probes, [^{11}C]-labeled Pittsburgh compound-B (PIB) and [^{11}C]-labeled BF-227 developed by Tohoku University will be available for the J-ADNI study. Nine PET centers will be collecting [^{11}C]PIB-PET data and two PET centers will deal with [^{11}C]BF-227. More than 200 cases with [^{11}C]PIB and 80 cases with [^{11}C]BF-227 had already scanned among the J-ADNI entry PET centers before starting the J-ADNI project. Based on these experiences, we planned to add some value by improving the US-ADNI PIB protocol. J-ADNI project adopts dynamic scan starting from the injection as a standard protocol so that we may be able to detect subtle β-amyloid deposition and slight alteration in the time-course, because a dynamic data may give us more sensitive and noiseless information than a late phase static image. Prior to starting the actual data acquisition, a phantom experiment to examine the dynamic range of each PET camera will be performed in order to optimize the administration dose. A common lot of precursor material will be supplied from the core to each PET center to standardize the drug quality. In order to examine inter-institutional variability, a limited number of AD patients were scanned with PIB in two PET centers. The reproducibility of qualitative distribution was quite satisfactory; however, a quantitative evaluation of data from different PET centers requires some interpretation. A direct comparison of [^{11}C]PIB and [^{11}C]BF-227 in the same subjects was performed in ten subjects; 5 AD patients, two FTD patients, one cerebral amyloid angiopathy patient and two healthy controls. [^{11}C]PIB and [^{11}C]BF-227 both seem to accumulate selectively to β-amyloid; however, the distribution was not identical. A comparison of [^{11}C]PIB and [^{11}C]BF-227 may provide useful information to help predict disease progression.

Amyloid deposition is associated locally with cortical thinning

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Background: A clear relationship between amyloid plaque burden and neuronal loss or regional atrophy has not been demonstrated in autopsy studies. We tested the hypothesis that regional fibrillar amyloid burden, as measured by PIB, is associated locally with reduced cortical thickness.

Methods: [^{11}C]PIB-PET data and 3T MRI-MPRAGE were acquired in 50 subjects, who were classified as CDR 0 (n = 30), CDR 0.5 (n = 12), or CDR 1 (n = 8). PIB retention was measured by DVR with cerebellar cortex as reference region and corrected for the partial-volume effect using Meltzer's two-compartment method. MPRAGE data were processed by FreeSurfer to generate cortical gray matter thickness at each vertex. Vertex-based thickness and DVR data were calculated in standardized space and average thickness and DVR were determined in FreeSurfer-defined cortical regions of interest (ROIs). Contrasts at each vertex between the CDR 0 group and the combined CDR 0.5/1 group of cortical thickness and DVR were assessed by ANCOVA with age as a covariate. Linear regression with age covariate was used to investigate the relationship of thickness and DVR at each vertex across the entire sample. Parallel analyses were performed on ROI data.

Results: At the vertex level, both amyloid deposition and cortical thinning were significantly greater in the CDR 0.5/1 group than in the CDR 0 group in superior temporal, lateral parietal, precuneus, posterior cingulate (PC), and medial frontal areas ($p < 0.001$). Greater amyloid deposition was significantly correlated with cortical thinning in PC/precuneus and temporal areas ($p < 0.001$). Post-hoc ROI analyses confirmed these significant differences.

Conclusion: Amyloid deposition is associated locally with cortical thinning, predominantly in posterior cingulate/precuneus and temporal cortices, areas where both dysfunction and atrophy are commonly observed in AD. Our findings suggest that damage to neuronal populations, whether due to soluble or insoluble amyloid or other factors, occurs at sites of amyloid deposition.

The local and global impact of amyloid burden on glucose metabolism in Alzheimer's disease: evidence from [^{11}C]PIB and [^{18}F]FDG PET imaging

AJ Furst, EC Mormino, RA Lal, GD Rabinovici, CM Madison, SL Baker, BL Miller, WJ Jagust

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Objective: To investigate the relationship between amyloid load and glucose metabolism in Alzheimer's disease (AD).

Methods: Patients meeting criteria for probable AD (n = 13, mean age 63.9 ± 7.1, MMSE 20.0 ± 7.0) and healthy controls (n = 11, mean age 72.6 ± 4.3, MMSE 29.4 ± 0.7) underwent structural MRI, [^{11}C]PIB and [^{18}F]FDG PET. Voxel-wise whole brain and native-space region-of-interest (ROI) comparisons of atrophy-corrected PIB distribution volume ratio (DVR, cerebellar reference) and FDG data (normalized to pons) were performed between groups and for AD patients separately.

Results: ROI analyses comparing AD patients with controls confirmed a typical temporo-parietal hypometabolic pattern and specific PIB binding in fronto-temporo-parietal regions in FDG and DVR ($p < 0.05$) scans, respectively. Voxel-wise analyses of FDG and DVR scans indicated severe hypometabolism in angular gyrus, precuneus, posterior cingulate, and middle/inferior temporal cortex (FDR, $p < 0.05$) and maximal amyloid load in precuneus, posterior cingulate, middle/inferior temporal cortex, fusiform gyrus, striatum, orbitofrontal cortex, superior/middle frontal cortex (FDR, $p < 0.01$) in AD. Voxel-by-voxel comparisons ($p < 0.05$) revealed that increased amyloid burden in temporo-parietal regions (including precuneus), and the anterior and posterior cingulate was coupled with decreased metabolism in these regions while severe amyloid burden in the frontal lobes, striatum and thalamus was not associated with comparable metabolic decreases. A PIB index averaging PIB uptake in multiple neocortical regions showed negative correlations ($p < 0.05$) with entorhinal ($r = -0.60$) and inferiotemporal cortex ($r = -0.56$) glucose metabolism. Further, PIB DVRs in posterior cingulate were inversely correlated with FDG counts in parahippocampus ($r = -0.58$), entorhinal cortex ($r = -0.63$) and the temporal pole ($r = -0.65$).

Conclusions: Local neurotoxicity of amyloid plaques is not uniform across the brain while global neocortical amyloid burden seems to exert remote effects on neural structures involved in memory.

[^{11}C]PIB retention is not associated with brain volume trajectories in clinically normal elderly: preliminary findings from the Baltimore Longitudinal Study of Aging (BLSA)

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Alzheimer's disease (AD) is hallmarked by amyloid-β plaques (Aβ) and neurofibrillary tangles (NFT) in conjunction with clinicopathological features. [^{11}C]PIB and other amyloid imaging agents may have utility in diagnosis and therapeutic monitoring of AD. Aβ is thought to be associated with neuronal loss, brain atrophy and cognitive impairment. The aim of the present study is to determine whether there is an association between [^{11}C]PIB retention and trajectories of brain volume in a prospectively followed community-dwelling BLSA cohort of 56 non-demented, highly educated participants (M(age) = 78.7 ± 6.2) underwent up to 10 consecutive MRI scans (M(follow-up) = 8.07 ± 0.83) with [^{11}C]PIB images acquired approximately 10 years after the initial MRI. PIB distribution volume ratios (DVR) of regions of interest were estimated by fitting a reference tissue model to the measured time activity curves. Principal Component Analysis (PCA) was performed on 15 PIB DVRs and explained 82.6 of variance. Trajectories of volume decline were calculated for the whole brain, ventricular CSF, white matter (WM), gray matter (GM), the hippocampus, and frontal, temporal, parietal, and occipital WM and GM, respectively. The 1st PCA score was used to predict the slopes and intercepts of regional brain volume trajectories. Despite significant declines in the volumes of all regions investigated ($p < 0.05$), no significant associations were detected with Aβ load ($p > 0.3$) in clinically normal elderly, consistent with recent post-mortem findings. Aβ may play a limited role in brain atrophy or conversely, consistent with a threshold model of disease, the Aβ load does not affect brain volume or performance within the clinically normal range of function. Moreover, PIB and MRI may be complimentary; hence, joint analysis of data may provide more diagnostic information than a single method alone.

Cortical amyloid deposition associated with impaired default network activity in non-demented older individuals

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Background: Recent functional imaging studies in both aging and Alzheimer's disease (AD) have reported alterations in a specific set of brain regions, including parietal and medial prefrontal cortices, that typically "deactivate" during cognitive tasks, often referred to as the "default network".

Objectives: In this study, we investigated the relationship of fibrillar amyloid deposition, as assessed by PIB-PET, to default network activity during successful encoding, as assessed by an event-related functional magnetic resonance imaging (fMRI) paradigm.

Methods: Thirty-one non-demented older individuals (CDR 0 = 19 and CDR 0.5 = 12; age = 77.7 +/- 5.2, MMSE = 29.0 +/- 0.9) were imaged with PIB-PET and fMRI during an associative memory paradigm. The CDR 0.5 subjects were very mildly impaired, not yet meeting Petersen criteria for mild cognitive impairment (MCI). PET datasets were corrected for the partial-volume effect with a two-compartment method. PIB distribution volume ratio (DVR) was calculated for the precuneus/posterior cingulate cortex (PCC) using individual anatomic regions defined on the high-resolution MP-RAGE sequence. Whole brain fMRI contrast maps for High-Confidence Correct Responses *vs* Fixation were generated in SPM2, with PCC PIB value, age, and task performance entered as regressors.

Results: Increasing PIB retention in PCC was correlated with reduced deactivation of the default network ($p < 0.001$). The PCC and medial frontal regions, which typically deactivate during successful encoding, demonstrated paradoxical increased MR signal (activation) at high levels of PIB retention. High PIB retention in PCC was associated with increased hippocampal activation during successful encoding trials ($p < 0.005$) but not during failed encoding trials.

Conclusions: These results suggest that amyloid deposition is associated with failure of deactivation in the default network, and that compensatory "hyperactivation" of the hippocampus may be required to maintain memory performance. These findings support the hypothesis that amyloid deposition is associated with altered neural activity in a distributed memory network in non-demented older individuals.

Correlations between psychometric performance, [^{11}C]PIB, and MRI in cognitively normal, amnestic MCI, and AD subjects

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Background: Our objectives in this study were to evaluate associations between psychometric performance, ^{11}C PIB, and structural MRI in cognitively normal (CN, n = 20), amnestic mild cognitive impairment (MCI) (aMCI, n = 17), and Alzheimer's disease (AD) (n = 8) subjects.

Methods: A global cortical PIB retention summary measure was derived from six cortical regions of interest (ROIs) and normalized by forming a ratio with cerebellar retention. A cut off value of 1.5 of this ratio was used to separate subjects into those labeled "PIB positive" *vs* "PIB negative". Hippocampal volumes were measured from MRI and corrected for age, gender and head size. General cognitive performance was assessed with the short test of mental status and CDR sum of boxes. Learning and memory performance was assessed with the WMS-R visual reproduction II, WMS-R logical memory II, AVLT delayed recall, and AVLT sum of learning trials 1–5.

Results: All AD subjects were PIB "positive" as were 6/20 CN subjects and 9/17 MCI subjects. Overall, there were no consistent differences in cognitive performance between high and low PIB CN or aMCI subjects, including tests of learning and memory. The hippocampi were slightly (non-significantly) more atrophic in high than low PIB CN and aMCI subjects. Across all 45 subjects in the study, imaging-cognitive correlations went in the expected directions for both PIB and MRI and nearly all were significant. The magnitudes of the correlations were greater for MRI than PIB.

Conclusions: We assume that PIB is an accurate marker of amyloid deposition, and structural MRI is an indirect but approximate marker of neurodegeneration. A possible sequence of events that integrates these PIB, MRI, and cognitive findings is that amyloid deposition is an early event that precedes clinical symptoms by years. Neurodegeneration occurs later and is the direct histological substrate of impaired cognition. Longitudinal studies are necessary to confirm or disprove this hypothesis.

Amyloid deposition is an early event in AD and shows a complex relationship with functional characteristics

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Background: *In vivo* imaging with the amyloid PET ligand [^{11}C]PIB has shown a robust difference between patients with Alzheimer's disease (AD) and healthy age-matched controls. The aim of this study was to investigate the relationship between [^{11}C]PIB retention in the brain, cerebral glucose metabolism, cerebrospinal fluid (CSF) biomarkers and episodic memory.

Methods: 37 AD patients and 21 subjects with mild cognitive impairment (MCI) underwent PET examinations with the amyloid ligand [^{11}C]PIB, and with [^{18}F]FDG to measure cerebral glucose metabolism (CMRglc). They underwent cognitive testing and CSF sampling for measurement of amyloid ß (Aβ1-42), total Tau and phosphorylated Tau. Analyses were performed using Statistical Parametric Mapping (SPM) and regions of interest (ROIs).

Results: Retention of [^{11}C]PIB in AD brains was widespread and it correlated significantly with CMRglc as well as with levels of CSF biomarkers, and episodic memory. The regional decrease in CMRglc was more focally located to the parietal cortex and posterior cingulum compared with [^{11}C]PIB retention, and the regional impairment of CMRglc also showed a stronger correlation with impairment in episodic memory. These relationships differed when analyzing the AD and MCI patients separately, which indicates differences in time course between the pathological and functional changes. The ApoE genotype did not have an influence on the level of [^{11}C]PIB retention, rCMRglc or levels of CSF biomarkers.

Conclusions: Amyloid deposition in the brain is related to levels of CSF biomarkers and seems to show a different distribution and time course compared with cerebral glucose metabolism, which shows a stronger correlation with memory.

PIB retention reflects episodic memory in cognitively intact subjects and global cognition in AD patients

POSTER ABSTRACT

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Background: The objective was to study the association between various cognitive functions and *in vivo* measurement of regional brain beta-amyloid deposition using the PET ligand ^{11}C-PIB.

Methods: The study included 60 subjects divided into four groups based on longitudinal clinical examinations: patients diagnosed with Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), Subjective Cognitive Impairment (SCI) and healthy controls (HC). PIB retention was measured in 47 regions of interest. Global as well as specific cognitive functions were assessed.

Results: For all subjects, decline of cognitive function was more strongly associated with PIB retention in all neocortical regions compared to point estimates in conjunction with PIB measurement. There was no association PIB retention and estimated premorbid cognitive function, age, other demograhic characteristic or APOE genedose. Within HC subjects, significant correlations were found for episodic memory *vs* PIB retention in a number of frontal, parietal and temporal regions. Within SCI subjects, significant correlations were seen for episodic memory in relation to PIB retention in some parietal and temporal regions. In contrast, significant associations were observed between PIB retention and non-memory domains within AD patients.

Conclusions: Patterns of relationship between cognition and PIB retention indicated subtle changes in episodic memory and some brain regions in HC and SCI subjects. During AD, changes were evident in non-memory cognitive functions and the majority of brain regions. Hypothetically, a disease-related pattern of cognition and PIB retention emerged.

Using the support vector machine to discriminate between probable AD cases and normal controls on the basis of their FDG-PET, PIB-PET or combined images

POSTER ABSTRACT

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Background: FDG-PET and PIB-PET have potentially complementary roles in the differential diagnosis, early detection and tracking of Alzheimer's disease (AD). The Support Vector Machine (SVM) has recently been shown to help distinguish probable AD cases and normal controls (NC) on the basis of their MRI measurements of gray matter density.

Objective: To characterize and compare the ability of SVM to distinguish between probable AD cases and NC on the basis of their FDG-PET images, PIB-PET images, and the combination of these images.

Method: SVM was used to analyze the FDG-PET images, PIB-PET images, and the combination of the two images, acquired at Austin Health, Australia, from 15 probable AD patients and 11 NC (71.57 ± 9.42 years of age). Each person's FDG-PET and PIB-PET images were spatially normalized using SPM5, mean voxel intensities were computed from the regions defined by Anatomical Automatic Labeling (AAL) (http://www.fil/ion.ucl.ac.uk/spm/ext/#AAL), and data from an AAL-defined cerebellar region was used to normalize each FDG or PIB image using proportionate scaling. 70% of the image pairs were randomly selected as the training set, the remaining 30% were used to independently characterize and compare the accuracy of each imaging modality, as well as the combination of the two image modalities, to discriminate between probable AD cases and controls, and the 70%/30% data partitioning and SVM data analysis sequence were repeated 10 times.

Results: Using SVM and the data from AAL-defined regions, probable AD patients and NC were distinguished with 77.5 11.5% accuracy using FDG-PET, 88.8 4.0% accuracy using PIB-PET, and 97.5 5.3% accuracy using both images together The combination of FDG-PET and PIB-PET yielded statistically significant improvement in accuracy from using FDG-PET or PIB-PET alone.

Conclusion: SVM and the combination of FDG-PET and PIB-PET images have promise in the classification of patients with Alzheimer's dementia.

PET amyloid imaging with Pittsburgh Compound B in Alzheimer's disease, Mild Cognitive Impairment, and healthy controls

POSTER ABSTRACT

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Background: PIB uptake using PET distinguishes AD from controls, but uncertainty remains about its utility in separating MCI patients from AD and controls.

Methods: AD (n = 16), MCI (n = 20) and healthy control subjects (n = 16) were studied. A brief neuropsychological test battery, PIB PET and MRI were done. Binding potential (BPND) from the Logan graphical method using cerebellar gray matter as reference region was obtained from PET images coregistered to their corresponding MRI scans. Individual BPND estimates were measured for cingulate, prefrontal cortex, hippocampus, parahippocampal gyrus.

Results: Across the entire sample, there were no age, sex, or education effects on BPND in any ROI. Prefrontal cortex BPND showed inverse correlations with MMSE ($r = -0.53$, $p < 0.001$), Selective Reminding Test (SRT) immediate recall ($r = -0.50$, $p = 0.004$) and SRT delayed recall scores ($r = -0.60$, $p < 0.001$), and a positive correlation with ADAS-cog scores ($r = 0.54$, $p < 0.001$). Cingulate BPND showed similar correlations with cognitive scores. Parahippocampal gyrus BPND showed less significant correlations and hippocampus BPND showed no significant correlations with cognitive scores. In ANOVAs on each ROI with subject group (control, MCI, AD) as the between subject factor, prefrontal cortex BPND ($F = 18.0$, $p < 0.0001$), cingulate BPND ($F = 10.2$, $p < 0.0001$) and parahippocampal gyrus were significant ($F = 5.7$, $p = 006$), but not hippocampus ($F = 0.26$, $p = 0.77$). In ANCOVA using a similar model with age and MMSE or the SRT measures included as covariates, prefrontal cortex and cingulate remained significant ($p < 0.02$ to 0.05). Amnestic MCI patients (n = 15) showed significantly greater prefrontal and cingulate BPND compared to non-amnestic MCI patients (n = 5).

Conclusions: [^{11}C]-6-OH-BTA-1 (PIB) PET BPND showed strong associations with cognitive performance. Its ability to distinguish AD, MCI and controls after controlling for age and cognitive performance underlines its potential use in differential diagnosis and prediction of conversion from MCI to AD.

Amyloid imaging in Lewy Body Diseases

POSTER ABSTRACT

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Background: Extrapyramidal motor symptoms precede dementia in Parkinson disease (PDD) by many years, whereas dementia occurs early in dementia with Lewy bodies (DLB). Despite this clinical distinction, the neuropsychological and neuropathological features of these conditions overlap. In addition to widespread distribution of Lewy bodies, both diseases have variable burdens of neuritic plaques and neurofibrillary tangles characteristic of Alzheimer disease.

Specific Aims: 1) To determine whether amyloid deposition, as assessed by PET imaging with the beta-amyloid-binding compound Pittsburgh Compound B (PIB), can distinguish DLB from PDD. 2) To assess whether regional patterns of amyloid deposition correlate with specific motor or cognitive features.

Methods: Eight DLB, 7 PDD, 11 PD, 15 AD, and 37 NC subjects underwent PIB-PET imaging and neuropsychological assessment. Amyloid burden was quantified using the PIB distribution volume ratio, with cerebellar cortex as the input function.

Results: Cortical amyloid burden was higher in DLB than PDD, comparable to AD. Amyloid deposition in PDD was low, comparable to PD and NC. Relative to global cortical retention, occipital PIB retention was lower in AD than the other groups. For the DLB, PDD, and PD groups, amyloid deposition in the parietal (lateral and precuneus)/ posterior cingulate region was related to visuospatial impairment. Striatal PIB retention in DLB and PDD was associated with less impaired motor function.

Conclusions: Global cortical amyloid burden is high in DLB but low in PDD. These data suggest that beta-amyloid may contribute selectively to the cognitive impairment of DLB and may contribute to the timing of dementia relative to the motor signs of parkinsonism.

Early detection of cerebral amyloid angiopathy with Pittsburgh Compound B

POSTER ABSTRACT

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Objectives: Patients with advanced cerebrovascular deposition of beta-amyloid (cerebral amyloid angiopathy, CAA) show increased PIB retention in an occipital predominant pattern (Johnson, *Ann Neurol*. 2007). There is no definitive proof, however, that this PIB signal represents CAA rather than accompanying Alzheimer's disease (AD) plaque pathology.

Methods: PIB-PET, CT, MRI, and genetic testing were evaluated in a 42 year old man with Iowa-type hereditary CAA (ICAA), a condition with severe CAA, but little or no fibrillar plaque amyloid. The subject presented clinically with a 10 year history of tremor and atypical migraine, but no dementia. Post-mortem brain from a first-degree relative with ICAA was stained with PIB. PET DVR values were compared to AD and normal control groups.

Results: Amyloid precursor protein exon 17 sequencing showed the characteristic Iowa mutation, substitution of asparagine for aspartic acid at position 23. Marked PIB retention (DVR > 1.8) was seen in occipital cortex, whereas regions typically involved in AD had low retention. PIB staining of post-mortem tissue showed exclusively vascular labeling, supporting the inference that the PIB-PET signal in the patient represented CAA rather than AD plaque pathology. CT demonstrated occipital calcifications characteristic of ICAA.

Conclusions: These findings offer strong evidence that PIB-PET Detects vascular as well as plaque amyloid and can identify the vascular deposits as an early manifestation of CAA. Advanced cerebrovascular amyloid deposition appears to precede other manifestations of CAA such as extensive hemorrhage or white matter damage.

Imaging of cortical amyloid load and cerebral glucose metabolism in patients with Alzheimer's disease and mild cognitive impairment

POSTER ABSTRACT

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Objective: The aim is to investigate the deposition of amyloid plaques by carbon 11-labeled Pittsburgh Compound B ([^{11}C]-PIB) in the brains with dementia (Alzheimer's type, AD) and mild cognitive impairment (MCI). We clarify the relationship between cerebral amyloid load and glucose metabolism.

Method: Sixty patients with dementia and MCI, and 22 healthy control (HC) were studied. All 82 patients underwent 90 min dynamic [^{11}C]PIB-PET and 20 min static [^{18}F]FDG-PET (ECAT ACCELL scanner). [^{11}C]PIB data was acquired from 35–60 min after injection. Regions of interest (ROI) were defined on co-registered MRI and used in the analysis of the PET data. Distribution volume ratio (DVR) measures of PIB retention were determined using Logan graphical analysis (cerebellar gray as reference region). [^{18}F]FDG-PET images were extracted using 3 dimensional stereotactic surface projections (3D-SSP) by a Z-score on a pixel-by-pixel basis. Quantitative analysis for both [^{11}C]PIB and [^{18}F]FDG used the standardized uptake value ratio (SUVR) values of cortical regions, using cerebellar cortex as the reference region.

Result: Sixteen of 28 AD patients (MMSE: 20.4 ± 4.6) had a robust increase in PIB binding in the posterior cingulate, precuneus, frontal, parietal, lateral temporal cortical areas (typical PIB AD pattern), relative to HC. The mean value of whole brain DVRs in AD patients was significantly greater than in HC (AD: 2.66 ± 0.56, HC: 1.32 ± 0.13, $p < 0.01$). Of the 26 MCI patients (MMSE: 27.0 ± 1.8), twelve showed typical AD patterns of amyloid deposition, and the value of whole brain DVRs in MCI was similar to that in AD (MCI: 2.32 ± 0.28). Among PIB positive patients, eleven of 16 AD patients showed a significant reduction of cortical glucose metabolism in temporo-parietal, frontal, and posterior cingulate cortex and precuneus on [^{18}F]FDG-PET 3D-SSP images (classic metabolic AD-pattern). The other 5 patients showed hypometabolism in posteior cingulate and precuneus, but not in cortical regions. In contrast, three of 12 MCI patients had the classic metabolic AD-pattern on 3D-SSP images. Only 3 patients showed no hypometabolism in any cortical regions. In AD and MCI patients with typical cortical PIB retention, there was no correlation between PIB and FDG SUVR values in different cortical regions.

Conclusion: The [^{11}C]PIB-PET scan could potentially determine characteristic cerebral pattern of amyloid-beta plaque load. This amyloid plaque formation is not directly responsible for cerebral glucose metabolism in cortical regions.

Regional analysis of FDG and PIB-PET images in normal aging, mild aging, mild cognitive impairment and Alzheimer's disease

POSTER ABSTRACT

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Objective: To compare the diagnostic value of the relative cerebral metabolic rate of glucose (MRglc) using [^{18}F]FDG-PET with amyloid-beta pathology using [^{11}C]PIB-PET in the evaluation of patients with Alzhieimer's disease (AD) and patients with mild cognitive impairment (MCI) as compared to normal elderly (NL).

Methods: Thirty seven subjects, including 7 NL, 13 MCI, and 17 AD patients, received clinical, neuropsychological, MRI, FDG and PIB-PET exams. Parametric images of PIB uptake and MRglc were sampled using an automated region-of-interest (ROI) analysis technique, and the regional MRglc and PIB uptake measures examined with logistic regressions as diagnostic discriminators of the NL, MCI, and AD groups.

Results: On FDG-PET, AD showed global MRglc reductions and MCI showed reduced hippocampus (HIP) and inferior parietal lobe (IP) MRglc as compared to NL. On PIB-PET, AD patients showed significantly increased PIB uptake in the middle frontal gyrus (MFG), posterior cingulate cortex (PCC), and IP cortex ($p < 0.05$). PIB uptake in MCI subjects was either AD-like or NL-like. HIP MRglc and MFG PIB uptake were the most significant discriminators of NL from MCI and NL from AD. Using these two best FDG-PET and PIB-PET measures, the two modalities showed high diagnostic agreement for AD (94%) and poor agreement for MCI (54%). For the NL and MCI discrimination, combining the 2 best measures improved the accuracy to from 75% (PIB-PET) and 85% (FDG-PET) to 90% (combined).

Conclusion: For AD and MCI the brain regions showing hypometabolism were different from those showing PIB uptake, therefore indicating a disassociation between neuronal metabolism and fibrillar amyloid deposition. FDG is superior to PIB in the classification of NL and MCI, but the modalities are of equal value for AD. Combining the two PET modalities improved the diagnostic accuracy of PIB for MCI. Longitudinal studies and post mortem assessments are needed to validate the FDG and PIB-PET diagnoses.

Clinical evaluation of ^{18}F-labeled AV-138 for PET amyloid imaging in Alzheimer's disease

POSTER ABSTRACT

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Objective: [^{11}C]PIB-PET has been shown to correlate with the presence of brain amyloid in patients with neurodegenerative disease. The short half-life of ^{11}C makes the clinical use of [^{11}C]PIB problematic. Imaging using [^{18}F]PET amyloid ligands would be preferable. Therefore, the brain amyloid imaging agent [^{18}F]AV-138 was evaluated clinically.

Methods: Five normal control (MMSE median 29.5, range 29–30) subjects (NC) and 4 mild to moderate Alzheimer's disease (MMSE median 22, range 14–24) patients (AD) were imaged with [^{18}F]AV-138 PET. Subjects received 5 mCi (mean 4.6, range 3.0–5.5) of [^{18}F]AV-138 and thereafter dynamic brain PET imaging for 3 hours was performed. Regional brain accumulation was evaluated with Logan plot analysis over 90 minutes to obtain a distribution volume ratio (DVR) and a 40–60 minute frame set was used to obtain a delay phase uptake ratio (DUR); the cerebellum was used as a reference region for both. PET image volumes were co-registered the individuals MRI scans. MRI scans were spatially normalized to the MNI template by which regions were defined. Global DVR and DUR ratios were calculated using a summation of pre-frontal, orbito-frontal, parietal, temporal, anterior cingulate, and posterior cingulate regional activity. Results from NC and AD subjects were compared.

Results: [^{18}F]AV-138 median global DVR (DUR) values were 1.14 (1.18) and 1.55 (1.51) for NC and AD subjects, respectively, which showed good separation of the groups ($p = 0.030$ for DVR and $p = 0.056$ for DUR). Bland-Altman plot comparing the DVR and DUR methods suggested good correlation. The DUR for [^{11}C]PIB and [^{18}F]AV-138 in an AD patient was 2.23 and 1.53, respectively, and was 1.10 and 1.11 in a NC subject.

Conclusion: [^{18}F]AV-138 is able to distinguish NC from AD subjects based on amyloid-related uptake as seen on PET.

Voxel-based analysis of [^{11}C]PIB scans for diagnosing Alzheimer's disease

POSTER ABSTRACT

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Introduction: The PET radioligand N-methyl-[^{11}C]2-(4-methylaminophenyl)-6- hydroxybenzothiazole (also known as [^{11}C]6-OH-BTA-1 and [^{11}C]PIB), binds to amyloid beta (Aβ) which accumulates pathologically in Alzheimer's Disease (AD). Although [^{11}C]PIB accumulation is greater in AD than healthy controls (CTR) at a group level, the optimal method for using individual scans to aid in diagnosis has not been established. We assessed the use of data determined standardized voxels of interest (VOI) to improve the classification capability of [^{11}C]PIB scans in Alzhiemer's patients.

Methods: Sixteen CTR and fourteen AD age-matched subjects were recruited. All subjects underwent a [^{11}C]PIB scan and had a structural MRI. Using the Logan graphical method with cerebellar gray matter as the reference region, BPND (a measure of amyloid burden) was calculated for each voxel. Voxel maps were then partial volume corrected and spatially normalized by MRI onto a standardized template. The subjects were divided into two cohorts; the first cohort (12 CTR, 9 AD) was used for SPM analysis and delineation of data-based VOIs. These VOIs were tested in the second cohort (4 CTR, 5 AD) of subjects.

Results: SPM analysis revealed significant differences between CTR and AD groups. The VOI map determined from the first cohort resulted in complete separation between the CTR and AD subjects in the second cohort ($p < 0.02$). BPND values based on this VOI were in the same range as other reported individual and mean cortical VOI results.

Conclusions: Using a standardized template VOI that is optimized for CTR/AD group discrimination provides excellent separation of CTR and AD subjects based on [^{11}C]PIB uptake. This VOI template can serve as a potential replacement for manual VOI delineation and can be completely automated, facilitating potential use in a clinical setting.

In vivo detection of Alzheimer's disease-linked Aβ peptide accumulation in the lens by non-invasive quasi-elastic light scattering

POSTER ABSTRACT

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Background: AD is characterized by excessive accumulation of Aβ peptide in the brain, which begins years before the onset of cognitive symptoms. Pre-symptomatic detection of the underlying disease will facilitate clinical testing and early intervention. We previously reported the presence of Aβ and distinctive AD-linked amyloid pathology in the lenses of AD patients (Goldstein *et al*., *Lancet*, 2003). Here we utilized non-invasive quasi-elastic light scattering (QLS) in the Tg2576 (Tg) mouse model of AD to quantitatively assess Aβ peptide deposition in the lens as a marker for AD-linked Aβ accumulation in the brain.

Objectives: To develop and test low-energy infrared laser quasi-elastic light scattering (QLS) technology for early quantitative detection and monitoring of AD-linked amyloid lens pathology *in vivo*.

Methods: Non-invasive infrared QLS, slit lamp stereophotomicroscopy, quantitative western blot, fluoro-ELISA, immunogold EM, tryptic digest MS sequencing.

Results: *In vivo* QLS measurements in non-anesthetized mice discriminated Tg mice from age-matched wild-type controls beginning at 10 months of age when Tg lenses were clear and amyloid plaque was not detectable in Tg brain. Human Aβ was generated from amyloid precursor protein in Tg mouse lens and confirmed by tryptic digest sequencing. In Tg2576 mouse lens. Human Aβ accumulated in the cytoplasm of lens fiber cells as electron-dense microaggregates that scatter light. *In vitro*, human Aβ promoted aggregation of mouse lens protein and QLS signal changes similar to those detected *in vivo*.

Conclusions: Our data support the use of *in vivo* lens QLS for quantitative non-invasive detection of AD-linked Aβ amyloid molecular pathology as an early AD-linked biomarker.

In vivo administration of a novel peptide based imaging agent for Alzheimer's disease

POSTER ABSTRACT

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One of the pathological features of Alzheimer's disease (AD) is the conversion of a normal soluble protein into insoluble beta amyloid aggregates. Aggregation and deposition of amyloid beta *in vivo* may precede clinical symptoms of AD by many years providing a window in which to diagnose AD and monitor progression prior to neurological decline. The primary objective was to develop an easily administered imaging agent that provides an early measure of plaque or amyloid aggregate burden associated with AD. We previously reported a novel Pronucleon™ peptide technology that specifically measures beta amyloid aggregates. The Pronucleon™ peptide undergoes a sequence-specific conformational change in the presence of the amyloid beta aggregates which can be used to measure beta amyloid in CSF and blood. Using the same Pronucleon™ peptide we have demonstrated *ex vivo* plaque specific staining on tissue sections. These, *ex vivo*, fluorescent bodies are plaque like in morphology and co merge with ThioflavinS staining. In addition, we have delivered Pronucleon™ peptides via *in vivo* peripheral administration to hAPP transgenic mice that develop extensive plaque pathology. Sections from these mice were subjected to *ex vivo* analyses including fluorescence, ThioflavinS staining, and anti-amyloid staining. Following *in vivo* administration of the Pronucleon™ peptide extensive labeling of plaques in the hippocampus and cortex of transgenic mice was observed. Fluorescent structures had plaque like morphology and co merged with anti-amyloid antibody or ThioflavinS staining on sequential sections. A significant positive correlation was observed between Pronucleon™ peptide labeling and ThioflavinS staining. These data suggest that the Pronucleon™ peptide sequence can efficiently cross the blood brain barrier, labelplaques, and may be an effective tool for *in vivo* imaging.

Amyloid and glucose metabolism in early versus late-onset AD: a comparative [^{11}C]PIB and [^{18}F]FDG PET study

POSTER ABSTRACT

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Objective: To compare the distribution and burden of fibrillar beta-amyloid ([^{11}C]PIB-PET) and glucose hypometabolism ([^{18}F]FDG-PET) in patients with early (age < 60) versus late (age > 60) age-of-onset Alzheimer's disease (AD).

Methods: Patients meeting criteria for AD (NINCDS-ADRDA, n = 20) were divided into early-onset (EO, n = 12, mean age at onset 52.2 ± 4.8) and late-onset (LO, n = 8, 66.6 ± 4.9) based on estimated age at first symptom. Patients were matched for disease duration (EO 6.3 ± 3.4, LO 6.2 ± 2.6, p = 0.99), MMSE (EO 18.7 ± 6.9, LO 21.8 ± 5.4, p = 0.30) and CDR sum-of-boxes (EO 6.2 ± 4.2, LO 5.5 ± 1.8, p = 0.65). A group of cognitively normal controls (n = 12, mean age 73.9 ± 6.1) was studied for comparison. PIB-PET images were analyzed using Logan graphical analysis (cerebellar reference) and FDG-PET images were divided by mean activity in pons. PET volumes were normalized to the MNI template. Whole-brain voxel-wise differences in PIB and FDG were assessed using statistical parametric mapping (SPM2).

Results: Compared to controls, both EO and LO patients showed increased PIB uptake throughout bilateral frontal, parietal and lateral temporal cortex and striatum (p < 0.01, FDR-corrected). The direct comparison of PIB uptake in EO and LO patients revealed elevated amyloid in left precuneus and left middle and inferior frontal gyri in LO compared to EO AD (p < 0.001 uncorrected). Compared to controls, both EO and LO patients showed significant reductions in glucose metabolism in bilateral temporoparietal, medial temporal and frontal cortex (p < 0.05, FDR-corrected). When directly compared to each other, EO patients showed greater hypometabolism than LO patients in bilateral posterior cingulate, precuneus, middle temporal gyrus and left superior temporal gyrus (p < 0.001 uncorrected).

Conclusions: A comparable distribution of fibrillar beta-amyloid was associated with greater metabolic deficits in early-onset AD. These results suggest that metabolic vulnerability to beta-amyloid may be increased in early age-of-onset AD.

Immature diffuse plaques found at autopsy in a patient with normal-range [^{11}C]PIB binding *in vivo*

POSTER ABSTRACT

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Background: The sensitivity of [^{11}C]PIB-PET for very early amyloid pathology is not well established. We report a patient with familial frontotemporal lobar degeneration with motor-neuron disease (FTLD-MND) who showed control-level [^{11}C]PIB uptake on PET, but a moderate degree of immature diffuse plaques (DPs) at autopsy. The patient was homozygous for apolipoprotein E4 and did not have a progranulin mutation.

Methods: The patient underwent [^{11}C]PIB-PET at age 58. Distribution volume ratios (DVRs) were calculated (Logan graphical analysis, cerebellar gray matter reference) and partial volume correction was performed based on a T1-weighted MRI. Native space regional [^{11}C]PIB DVRs were derived using automated procedures. The patient died eleven months later and underwent autopsy. [^{11}C]PIB DVRs were compared to autopsy findings and to values in AD patients (n = 8, age 66.9 ± 7.1) and controls (n = 18, age 72.2 ± 6.2, all negative for cortical PIB by visual inspection).

Results: The primary pathological diagnosis was FTLD-MND with ubiquitin-and TDP-43-immunoreactive inclusions. Bielschowsky silver staining revealed sparse to frequent DPs in various cortical regions. Neuritic plaques were rare. Aβ immunohistochemistry using an N-terminus-specific polyclonal antibody did not stain the vast majority of DPs, but did demonstrate mild amyloid angiopathy in calcarine cortex. Neurofibrillary tangle pathology conformed to Braak Stage 1. The patient's PIB DVRs were in the control range in regions in which moderate or moderate-to-frequent DPs were found on autopsy: superior parietal lobule DVR = 1.51, mean controls 1.50 ± 0.11, mean AD 2.10 ± 0.34; inferior temporal cortex DVR = 1.30, controls 1.31 ± 0.07, AD 2.16 ± 0.50; calcarine cortex DVR = 1.12, controls 1.27 ± 0.10, AD 1.46 ± 0.20. DVRs in a similar range were found in regions with absent to sparse DPs.

Conclusions: The findings in this case suggest that PIB-PET may be insensitive to immature DPs lacking Aβ immunoreactivity.

Cognitive change in non-demented subjects with amyloid deposition

POSTER ABSTRACT

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Background: Amyloid deposition, as measured with Pittsburgh Compound-B (PIB)-PET, has been observed in a substantial proportion of non-demented subjects. However, longitudinal followup will be required to understand the implication of amyloid deposition in of these subjects.

Objective: To determine whether non-demented PIB-positive subjects show evidence of cognitive decline that is consistent with prodromal AD.

Methods: Thirty-one non-demented older subjects (CDR 0 n = 16; CDR 0.5 n = 15); underwent PIB-PET at baseline and neuropsychological assessments at baseline and follow-up (mean duration = 11.8 ± 4.2 months). PIB-PET DVR values were averaged over a composite cortical region. Multiple linear regression analyses relating PIB retention at baseline with neuropsychological test scores at follow-up were performed, covarying age, education, estimated IQ and baseline neuropsychological performance.

Results: At baseline, 10 subjects were classified as PIB-negative (mean age = 71.9 ± 8.1, mean MMSE = 29.3 ± 1.1, estimated IQ = 126.4 ± 5.8) and 21 were PIB-positive (mean age = 76.8 ± 5.7, mean MMSE = 28.9 ± .81, estimated IQ = 124.0 ± 9.8). We found a significant relationship between PIB retention at baseline and decline in neuropsychological performance on the Buschke Selective Reminding Test (SRT), 30-minute delayed recall ($p = 0.045$). There was also a trend toward significance on the 30 minute delayed multiple-choice SRT ($p = 0.145$).

Conclusions: These preliminary findings suggest a small but detectable association of amyloid deposition at baseline with change in memory performance one year later, in a sample of non-demented, highly intelligent subjects. High cognitive reserve may be contributing to the maintenance of cognitive stability. Ongoing longitudinal follow-up will be necessary to determine if high amyloid burden is predictive of further cognitive decline and eventual clinical diagnosis of AD.

Follow-up study of a new amyloid binding ligand carbon-11 3'-F-PIB ([^{11}C]AH110690) in Alzheimer's disease

POSTER ABSTRACT

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We explored the usefulness of two novel candidates for brain amyloid imaging denoted as 3'-F-PIB and 4'-F-PIB. The 3'-F-PIB was labelled with carbon-11 ([^{11}C]AH110690) and the 4'-F-PIB with fluorine-18 ([^{18}F]AH110691). [^{18}F]AH110691 did not exhibit adequate brain uptake and further studies were conducted with [^{11}C]AH110690. We investigated 9 patients with Alzheimer's disease (mean age 73.2 years, MMSE score 22.9) and 10 elderly healthy volunteers (mean age 67.8 years, MMSE score 29.1). Each subject was scanned twice with [^{11}C]AH110690 with a one-year interval.

PET scanning was performed with a Siemens HR+ scanner, with a mean injected activity of 442 MBq. Imaging data were realigned and 60-90 min sum images were created. A ROI template was applied and target region to reference region ratios were computed. [^{11}C] 3'-F-PIB uptake was quantified by calculating distribution volume ratios using the Logan graphical method with the cerebellar cortex as reference region.

At baseline the AD patients showed increased [^{11}C]AH110690 uptake in the frontal cortex (to 143% of the control mean, $p < 0.01$), parietal cortex (to 144%, $p < 0.01$), anterior cingulate (to 136%, $p < 0.01$), posterior cingulate (to 126%, $p < 0.05$), and occipital cortex (to 126%, $p<0.05$). No significant differences were seen n the medial temporal lobe, white matter or pons.

At follow-up the MMSE score had declined by 1.1 point and the ADAS- Cog score increased by 2.2 points in the AD subjects. There were no changes in [^{11}C]AH110690 uptake during the follow-up, with mean uptake ratios varying between 98 to 103 % of the baseline values. Brain MRI showed increases in ventricular size and increasing atrophy in the temporal and parietal cortices in the AD patients but not in the controls.

Our results suggest that [^{11}C]AH110690 is a useful ligand for brain amyloid imaging in human subjects with AD. There was no significant change in the uptake of this amyloid ligand during clinical progression of AD over one year. Further studies are ongoing with fluorine-18 labelled AH110690.

In vivo characterization of ^{18}F-BAY94-9172: a novel β-amyloid PET ligand for the diagnosis of Alzheimer's disease

POSTER ABSTRACT

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Background: Access to the Aβ tracer [^{11}C]PIB is restricted by its short half-life. [^{18}F]BAY94-9172 is a new Aβ tracer with a longer decay half-life better suited to widespread clinical use. We evaluated this tracer in humans and calculated the radiation dosimetry.

Methods: Fifteen healthy elderly controls (HC), 15 AD, and 5 FTLD patients with mild to moderate dementia, underwent PET imaging after injection of 300 MBq of [^{18}F]BAY94-9172. Scans were acquired 90–120 min. post injection and Standardized Uptake Value ratios (SUVR) were calculated using the cerebellum as reference region. Three of the HC underwent serial whole body scans for the determination of biodistribution and radiation dosimetry calculation using OLINDA.

Results: Cortical [^{18}F]BAY94-9172 binding was markedly elevated in all AD patients. There was no cortical binding in most FTLD or HC subjects. One FTLD and three HC showed mild cortical binding but less than in AD. Binding was greatest in the precuneus/posterior cingulate and frontal cortex, followed by lateral temporal and parietal cortex. [^{18}F]BAY94- 9172 binding did not correlate with dementia severity in AD. Higher SUVR in neocortical areas were observed in AD (2.02 ± 0.28) when compared with HC (1.29 ± 0.17) and FTLD (1.22 ± 0.17). Visual interpretation was 100% sensitive and 90% specific for detection of AD. Whole body imaging and blood measurements showed rapid metabolism with predominantly hepatic clearance. The mean effective radiation dose was 14.67 ± 1.39 μSv/MBq resulting in radiation exposure of 4.4 mSv from a 300MBq (8 mCi) study.

Conclusions: [^{18}F]BAY94-9172 should assist in the early diagnosis of AD and the differential diagnosis of AD from FTLD. The radiation dose compares favourably to other radiological investigations and is slightly less than that of [^{18}F]FDG. The robust visual findings, acceptable radiation exposure, and the longer radioactive half-life make [^{18}F]BAY94-9172 attractive for clinical use.

Longitudinal changes in rCBF and amyloid deposition in non-demented elderly

POSTER ABSTRACT

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Introduction: In an initial investigation of associations between longitudinal change in regional cerebral blood flow (rCBF) and amyloid deposition in 28 non-demented older adults, individuals with high compared to low amyloid deposition showed both regions of greater decreases and greater increases in rCBF change. Here, we extend these findings to a larger sample using a confirmatory analysis of regions identified in our initial analysis.

Methods: 57 non-demented participants (baseline age 67.8 ± 6.1 years) from the Baltimore Longitudinal Study of Aging underwent yearly [^{15}O]H2O PET scans over 8 years and a single [^{11}C]PIB PET scan on average 11 years after the initial rCBF study. [^{11}C]PIB distribution volume ratios (DVR) of regions of interest were estimated by fitting a reference tissue model to the measured time activity curves. Based on the distribution of mean neocortical DVRs for amyloid binding, individuals were divided into tertiles. Longitudinal changes in rCBF for the upper (n = 19) versus the lower tertile (n = 19) were investigated using a region-specific analysis in SPM2. A masked analysis (p = 0.05) limited to voxels showing significant differences in longitudinal rCBF change between high and low amyloid groups in our initial report was performed, adjusting for sex and time between the last rCBF and [^{11}C]PIB scans.

Results: SPM analysis confirmed that non-demented older adults with higher neocortical amyloid deposition show greater longitudinal rCBF decreases in right cingulate gyrus, right supramarginal gyrus, midbrain, and left thalamus, and greater longitudinal rCBF increases in left inferior frontal gyrus, left medial frontal gyrus, left inferior parietal lobule, and right precuneus.

Discussion: In this larger sample, we confirmed that non-demented older adults with higher amyloid load show both regions of greater longitudinal decline and greater longitudinal increase in rCBF over time. These findings suggest that increased amyloid deposition in individuals without dementia is associated with a complex pattern of rCBF change.

Phase I study of the ^{18}F-labelled benzothiazole derivative [^{18}F]AH110690 as an *in vivo* biomarker of AD-related brain amyloidosis

POSTER ABSTRACT

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Background: Access to the [^{11}C]labeled Aβ amyloid ligand Pittsburgh Compound B is limited by the need of an on-site cyclotron therefore an F-18 labelled derivative [^{18}F]AH110690 was developed.

Objectives: 1. To evaluate the safety of [^{18}F]AH110690 in cognitively intact volunteers (HV) and in subjects with early-stage clinically probable Alzheimer's disease (AD). 2. To compare [^{18}F]AH110690 brain retention in HV versus AD.

Methods: A multi step phase I, single-centre study trial was conducted: after evaluation of whole-body biodistribution and radiation dosimetry (n = 6 HV, 4 men/2 women, age 51–73 yrs, step 1), we dynamically scanned 3 HV (1 men/2 women, age 56–71 yrs, education 18–20 yrs, MMSE 28–30 out of 30, CDR 0) and 3 AD patients (3 men, age 55–68 yrs, education 18–30 yrs, MMSE 22–24, CDR 0.5, time-to-AD-diagnosis 1–1.5 yrs) on a Siemens Biograph PET-CT scanner during 0–90, 150–180 and 220–250 min post-injection with arterial sampling (step 2). Distribution volume ratios (DVR) were computed using Logan graphical analysis (60–190 min time interval) with the cerebellar cortex as reference region. We used the DVRs to compare brain distribution between HV and AD. Step 3 (n = 5 HV, 5 AD) using a shorter scanning window is ongoing.

Results: Safety measures remained within the normal range. On the basis of step 1 the injected dose in step 2 was set at approximately 185MBq. In each of the 3 AD patients (DVR 1.49–1.71), specific binding in neocortical regions was higher than in each of the 3 healthy controls (DVR 1.10–1.43), with highest values in lateral frontal and lateral temporal as well as medial parietal cortex and lowest values in occipital cortex. Inversely, in HV DVR in white matter was higher than in AD.

Conclusions: These initial findings indicate the potential of [^{18}F]AH110690 PET as a novel *in vivo* marker of AD-related brain amyloidosis with binding characteristics similar to that of [^{11}C]PIB, but with higher accessibility to clinical centres.

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