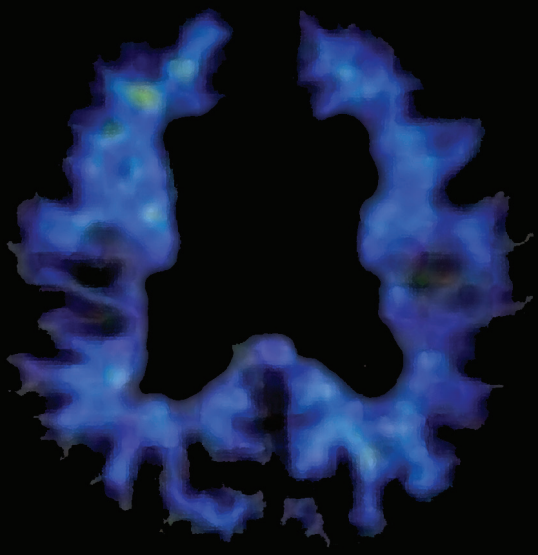

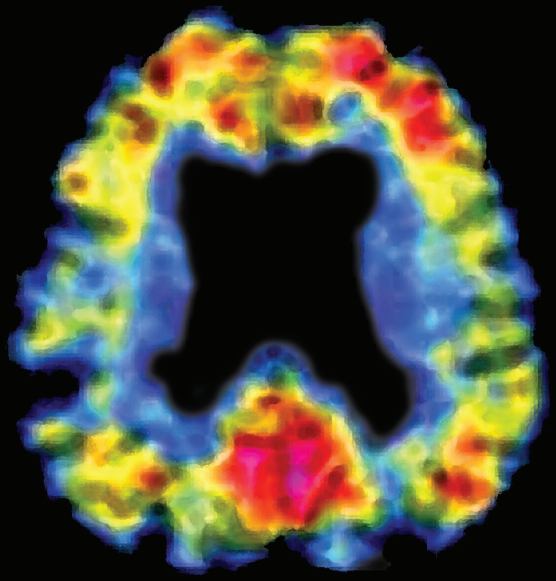

Human Amyloid Imaging

Seattle 2009

Friday, April 24th 2009

The Crowne Plaza Hotel

Schedule & Abstract Book

Schedule - Human Amyloid Imaging Meeting - 24th April 2009
The Crowne Plaza Hotel, Seattle

07:30 – 08:00	**Continental Breakfast; Posters to be installed**
08:00 – 08:15	**Introduction**
08:15 – 09:30	**Session 1: Amyloid and FDG Metabolism** **William Jagust, Agneta Nordberg (Chairs)**
08:15 – 08:30	Elevated beta-amyloid deposition is related to reduced posterior cingulate glucose metabolism in normal elderly subjects *E Mormino, University of California, Berkeley, CA, USA*
08:30 – 08:45	Disruption of FDG-PET functional networks in amyloid positive normal elderly *J Becker, Massachusetts General Hospital, MA, USA*
08:45 – 09:00	Combining amyloid imaging and measurement of regional cerebral glucose metabolism to evaluate dementia state and progression *D Matthews, Abiant Inc/New York University, NY, USA*
09:00 – 09:15	Clinical different stage of Alzheimer's disease associated with amyloid deposition by [^{11}C] PiB-PET imaging *S Hatashita, Shonan-Atsugi Hospital & Clinic, Kanagawa, Japan*
09:15 – 09:30	Comparison of ^{11}C-PiB and ^{18}F-FDG PET in the differential diagnosis of Alzheimer's disease and frontotemporal lobar degeneration *GD Rabinovici, UCSF Memory and Aging Center, CA, USA*
09:30 – 10:00	**General Discussion (Chairs and Speakers)**
10:00 – 10:15	**Morning Break**
10:15 – 11:00	**Session 2: Cognitive Reserve, Network Integrity, ApoE** **Mark Mintun, William Klunk (Chairs)**
10:15 – 10:30	Challenging tests of episodic memory reveal association with amyloid burden in cognitively normal older individuals *D Rentz, Massachusetts General Hospital, MA, USA*
10:30 – 10:45	Relationship of amyloid deposition to default network functional connectivity in non-demented older adults *T Hedden, Harvard University, MA, USA*
10:45 – 11:00	Relationship between ApoE genotype and β-amyloid deposition: results of florpiramine F18 (^{18}F-AV-45) PET imaging in asymptomatic elderly, mild cognitive impairment subject and clinical dementia patients *D Skovronsky, Avid Radiopharmaceuticals, Inc, PA, USA*
11:00 – 11:45	**Keynote presentation by Marsel Mesulam, Ruth and Evelyn Dunbar Professor of Neurology, Psychiatry and Psychology, Director, The Cognitive Neurology and Alzheimer's Disease Center (CNADC), Feinberg School of Medicine, Northwestern University (30 min talk / 15 min Q&A)**

11:45 – 13:00	**Buffet, Sit-down Lunch; Posters will be up**
13:00 – 14:15	**Session 3: Longitudinal Studies** **Keith Johnson, Reisa Sperling (Chairs)**
13:00 – 13:15	Longitudinal patterns of amyloid deposition in non-demented older adults *S Resnick, National Institute on Aging/NIH; Johns Hopkins Medical Institutions, MD, USA*
13:15 – 13:30	Serial PiB and MRI in normal, MCI and AD: implications for sequence of pathological events in AD *C Jack, Mayo Clinic, MA, USA*
13:30 – 13:45	Potential of PET to monitor development of Aβ plaques in the non-demented *M Mintun, Washington University School of Medicine, MO, USA*
13:45 – 14:00	A five years follow-up study with PiB in Alzheimer patients *A Nordberg, Karolinska Institutet, Uppsala, Sweden*
14:00 – 14:15	Longitudinal changes in amyloid deposition in normal elderly, mild cognitive impairment and AD *W Klunk, University of Pittsburgh, PA, USA*
14:15 – 15:00	**Keynote presentation by Tom Montine, Alvord Endowed Chair in Neuropathology, Professor of Pathology, Director, Division of Neuropathology, Adjunct Professor of Neurological Surgery, University of Washington, Adjunct Professor of Neurology, Oregon Health & Sciences University (30 min talk / 15 min Q&A)**
15:00 – 15:15	**Afternoon Break**
15:15 – 16:00	**Session 4: Neuropathology** **Chester Mathis, Tom Montine (Chairs)**
15:15 – 15:30	*In vivo* amyloid deposition detected by [^{11}C]PiB PET and neuropathology in non-demented older adults *J Sojkova, National Institute on Aging/NIH; Johns Hopkins Medical Institutions, MA, USA*
15:30 – 15:45	PiB binding of cerebral Aβ may lag clinical, cognitive, and CSF markers in Alzheimer's disease *J Morris, Washington University School of Medicine, MO, USA*
15:45 – 16:00	Assessing the threshold for *in vivo* detection of β-amyloid plaques using PiB-PET imaging *C Mathis, University of Pittsburgh, PA, USA*
16:00 – 16:30	**General Discussion (Chairs and Speakers)**
16:30 – 18:00	**Poster Session: 15 Posters** Wine and cheese to be served

Elevated beta-amyloid deposition is related to reduced posterior cingulate glucose metabolism in normal elderly subjects

EC Mormino, AO Hayenga, GD Rabinovici, S Onami, A Smiljic, SL Baker, CM Madison, BL Miller, WJ Jagust.

University of California, Berkeley, CA, USA

Objective: To evaluate the association between beta-amyloid deposition and glucose metabolism in cognitively normal control (NC) subjects.

Methods: 32 NC subjects and 12 Alzheimer's disease (AD) subjects underwent PET (PiB and FDG) and structural MRI scanning (NC: mean age=73.72, SD=6.4, mean MMSE=29.2, SD=0.9; AD: mean age=64.72, SD=11.57, mean MMSE=20.83, SD=7.71). Anatomical regions of interest (ROIs) were defined on structural MRI scans with Freesurfer software. PiB frames 35-90 minutes post-injection were used to create distribution volume ratios (DVRs, Logan plotting with cerebellum reference region), whereas FDG frames were summed and normalized to mean pons activity. PET images were corrected for partial volume effects. A neocortical PiB index was obtained for each subject by averaging DVR values across multiple ROIs (prefrontal, lateral temporal, parietal, and cingulate). NC subjects were divided into high and low PiB groups based on a median split of PiB index values. FDG images were spatially normalized to a study specific template and smoothed 12mm. FDG values at each voxel were contrasted between AD and low PiB NC, as well as high PiB NC and low PiB NC groups. Group differences in FDG were also explored using a native-space ROI approach (*a priori* ROIs: isthmus/posterior cingulate, precuneus, supramarginal, inferior parietal, superior temporal gyrus, middle frontal gyrus).

Results: The voxelwise FDG analysis revealed large areas of reduced metabolism in AD compared to the low PiB NC group (bilateral medial parietal, posterior cingulate, lateral temporoparietal, lateral prefrontal cortex; $p<0.001$, $k=100$), whereas the contrast between high and low PiB NC groups revealed localized hypometabolism in the right posterior cingulate ($p<0.05$, $k=100$). Post-hoc examination of the right posterior cingulate cluster revealed that the high PiB NC group fell in between AD and low PiB NC groups. This pattern of results was confirmed in the native space ROI approach.

Conclusions: Although diffuse hypometabolism is observed throughout association cortices in AD, the correlation between beta-amyloid deposition and glucose metabolism in normal elderly individuals is restricted to the posterior cingulate. This finding indicates that beta-amyloid deposition is associated with hypometabolism in the posterior cingulate well before the onset of cognitive decline.

Disruption of FDG-PET functional networks in amyloid positive normal elderly

JA Becker, T Hedden, A Mehta, B Fischl, DR Rentz, RA Sperling, RL Buckner, KA Johnson.

Massachusetts General Hospital and Harvard Medical School, Massachusetts, USA.

Background: Amyloid deposition is commonly found in 30-50% of normal elderly, but the functional significance of this finding has not been established.

Objective: To evaluate the functional significance of amyloid deposition in normal aging, we utilized a novel method to derive cortical maps of FDG functional correlations. We then compared the FDG functional connectivity between cognitively normal older subjects with and without amyloid burden, as assessed by PiB PET.

Methods: FDG and PiB PET were acquired in 53 normal subjects (CDR0; mean [SD] age=73.3 [7.1] years) and resampled to the vertices of a standardized surface space using Freesurfer. FDG data were summed over a 30 minute acquisition and scaled by cerebellar cortex; PiB was expressed as the DVR using the Logan method with cerebellar cortex input function. A seed region 5mm in radius was placed at a surface vertex in the medial temporal lobe centered at Talairach coordinates x=-21, y=-25, z=-15. The correlation between the average FDG value in the seed region and vertex FDG value was calculated across subjects at each vertex of the standardized surface space. Subjects were dichotomized into PiB+ and PiB- based on a global average PiB DVR threshold of 1.25. Connectivity differences between the two groups were measured by the contrast of these vertex-level correlations.

Results: The contrast of FDG connectivity in PiB positive versus negative subjects revealed significant reduction of seed-to-vertex correlations from medial temporal lobe to posterior cingulate-precuneus, ventromedial prefrontal, and inferior parietal lobular cortex ($p<0.0001$ at the vertex level, uncorrected for multiple comparisons).

Conclusions: Amyloid deposition is associated with specific disruption of hippocampal-cortical metabolic connectivity in the default network in normal elderly. These findings support the hypothesis that occult amyloid deposition is linked to early brain dysfunction, even among cognitively intact older individuals.

Combining amyloid imaging and measurement of regional cerebral glucose metabolism to evaluate dementia state and progression

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Abiant Inc, New York University Center for Brain Health, New York, USA.

Amyloid imaging with [^{11}C-PiB] PET and similar tracers has shown great promise in increasing the specificity of Alzheimer's Disease (AD) diagnosis and in measuring therapeutic impact on amyloid accumulation. Despite marked differences in PiB retention between cognitively normal (NL) individuals and AD patients, high tracer uptake (reflecting higher amyloid burden) is measured in ~25% NL, while uptake within normal range (low burden) is found is ~10% AD patients. Moreover, a continuum of low to high burden is found in MCI patients. Amyloid levels have been found to plateau in later disease stages while clinical symptoms continue to progress (Klunk, 2006). Measurement of regional glucose metabolism (rCMRglc) using FDG-PET provides complementary information that can be used to evaluate disease status and progression. Amyloid levels were measured in the longitudinal [^{11}C]-PiB scans of 50 ADNI subjects (36 M, 14 F) who were followed for 24 +/- 12 months. This included 11 NL who remained NL, 3 NL who declined to MCI, 21 non-converting MCI, 6 MCI who declined to AD, and 6 AD. PiB uptake was measured in 32 pre-selected regions of interest (ROI) and normalized to cerebellum (Price, 2005). rCMRglc was measured in FDG-PET scans of the same subjects within the same ROI. Our main analyses focused on the posterior cingulate cortex, medial frontal and prefrontal gyri, parietal and temporal lobes, thalamus, and hippocampus. ROI measurements were made using an automated method that has been demonstrated to achieve accurate, rapid sampling, and to optimize sensitivity and specificity without compromise from spatial normalization, smoothing, adjacent region spillover, atrophy, and white matter noise, for both FDG and PiB-PET (Mosconi, 2005; Li, 2008). We observed a negative correlation between hippocampal (HIP) rCMRglc at baseline and subsequent amyloid load. In subjects who showed clinical progression (converting to MCI or AD, or with declining cognitive scores), rCMRglc levels in HIP and other AD regions declined, while amyloid load increased in most but not all subjects. The combination of information obtained from amyloid imaging with rCMRglc information on neuronal function, particularly in the HIP, can provide enhanced insight to the onset and progression of dementias.

* Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu\ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. ADNI investigators include (complete listing available at www.loni.ucla.edu\ADNI\Collaboration\ADNI_Manuscript_Citations.pdf).

Clinical different stage of Alzheimer's disease associated with amyloid deposition by [^{11}C] PiB-PET imaging

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Objective: The AD pathology is detectable *in vivo* using selective imaging ligand for beta-amyloid by carbon 11-labeled Pittsburgh Compound B ([^{11}C]-PiB) PET. We clarify the association between cerebral amyloid load, glucose metabolism and cognitive function in subjects with Alzheimer's disease (AD), mild cognitive impairment (MCI) and well-documented cognitive function.

Method: 114 patients who met criteria for AD or MCI and 91 age-matched healthy controls (HC) were included. Subjects underwent cognitive testing and 60-min dynamic [^{11}C]-PiB PET and 15-min static [^{18}F]-FDG PET imaging. [^{11}C]-PiB data was acquired from 35-60 min after injection. Regions of interest (ROI) were defined on co-registered MRI. Distribution volume ratios (DVR) 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.

Result: All of 56 AD and 28 of 58 MCI had a robust increase of PiB binding in different cortical areas (typical PiB AD-pattern). On FDG-PET 3D-SSP images, twenty-nine (55%) of AD and two (8%) of PiB positive MCI showed a significant reduction of glucose metabolism in temporo-parietal cortex (metabolic AD-pattern). Furthermore, seventeen HC had same typical PiB AD-pattern, but no metabolic AD-pattern. The mean DVR values of whole cortical areas in PiB positive groups increased significantly compared with PiB negative MCI or HC. The DVR value in AD (MMSE: 18.84±5.95, CDR: 1.03±0.63) was the highest among all groups (2.29±0.45, $p<0.01$). The DVR values in PiB positive MCI (MMSE: 26.96±1.91, CDR: 0.5) and PiB positive HC (MMSE: 29.06±1.09, CDR: 0) were 2.06±0.28 and 2.08±0.35, respectively. The cortical PiB retention was significantly correlated negatively to MMSE scores ($r=-0.23$, $p<0.05$), and positively to CDR sum of the box scores ($r=0.22$, $p<0.05$).

Conclusion: The [^{11}C]-PiB PET determines cortical amyloid load at different stage of AD, but the pattern of amyloid deposition is not identical to hypometabolic pattern with the [^{18}F]-FDG PET. This cortical amyloid can be antecedent biomarkers of AD.

Comparison of ^{11}C-PiB and ^{18}F-FDG PET in the differential diagnosis of Alzheimer's disease and frontotemporal lobar degeneration

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Helen Wills Neuroscience Institute, University of California, Berkeley, Memory and Aging Center and Department of Neurology, University of California San Francisco, Lawrence Berkeley National Laboratory, California, USA.

Objective: To compare the utility of ^{11}C-PiB and ^{18}F-FDG PET in discriminating clinically-diagnosed Alzheimer's disease (AD, n=40, age 68.3±10.3, MMSE 22.4±5.6) and frontotemporal lobar degeneration (FTLD, n=36, age 64.5±7.0, MMSE 21.2±8.6).

Methods: PiB (Logan, cerebellar reference) DVR images were visually classified blind to diagnosis as positive or negative for cortical PiB binding, while FDG (pons-normalized) images were categorized as consistent with the metabolic pattern of AD or FTLD. A quantitative threshold for PiB-positivity was empirically derived from a cognitively normal control group (n=30, age 73.7±6.4) using the method described by Aizenstein (2008). Patient FDG scans were quantitatively classified as AD or FTLD based on the region of lowest metabolic activity compared to controls, following Z-transformation of FDG data.

Results: The sensitivity of PiB visual reads for AD was 88% (95% confidence interval 72%-95%) and specificity was 85% (68%-94%). Quantitative PiB dichotomization improved sensitivity to 90% (75%-97%) but reduced specificity to 76% (57%-88%). FDG visual reads had a sensitivity of 69% (51%-83%) and specificity of 87% (69%-96%), while quantitative FDG classification showed 89% sensitivity (72%-96%) and 71% specificity (52%-85%). Agreement between PiB and FDG was moderate (kappa=0.53-0.60 depending on classification method). Visual and/or quantitative FDG suggested AD in 4/6 PiB-positive FTLD patients, and suggested FTLD in 4/5 PiB-negative AD patients. FTLD was confirmed at autopsy in three patients. All were PiB-negative on visual read, though one was marginally positive by quantitative PiB despite the absence of amyloid pathology.

Conclusions: PiB and FDG both demonstrated high sensitivity and specificity in discriminating AD and FTLD. The two tracers showed only moderate agreement with each other, implying they provide complementary diagnostic information. In most cases in which PiB conflicted with clinical diagnosis, FDG results agreed with PiB, suggesting these patients may have been clinically misclassified. These findings need to be confirmed in autopsy-based studies.

Challenging tests of episodic memory reveal association with amyloid burden in cognitively normal older individuals

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Background: Extensive amyloid deposition detected *in vivo* using PET with Pittsburgh Compound B (PiB) has been reported in a large fraction of normal subjects who have no clinical impairment. It remains unknown whether amyloid burden in these individuals is related to more subtle impairment that could portend further decline toward Alzheimer's disease (AD).

Objective: We tested whether amyloid burden is related to neuropsychological (NP) performance, particularly when more challenging tests are used, and sought to determine if cognitive reserve (CR) modifies the relationship in normal older adults.

Methods: We studied 84 normal subjects (mean age = 73.7±8.3) with Clinical Dementia Rating (CDR) score = 0. We related precuneus PiB retention (adjusted for age, education and AMNART IQ) to NP scores, and tested for an interaction of PiB retention with AMNART, our proxy for CR. A subset of subjects (n=35) underwent a more challenging memory test with two lists of category associates, called the Memory Capacity Test (MCT).

Results: We found a significant inverse relationship between amyloid deposition and memory performance, in tasks of semantic memory (p=0.044) and cued recall (p=0.035). Executive functions, naming and visuospatial perception were not related. CR significantly modified the relationship of PiB and NP in semantic memory (p=0.040), and in cued recall (p=0.038) such that at progressively higher levels of CR, NP performance was less affected by increased amyloid levels. Using the MCT, we found a significant main effect of amyloid in memory performance on second-list learning (p=0.013); and an interaction with CR (p=0.014).

Conclusions: Cognitive reserve appears to mediate the relationship between amyloid pathology and memory performance. More challenging tests of memory may be useful in detecting very early memory impairment and tracking disease progression prior to significant cognitive impairment.

Relationship of amyloid deposition to default network functional connectivity in non-demented older adults

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Athinoula A. Martinos Center, Massachusetts General Hospital, Charlestown, Massachusetts, Radiology, Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, Boston, Neurology, Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, Boston, Massachusetts Alzheimer's Disease Research Center, Massachusetts General Hospital, Boston, Psychology and Center for Brain Science, Harvard University, Cambridge, Neurology, Brigham & Women's Hospital, Boston, Howard Hughes Medical Institute at Harvard University, Cambridge, Massachusetts, USA.

The relationship between fibrillar amyloid burden, measured via positron emission tomography imaging using C-11 Pittsburgh Compound-B (PiB), and functional correlations within large-scale brain networks, measured via functional magnetic resonance imaging (MRI) during both rest and task performance, was investigated in a cohort of 44 healthy, non-demented, community dwelling older adults (aged from 60 to 87, M=73.16). Fibrillar amyloid burden was defined by specific binding (indexed to a cerebellar reference region) of PiB in gray matter within a large region of interest that included frontal, lateral, and retrosplenial cortices (FLR). Individuals with distribution volume ratios (DVR) within the FLR region of 1.15 or greater were classified as PiB positive, as opposed to PiB negative. Analyses treating DVR within the FLR region as a continuous measure were also conducted. Functional correlation MRI (fcMRI) was measured among regions of interest within the default network, including *a priori* defined regions in posterior cingulate, medial prefrontal, and lateral parietal cortices. Functional correlations were computed among these regions for scans during which participants passively viewed a fixation point (rest) and separately for scans during which participants performed a word-pair memory recognition task. Participants were screened using the Clinical Dementia Rating (CDR) scale and the Mini-Mental State Examination (minimum score of 27). PiB negative individuals exhibited significantly higher estimates of fcMRI than PiB positive individuals during rest; in addition, DVR within the FLR region was significantly negatively correlated with fcMRI. During task performance, significant relationships between PiB and fcMRI were also observed, although weaker in extent than when measured during rest. The qualitative pattern of these results remained unchanged when excluding seven individuals with CDR 0.5 and when controlling for chronological age. These data suggest that amyloid deposition is related to disruption of the spontaneous coherence of default network activity in non-demented older adults.

Relationship between ApoE genotype and β-amyloid deposition: results of florpiramine F18 (^{18}F-AV-45) PET imaging in asymptomatic elderly, mild cognitive impairment subject and clinical dementia patients

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Avid Radiopharmaceuticals, Inc, Philadelphia, Pennsylvania, University of Pennsylvania, Philadelphia, Pennsylvania, Duke University, Durham, North Carolina, Meridien Research, St Petersburg, Florida, Neurological Associates, Albany, New York, Banner Good Samaritan Medical Center, Phoenix, Arizona, MD Clinical, Hallendale Beach, Florida, Medical University of South Carolina, Charleston, South Carolina, Massachusetts General Hospital, Boston, Massachusetts, Premiere Research Institute, West Palm Beach, Florida, Mount Sinai, Miami, Florida, Sun Health Research Institute, Sun City, Arizona, USA.

Background: ApoE genotype is a known risk factor for AD. Here we tested whether or not it is also a risk factor for amyloid deposition by using florpiramine F18 (^{18}F-AV-45) PET imaging to measure *in vivo* amyloid burden.

Methods: 79 cognitively healthy controls (HC: MMSE>29) 50-95 years old, 60 subjects with mild cognitive impairment (MCI: CDR 0.5, MMSE>24), and 45 Alzheimer's disease patients (AD: MMSE<24) were enrolled in this study, and underwent a detailed neurological exam including cognitive battery and ApoE genotyping. A 10-min PET image was obtained 50 min following injection of 10 mCi florpiramine F18. Images were evaluated qualitatively by a reader blind to the patient's diagnostic classification. A semi-automated algorithm also calculated the average ratio tracer uptake (SUVR) in cortex relative to the cerebellum. Correlations between imaging outcomes and ApoE genotype were assessed.

Results: ApoE genotype was a significant risk factor for amyloid deposition in all three groups (HC, MCI, AD), with ApoE e4 increasing both the likelihood of amyloid positivity, and degree of amyloid deposition. ApoE e2 was protective against amyloid deposition, with 18 out of 18 subjects carrying ApoE e2 (including 2 with clinical diagnosis of AD, 4 with MCI and 12 HCs) negative for amyloid depositions.

Conclusions: The results confirm findings of histopathologic studies that have shown that ApoE genotype has a significant influence on amyloid levels. In addition, the PET imaging findings with florpiramine F18 indicate that ApoE e4 is also a risk factor for β-amyloid deposition even in the absence of dementia, thus supporting a mechanistic connection between elevation of brain β-amyloid and eventual onset of dementia.

Longitudinal patterns of amyloid deposition in non-demented older adults

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National Institute on Aging, National Institutes of Health, Bethesda, Maryland, Johns Hopkins Medical Institutions, Department of Radiology, Baltimore, Maryland, MedStar Research Institute, Hyattsville, Maryland, USA.

The high levels of amyloid-β that characterize Alzheimer's disease (AD) appear stable over time in *in vivo* imaging studies. More rapid increases in Aβ may occur during the asymptomatic prodromal stage, contrasting with lower rates of deposition in normal aging. We investigate whether longitudinal changes in amyloid deposition occur in non-demented older adults.

Methods: Non-demented participants (n=24, baseline age 79.2 [8.1] years) of the Baltimore Longitudinal Study of Aging Neuroimaging Study had [^{11}C]PiB PET at baseline and after 1.5 (0.5) years. Mean cortical distribution volume ratios (cDVR) were calculated from the distribution volume ratio (DVR) for 8 cortical regions. Parametric DVR images were also generated from dynamic PET images quantified by SRTM-LRSC (Zhou, 2003). Changes in cDVR (ΔcDVR) over time were assessed by one-tailed Wilcoxon Signed-Rank Test, and group differences in ΔcDVR by exact Wilcoxon Rank Sum tests. Parametric images and voxel-based analysis, adjusted for baseline age (SPM5, $p<0.005$, spatial extent 100 voxels), were used to identify regional changes in [^{11}C] PiB retention.

Results: Mean baseline cDVR was 1.2 (0.3SD). No significant change over time was seen in ΔcDVR for the whole sample or in the 14 participants with baseline cDVR <1.05. However, cDVR increased over time in the subgroup of 10 individuals with baseline cDVR >1.05 ($p< 0.01$). The two subgroups differed significantly in ΔcDVR ($p<0.01$). Voxel-based analysis for the whole sample showed significant longitudinal increases in amyloid deposition in left precuneus, superior and orbitofrontal regions and right fusiform, lingual, and medial frontal and anterior cingulate regions.

Conclusions: Longitudinal changes in amyloid deposition can be detected in non-demented older adults. Elevated baseline amyloid load is associated with increased amyloid deposition over time, and the earliest changes appear to be detectable in the precuneus region and the prefrontal cortex. Continued follow up will determine which individuals go on to develop cognitive impairment.

Support: This research was supported in part by the Intramural Research Program of the National Institute on Aging, NIH and N01-AG-3-2124. A portion of that support was through a R&D contract with MedStar Research Institute.

Serial PiB and MRI in normal, MCI and AD: implications for sequence of pathological events in AD

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The purpose of this study was to use serial imaging to gain insight into the sequence of pathologic events in Alzheimer's disease (AD), and the clinical features associated with this sequence. We measured change in amyloid deposition over time using serial ^{11}C Pittsburgh Compound B (PiB) PET and progression of neurodegeneration using serial structural Magnetic Resonance Imaging (MRI). We studied 21 healthy cognitively normal subjects (CN), 32 with amnestic MCI (aMCI), and 8 with AD. Subjects were drawn from two sources; ongoing longitudinal registries at Mayo Clinic, and the Alzheimer's Disease Neuroimaging Initiative (ADNI). All subjects underwent clinical assessments, MRI, and PiB studies at two time points roughly one year apart.

The annual change in global PiB retention did not differ by clinical group ($p=0.90$), and while small (median 0.042 ratio units/year overall) was greater than zero among all subjects ($p<0.001$). Ventricular expansion rates differed by clinical group ($p<0.001$) and increased in the following order, CN < aMCI < AD. Among all subjects there was no correlation between PiB change and concurrent change on CDR-SB but some evidence of a weak correlation with MMSE. In contrast, greater rates of ventricular expansion were clearly correlated with worsening concurrent change on both CDR-SB and MMSE.

Our data are consistent with a model of typical late onset AD derived from imaging that has three main features: (1) dissociation between the rate of amyloid deposition and the rate of neurodegeneration late in life, with amyloid deposition proceeding at a constant slow rate while neurodegeneration accelerates; (2) clinical symptoms are primarily coupled to neurodegeneration not amyloid deposition; (3) significant plaque deposition occurs prior to clinical decline. This model implies a complimentary role for MRI and PiB imaging in AD.

Potential of PET to monitor development of Aβ plaques in the non-demented

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Background: PET imaging with the [^{11}C] benzothiazole tracer, PiB, can be employed to detect levels of Aβ plaques in non-demented populations, typically using a minimum level of PiB binding to categorize subjects as 'positive' or 'negative'.

Methods: PET amyloid imaging using the [^{11}C] benzothiazole tracer, PiB, from several populations was reviewed (n=275) that included a group of non-demented subjects in a longitudinal study of memory and aging (n=241), a group of subjects had undergone repeat PiB PET scans within one month (n=20) and a subset of subjects that had undergone two PiB PET scans at intervals >12 months (n=37). All PET scans were conducted with PiB injection (~12 mCi) and a 60 min dynamic scan. Binding estimates from precuneus, gyrus rectus, prefrontal and lateral temporal regions were averaged to create the Mean Cortical Binding Potential (MCBP).

Results: Subjects under 55 years, assumed to have minimal amyloid plaques, had mean MCPB = -0.014 with a very small SD = 0.036 (n=38). In contrast, approximately 18% of the 241 non-demented subjects >55 year had elevated PiB (MCBP >0.18). In the 20 subjects that underwent repeat PiB scans after a short interval, correlation of MCBP across the two scans was excellent (r2=0.975). Of the 37 subjects with repeat PiB scans after a longer interval, 25 had initially negative scans and 3 of these 25 subjects (12%) showed positive PiB scans upon follow up (mean interval 2.05 year).

Conclusions: Quantitative PiB PET metholodogy has excellent reliability, a very small variation in younger subjects known to be without plaques, and appears to have potential to monitor development of Aβ plaques in aging.

Support: Supported by National Institute of Aging grants P50AG05681; P01AG03991; and P01 AG026276

A five years follow-up study with PiB in Alzheimer patients

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High PiB retention has been observed in MCI patients later converting to Alzheimer's disease (AD) (Forsberg *et al* 2008). A crucial question for the role of amyloid in AD is to understand the evolution of amyloid during the whole disease progression. The first cohort of mild Alzheimer patients (AD) that was scanned by PiB and FDG in 2002-2003 (Klunk *et al* 2004) and followed up by repeated PiB and FDG scans 2 years later (Engler *et al* 2006) have now been re-scanned 5 years after baseline. Nine of the initial 16 AD patients participated in the second follow-up study. The mean age was 75±3 years (range 61-86 years) and the mean MMSE was 21±3 (range 5-29). Four out of nine patients were ApoE e4 carriers. All 7 patients were on cholinesterase inhibitor treatment since 8±1 years and 5 also on memantine. Of the remaining seven AD patients from the initial cohort of 16 AD patients, 4 patients could not participate in the 5-years follow-up PET scans due to severe dementia (MMSE <5) and 3 patients were diseased.

No significant change in mean cortical PiB retention was observed at 5-years follow-up in the seven patients as an overall group compared to baseline and 2-years follow-up respectively. This findings with PiB contrasted to the significant decrease in cortical cerebral glucose metabolism (FDG uptake) and cognition measured at 5-years follow up compared to baseline and 2-years follow up. Large variation and different regional patterns in time courses of changes in PiB retention and FDG uptake were however observed between the individual patients suggesting a complex pattern of changes during AD disease progression. Three patients with low PiB retention at baseline (Klunk *et al* 2002) still showed low PiB retention at 5-years follow up. An 82 year-old healthy control, with a initial high cortical PiB retention (Klunk *et al* 2002), showed after 5-years follow-up unchanged high PiB retention as well as unchanged glucose metabolism and cognition.

References:

Klunk *et al*. Ann Neurology 2002; **55**: 306-319.
Engler *et al*. Brain 2006; **129**; 2856-2866.
Forsberg *et al*. 2008; **29**: 1456-1465.

Longitudinal changes in amyloid deposition in normal elderly, mild cognitive impairment and AD

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Background: Postmortem studies of amyloid deposition have contributed greatly to our understanding of the variations in amyloid load across individuals at different levels of severity. However, *in vivo* amyloid imaging opens a new opportunity to follow the deposition of amyloid within individuals over time.

Objective: Determine the change in amyloid deposition over time in normal controls (NC), Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD).

Methods: Twenty-two subjects (6-AD, 7-NC, 9-MCI) received two PiB-PET scans (15mCi, 40-60 min; ECAT HR+) within 28 days to serve as controls for test-retest variability. The changes in these subjects were compared to that in 40 NC [14 (35%) PiB(+)], 15 MCI [10 (67%) PiB(+)] and 15 AD patients [100% PiB(+)] who were imaged 12-24 months after their baseline. Tissue ratios were calculated for regions-of-interest in anterior cingulate, precuneus and a global cortical region, normalized to cerebellum after atrophy correction (SUVR). The delta-SUVR (follow up minus baseline SUVR) was calculated.

Results: Test-retest variability over 28 days did not differ by diagnostic groups (average delta-SUVR= -0.001±0.146), so the data were combined to define the 95% confidence interval for noise in the PiB PET measurement. An increase above this interval (~0.225 SUVR units) was defined as significant ($p<0.05$). Five of the 14 (36%) PiB(+) NC had a significant increase in PiB retention and all 14 remained PiB(+). Five of the 26 (19%) PiB(-) NC had significantly increased PiB retention. Six PiB(-) NC (2 with significant increases and 4 with smaller increases) became PiB(+) at follow up. Seven of the 10 (70%) PiB(+) MCIs had increased PiB retention and all 10 remained PiB(+). One of the 5 (20%) PiB(-) MCIs had increased PiB retention and this subject became PiB(+). Of particular note, 8 of the 15 (53%) PiB(+) AD subjects had a significant increase in PiB retention.

Conclusions: A progressive accumulation of Aβ deposits was detectable with PiB-PET in normal controls, MCI and AD. The frequency of increased PiB retention was greatest in the MCI, but the magnitude was similar across diagnoses. The use of delta-SUVR rather than percent change may be critical to detect these changes, particularly in AD. Information about the natural history of amyloid deposition could be important in detecting the effects of anti-amyloid therapies.

In vivo amyloid deposition detected by [^{11}C] PiB PET and neuropathology in non-demented older adults

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Although up to 30% of non-demented older adults have elevated levels of β-amyloid, the relationship between *in vivo* imaging and postmortem assessment of β-amyloid load remains unclear.

Methods: Six non-demented participants of the Neuroimaging Substudy of the Baltimore Longitudinal Study of Aging (NI-BLSA) were prospectively followed by [^{11}C]PiB PET imaging and neuropsychological testing and evaluated postmortem a mean of 1.5 (SD 0.9) years after their last [^{11}C] PiB study. Mean cortical DVR (cDVR) and parametric images reflecting the distribution volume ratio (DVR), were generated from [^{11}C] PiB dynamic PET using SRTM-LRSC (Zhou *et al* 2003). Neuropathology evaluation included CERAD rating and assessment of amyloid angiopathy. The associations between antemortem [^{11}C] PiB retention and neuropathological findings were investigated in the context of cognitive status.

Results: On postmortem evaluation, 4/6 participants had moderate, 1/6 sparse, and 1/6 no detectable neuritic plaques. Of the two participants with higher *in vivo* amyloid load (cDVR >1.4), one individual became demented before the third [^{11}C] PiB PET, and this individual had a moderate number of neuritic plaques on postmortem evaluation. The other individual with cDVR >1.4 had sparse neuritic plaques and amyloid angiopathy on postmortem evaluation. Three of the 4 participants with lower *in vivo* amyloid load (cDVR <1.2) had moderate numbers of neuritic plaques. 3/6 individuals (1 of whom had cDVR <1.2) were found to have amyloid angiopathy on postmortem evaluation.

Discussion: While *in vivo* imaging and neuropathology were concordant with respect to β-amyloid load in the non-demented older adult who progressed to dementia, in some non-demented adults differences were observed between amyloid load detected *in vivo* by imaging and CERAD ratings of amyloid plaques. More detailed investigations are needed to provide better understanding of the relationship between imaging and neuropathological measures of β-amyloid load in non-demented older adults.

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PiB binding of cerebral Aβ may lag clinical, cognitive, and CSF markers in Alzheimer's disease

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This case study provides preliminary insight about the sequence of pathogenetic events in histological Alzheimer's disease (AD) and dementia of the Alzheimer type (DAT).

At age 85 years a male civil servant (ApoE 3/3) without family history of dementia enrolled in a longitudinal study of memory and aging. His Clinical Dementia Rating (CDR) score was 0 (non-demented) at entry and at the next 4 annual assessments (through age 89 years). At age 90 years, his collateral source reported declining cognitive abilities with forgetfulness, poor decisional capacity, and mild interference with daily function (e.g., involvement in a motor vehicle accident). The participant could not recall recent autobiographical events. The Mini Mental State score was 27. He was diagnosed with very mild DAT (CDR 0.5) and died of congestive heart failure 6 months later (age 91 years).

At age 88 years (2 years prior to diagnosis) his performance on measures of episodic memory began progressively declining. At age 88.5 years a PET PiB scan was unremarkable (mean cortical binding potential =-0.006). At age 89.5 years cerebrospinal fluid (CSF) assays showed elevated tau (575 pg/mL) and ptau (83 pg/mL) and lowered Aβ42 (303 pg/mL). Neuropathological examination (2.5 years after PiB scan) using Aβ immunohistochemistry revealed focally numerous neocortical diffuse plaques (Khachaturian criteria fulfilled) but sparse neuritic plaques or neurofibrillary tangles ("low" probability, NIA-Reagan criteria) using Bielschowsky silver staining (Braak stage = III). Postmortem [H-3]PiB binding to brain tissue homogenates was below levels needed for *in vivo* detection, and 6-CN-PiB histofluorescence staining revealed only scarce fibrillar plaques.

The clinical diagnosis of DAT was independently supported by episodic memory decline and an AD CSF phenotype. We conclude that prior to the appearance of fibrillar PiB-binding plaques that are detectable by PET and before abundant neurofibrillary changes, cerebral Aβ accumulation in the form of diffuse plaques or oligomeric species has pathological consequences.

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Assessing the threshold for *in vivo* detection of β-amyloid plaques using PiB-PET imaging

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Background: Amyloid plaques containing β-amyloid (Aβ) peptide are a major histopathological hallmark of Alzheimer's disease (AD). This pathology is detectable *in vivo* using Pittsburgh Compound-B (PiB) and positron emission tomography (PET), however the threshold level of Aβ plaque load necessary for positive PiB-PET signal is unknown.

Methods: We examined autopsied brain tissues from a 79 year-old man with a clinical diagnosis of dementia with Lewy bodies (DLB) and a negative PiB-PET scan obtained 1.5 years before death. Fixed tissue sections were processed for histochemistry using the Bielschowsky method, the histofluorescent amyloid marker X-34, and immunohistochemistry using Aβ antibodies, frozen tissue samples were assayed using an Aβ1-42-specific ELISA, and a [H-3]PiB binding assay.

Results: Neocortical areas contained focally frequent neuritic plaques. Plaques were most frequent in the temporal cortex (TC) and were primarily of diffuse morphology. In the frontal cortex (FC), plaques were more compact, intensely labeled, and associated with vascular deposits. X-34 labeled amyloid load was higher in the FC (2.45±1.11%) versus TC (1.71±0.49% area). The highest formic acid-extracted Aβ1-42 concentrations were observed in FC (0.79 pmol/mg), TC (0.45) and precuneus (0.45). Only the FC was near the level expected to be detected by *in vivo* PiB-PET. [H-3]PiB binding was <0.1 pmol/mg in all three regions, predictive of *in vivo* PiB-negativity.

Conclusion: Postmortem examination of a person with a negative PiB-PET scan demonstrated the presence of neocortical Aβ plaques and moderate concentrations of insoluble Aβ1-42 peptide in the FC. This suggests that substantial amounts of Aβ (by neuropathological standards) can be present when the *in vivo* PiB-PET scan is negative. Thus, even weakly positive PiB-PET scans may indicate the presence of extensive Aβ deposits. The low level of postmortem [H-3]PiB binding despite frequent Aβ plaques suggests that PiB binding may be influenced by distinct pathological conformations of Aβ in humans, as previously shown in transgenic mice.

Amyloid burden and glucose metabolism in non-demented Parkinson's disease patients and healthy controls

POSTER ABSTRACT

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Objective: To test the hypothesis that increased amyloid accumulation measured as [^{11}C]PIB retention is associated with cerebral hypometabolism, measured as regional cerebral glucose metabolism with [^{18}F]FDG, among non-demented patients with Parkinson's disease (PD) and normal controls (NC).

Methods: 17 non-demented PD patients and 58 cognitively normal healthy individuals underwent a comprehensive battery of neuropsychological (NP) tests and PET imaging with [^{11}C]PiB and [^{18}F]FDG.

Results: Neither global nor regional PiB retention differed between NC and PD, however, PD patients had hypometabolism in the parietal, occipital and medial frontal regions and in the midbrain compared to NC. Age-adjusted regression analyses revealed a quadratic relation between PiB DVR and glucose metabolism most prominent in the left anterior cingulate and left parietal region ($p<0.05$). Thus, low to intermediate levels of amyloid were associated with increased metabolism, while high levels of amyloid were associated with hypometabolism. The quadratic relation for the PD patients showed a similar peak, but a significantly sharper curvature compared to controls ($p<0.05$).

Conclusions: These results indicate that, compared to age-matched controls, non-demented PD patients have similar amyloid burden, but have parieto-occipital hypometabolism. Similar to Alzheimer's disease, high levels of amyloid deposition were associated with parietal hypometabolism, but surprisingly, intermediate levels were associated with elevated metabolism.

Computing PiB DVR using a short emission scan and a revised version of the logan method

POSTER ABSTRACT

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Background: While the Logan Graphic Analysis (LGA) can be used to compute Pittsburgh Compound B Distribution Volume Ratios (PiB DVR), a quantitative measure of fibrillar amyloid-β (Aβ) burden, it typically requires 60-90 min of dynamic emission data to generate tissue time-activity curves (tTACs) beginning immediately after radiotracer administration. We recently used the LGA and a 90-min dynamic scan to demonstrate a relationship between apolipoprotein E (ApoE) ε4 gene dose, in cognitively normal people with two copies, one copy and no copies of the Alzheimer's disease (AD) susceptibility gene (Reiman *et al* in press).

Objective: In this study, we revised the Logan method (which we call T_0-Logan) to permit the computation of PiB DVR using a shorter dynamic emission scan beginning after the radiotracer reaches equilibrium (T_0). (A revision that could be applied to other graphical analysis procedures.) We then compared PiB DVR measurements using T0-Logan and data from a 40-70 min post-injection scan to those using the conventional LGA and data from a 0-90 min scan in 28 cognitively normal ApoE ε4 homozygotes, heterozygotes and non-carriers on a voxel-by-voxel basis.

Methods: The original LGA can be expressed bilinearly as $\int_0^t C_T(s)ds=DVR\int_0^t C_R(s)ds+\delta C_T(t)$ for any time t at which we can assume equilibrium. In this expression, C_T/C_R is the targeted/reference tTAC and δ is a constant. Subtracting the LGA expression corresponding to a fixed T_0 from that corresponding to a variable t, we have $\int_{T_0}^t C_T(s)ds=DVR\int_{T_0}^t C_R(s)ds+\delta C_T(t)-\delta C_T(T_0)$. PiB DVR was characterized and compared on a voxel-by-voxel basis using our revised approach and emission data from the 40-70 min interval and using the original LGA and emission data from the 0-90 min interval in each of the same subjects, including 8 ε4 homozygotes, 8 heterozygotes, and 12 non-carriers. Using data generated from these two different methods, we used SPM5 to characterize and correlate t-score maps of the PiB DVR differences between each of the ε4 carrier groups and the non-carriers and to compare the correlations between cerebral-to-cerebellar PiB DVR and ApoE ε4 gene dose in spatially standardized frontal, posterior cingulate/precuneus, lateral parietal, lateral temporal, occipital, medial temporal and basal ganglia regions-of-interest (ROIs).

Results: There were strong correlations between the t-score maps showing PiB DVR differences between the ε4 carrier and non-carrier groups ($p<1e-16$, regressing the two corresponding t-maps in both homozygote>non-carrier and heterozygote>non-carrier comparisons). Significance of the correlations between PiB DVR and ApoE ε4 gene dose were very similar in each of the seven ROIs (e.g., $p=4e-4$ significance either the original Logan or the T_0-Logan method). (We have not yet evaluated the effects of using a post-emission versus pre-emission transmission scan.)

Conclusion: Our revised Logan method can be used to quantify PiB DVR measurements using a shorter scanning interval than that required using the original Logan method without significantly comprising the ability to detect small increases in fibrillar Aβ burden.

What may PET imaging of amyloid with florpiramine F18 tell us about subjects with mild cognitive impairment?

POSTER ABSTRACT

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It has been proposed that many patients who develop Alzheimer's type dementia go through a prodromal stage of mild cognitive impairment (MCI). However, it has been difficult to clinically distinguish MCI due to underlying AD from MCI of other causes. Autopsy studies have shown that a significant percentage of subjects with MCI have relatively low levels of AD neuropathology. PET amyloid imaging agents may make it possible to evaluate *in vivo* which subjects with MCI have evidence of Alzheimer's amyloid pathology.

As part of a larger study that include patients with AD and healthy controls, 60 subjects were identified within the past year as having mild cognitive impairment based on clinical judgment, CDR score of 0.5 and an MMSE >24. In order to better evaluate the relationship between cognitive performance and amyloid burden, a cognitive test battery was performed but there were no cutoff values established for any of the memory or cognitive tests. All subjects received a 10-min PET scan, 50 min after injection of 370 MBq of the amyloid imaging agent, florpiramine F18. Images were evaluated visually, by readers blind to the subject's diagnostic and demographic characteristics and quantitatively via a semiautomated algorithm that calculated the ratio of tracer uptake (SUVR) in cortex relative to the cerebellum.

All but two subjects had subjective memory impairment as indicated by a CDR memory score of >0.5. Approximately 40% of MCI subjects had images consistent with elevated amyloid burden by SUVR and visual interpretation. Tracer uptake by either visual read or SUVR was not significantly correlated with Wechsler memory scores. MCI subjects with the most impaired memory scores had tracer uptake/amyloid burden similar to subjects with memory scores within the normal range.

The results are consistent with the hypothesis that only a portion of subjects with mild cognitive impairment have Alzheimer's disease pathology and that memory performance alone may not be sufficient to predict which subjects will have Alzheimer's pathology. Long-term follow up of these subjects may determine whether amyloid burden as assessed by florpiramine F18, in combination with cognitive scores can predict progression of subjects with MCI.

Comparison of cerebral metabolism and amyloid deposition in clinically unimpaired elderly

POSTER ABSTRACT

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Background: We previously characterized prevalence of amyloid deposition by PiB PET imaging in clinically unimpaired elderly and related this to cognitive function. We found ~25% of the community-based sample of volunteers displayed early amyloid deposition [PiB(+)] in at least one brain area using an objective DVR cutoff. Demographics and neurocognitive performance did not differ significantly between the amyloid-positive and amyloid-negative subjects.

Objective: To compare cerebral metabolism (FDG PET) with amyloid deposition (PiB PET) in clinically unimpaired elderly.

Methods: Subjects underwent cognitive testing, PiB PET (15mCi, 90 min; ECAT HR+) and FDG PET (7mCi, 35-60 min). Logan graphical analysis was applied to estimate regional PiB retention (distribution volume ratio). The FDG PET data were analyzed using the Alzheimer's discrimination analysis software "PALZ", available with the PMOD software. PALZ implements the automatic Alzheimer discrimination method developed by Herholz *et al* (2002). An AD-t-sum >11,090 is considered abnormal, determined previously as the upper 95% confidence limit in an independent normal data base of 61 healthy subjects.

Results: Of the 51 subjects with valid FDG-PALZ data, 5 (9.8%) were abnormal by FDG-PALZ criteria (PALZ score >11,090). There appeared to be another breakpoint, at a PALZ score of ~5,700 between clearly normal PiB and FDG-PALZ data and possibly abnormal FDG-PALZ data. Using this lower cutoff, 2 additional subjects (7 total; 14%) appeared possibly abnormal by FDG-PALZ score. Of these 51 subjects, 13 (25%) were PiB(+). Five of these fell into possibly abnormal FDG-PALZ range and 3 into definitely abnormal FDG-PALZ range. Two definitely abnormal FDG-PALZ subjects were PiB(-). The subjects were classified into four mutually exclusive categories: PiB(+)/PALZ(+) (n=5), PiB(-)/PALZ(-) (n=36), PiB(+)/PALZ(-) (n=8) and PiB(-)/PALZ(+) (n=2).

Conclusions: Within this group, there appear to be twice as many PiB(+) subjects as subjects with possibly abnormal (or definitely abnormal) PALZ scores for cerebral metabolism. It will be of great interest to follow the four subject categories: PiB(+)/PALZ(+), PiB(-)/PALZ(-), PiB(+)/PALZ(-) and PiB(-)/PALZ(+) over time to determine clinical outcome.

Cognitive status does not correlate with amyloid burden in Alzheimer's disease as measured by [^{11}C]PiB and [^{18}F]FDG PET imaging

POSTER ABSTRACT

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Objective: To investigate the impact of amyloid load on cognition/dementia severity and glucose metabolism in Alzheimer's disease (AD).

Methods: Patients meeting criteria for probable AD (n=37, age 68.0±10.6, MMSE 21.6±5.7, years of education 16.8±2.8) underwent [11C]PiB (n=37) and [18F]FDG PET (n=32) imaging and a set of cognitive/clinical tests (CDR-SOB, CVLT, Verbal Fluency, Modified Rey). PiB Distribution volume ratios (DVR, cerebellar reference) and FDG scans (normalized to pons) were spatially normalized to the SPM2 MNI PET template using parameters derived from the mean of the PiB/FDG scans of each patient. Average PiB counts of regions-of-interest known to be high in amyloid burden were used to compute a measure of global PiB uptake. Separate voxel-wise multiple regressions with age, sex and years of education as nuissance variables were then performed to explore the local/global relationship of amyloid burden and glucose metabolism/test performance.

Results: MMSE scores were positively correlated (FDR, $p<0.05$) with glucose metabolism in bilateral precuneus, posterior cingulate, angular gyrus, left middle temporal, supramarginal, middle frontal, orbitofrontal cortex and the striatum. In subsets of these regions metabolism was also correlated with scores on the CDR-SOB, CVLT, Verbal Fluency (uncorrected $p<0.001$) and Modified Rey test (FDR, $p<0.05$). There was no association between global PiB uptake and glucose metabolism for any voxel. Similarly no effects were found when regressing the same test scores with voxel-wise PiB uptake. Finally, there were also no significant Spearman rank correlations between global PiB uptake and any of the test scores.

Conclusions: There does not appear to be any relationship between global amyloid burden and glucose metabolism in AD. Furthermore neither local nor global amyloid concentrations seem to predict cognitive status.

Amyloid-β deposition: as a cause or a result? ^{11}C-PiB PET study in non-Alzheimer type degenerative dementias

POSTER ABSTRACT

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A serial neuropathological investigations of our Gerontology Hospital autopsies composed of more than 8000 cases has demonstrated that an amyloid-β (Aβ) deposition is observed as a continuous profile among normal aging and even in non-Alzheimer type degenerative disorders such as tauopathies and argiophilic grain disorders. Multiple pathologies are often recognized as a basis of dementia in older old populations. The purpose of this study was to examine if the Aβ deposition observed in the non-Alzheimer type degenerative disorders plays any pathological role.

We studied 15 patients with fronto temporal dementia (FTD), 15 Alzheimer's disease (AD), and 10 healthy controls (HC). All the subjects underwent PET study with ^{11}C-PiB and ^{18}F-FDG. All the patients were followed up clinically at least two years. Four FTD patients had two or three ^{11}C-PiB scans with one-year interval, and nine FTD patients had multiple ^{18}F-FDG PET scans to monitor the disease progression. The ^{11}C-PiB accumulation was evaluated in the summing image scanned from 40 to 60 min after the injection taking the cerebellar cortex as a reference region.

Three FTD patients had an accumulation of ^{11}C-PiB as high as that in AD group. In the rest of 12 FTD patients, the cerebral ^{11}C-PiB accumulation was not significantly different from that of HC. However, five of FTD patients had slight cortical accumulation of ^{11}C-PiB, and four of them revealed increasing ^{11}C-PiB accumulation by repeated ^{11}C-PiB scans. The ^{11}C-PiB accumulator FTD patients have shown relatively rapid progression in the clinical symptoms compared to the ^{11}C-PiB negative FTDs. The latest image of some rapid ^{11}C-PiB accumulator in FTD became as cannot be differentiated from that of AD any more. Our results suggest that a certain population of AD diagnosed by pathology or amyloid imaging might have started as non-AD disease overlapped by Aβ deposition afterward. A serial ^{11}C-PiB study and careful clinical observations are necessary to understand the dynamic pathological processes that cause degenerative dementias.

^{11}C-PiB PET and hippocampal volumes are complementary in distinguishing dementia with Lewy bodies and Alzheimer's disease

POSTER ABSTRACT

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Background: The two most common neurodegenerative disorders associated with dementia in the elderly are Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). Early in the disease process, clinical differentiation between these disorders is often difficult; hence imaging markers for differential diagnosis would be useful. ^{11}C–Pittsburgh Compound-B (PiB) retention on PET is a surrogate marker for amyloid pathology and hippocampal volume on MRI is associated with the neurofibrillary pathology of AD. We propose that imaging markers closely associated with neurofibrillary and amyloid pathologies of AD may provide complementary information for the differential diagnosis of DLB and AD.

Methods: We studied clinically diagnosed patients with AD (n=13), DLB (n=5), and cognitively normal subjects (n=20) who were consecutively recruited from the Mayo Clinic Alzheimer's Disease Research Center. All subjects underwent clinical evaluation, MRI and PiB PET within six weeks. A global cortical PiB retention summary measure was formed by combining prefrontal, orbitofrontal, parietal, temporal, anterior cingulate and posterior cingulate/precuneus values divided by the cerebellar cortical PiB retention for each subject, with equal weighting of the individual values in computing the summary measure. Hippocampal volumes were analyzed as adjusted W scores for head size, age and gender.

Results: The global cortical PiB retention in DLB patients was on average lower than AD, but higher than cognitively normal subjects. Similarly, hippocampal W-scores of DLB patients were on average higher than AD, but lower than cognitively normal subjects. Three of the five (60%) DLB patients were "PiB positive" (global cortical PiB retention summary measure >1.5), and one subject was "borderline" (1.49). Hippocampal W-scores were lower than zero in three of the five (60%) DLB patients. Only one DLB patient had both hippocampal atrophy and "positive PiB." Plotting hippocampal W-scores against global cortical PiB retention completely separated the DLB and AD subjects.

Conclusions: MRI and PiB PET are complementary in distinguishing patients with DLB and AD, and provide insight into the pathological mechanisms underlying dementia in DLB patients. A majority of the DLB patients had PiB retention and/or hippocampal atrophy, in agreement with pathology studies showing that patients with clinically diagnosed DLB may often have some degree of additional AD pathology.

PiB-positive *vs* PiB-negative subcortical ischemic vascular dementia

POSTER ABSTRACT

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Background & Objective: Subcortical ischemic vascular dementia (SIVD) is thought to be the most common type of vascular dementia. Whether the progressive cognitive decline of alleged SIVD is due to pure vascular lesion or underlying Alzheimer's disease remains unanswered. We tried to look at how much SIVD is superimposed on by Alzheimer's pathology using Pittsburgh compound-B (PiB) positron emission tomography (PET), an amyloid imaging.

Methods: SIVD was based on Erkinjuntti's MRI and clinical criteria. All subjects underwent a neuropsychological battery, brain MRI, and PiB-PET imaging. The pattern of amyloid uptake on PiB PET was compared with that of typical Alzheimer's disease. Subcortical ischemic vascular lesion was divided into lacunar and white matter types. Hatchinski ischemic scale (HIS) was applied. Focal neurological deficits were measured using a scoring system. Apolipoprotein E (ApoE) genotype status was investigated.

Results: Twenty-two subjects with SIVD were divided into two groups: pure vascular *vs* mixed Alzheimer's disease. Eight patients (36%) showed positive for PiB imaging. The large numbers of lacunes were associated with PiB-negative scan in SIVD. Among neuropsychological tests, delayed recall was the discriminating factor between PiB (+) vs PiB (-) SIVD. PiB-postive SIVD patients tended to be older than those with PiB-negative scan. There was no significant difference between the two group in terms of disease duration, vascular risk factors, HIS, motor deficits, white matter lesion, and ApoE ε4.

Conclusion: SIVD comprises two different subsets of patients according to the presence of amyloid plaques. Further longitudinal study is warranted to investigate how cortical PiB binding may affect the course of SIVD.

Amyloid deposition, disease severity, and activities of daily living impairment in MCI and AD

POSTER ABSTRACT

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Background: Instrumental activities of daily living (IADL) impairment leads to early loss in productivity and adds significant premature burden to caregivers. IADL impairment has been associated with global amyloid deposition in post-mortem studies, while Alzheimer's disease (AD) disease severity has been shown to correlate better with neurofibrillary tangles than with amyloid deposition. With the advent of Pittsburgh Compound B (PiB) PET imaging, disease severity has been shown to correlate with global amyloid deposition *in vivo*.

Objective: We sought to determine whether disease severity and IADL impairment are related to cortical PiB retention in normal control (NC) subjects, mild cognitive impairment (MCI), and AD.

Methods: Sixty-six subjects (17 NC, 35 MCI, and 14 mild AD) participating in ADNI or an investigator-initiated fMRI ADNI ancillary study underwent clinical evaluations and dynamic PiB PET imaging. Cortical PiB retention was evaluated using the DVR (cerebellar reference). Global PiB retention and 6 individual cortical regions of interest (ROIs) were correlated with disease severity (using Clinical Dementia Rating (CDR) sum of boxes) and in a subset of 44 subjects with IADLs (using the Functional Activities Questionnaire (FAQ)). Linear multiple regression analyses were conducted with CDR or FAQ as the dependent variable and PiB retention, age, and education as predictors.

Results: Mean age was 74.7±8.4 years, 56% male, education 16.3±2.9 years, MMSE 27.2±2.5, CDR sum of boxes 1.7±1.7, and FAQ 3.1±4.4. In the linear regression model, CDR was associated with greater global ($pr=2.4$, $p=0.0004$) and precuneus ($pr=2.2$, $p<0.0001$) PiB retention. Greater IADL impairment was associated with greater global ($pr=6.3$, $p=0.011$) and precuneus ($pr=5.3$, $p=0.008$) PiB retention. When looking at MCI and AD subjects only, these associations remained significant for CDR only.

Conclusions: These results suggest that greater disease severity and IADL impairment are related to greater global and medial parietal amyloid burden in mildly clinically impaired subjects. Additional longitudinal studies are required to determine if early amyloid deposition in specific brain regions will predict rapid decline and progression to clinical dementia.

Precuneus amyloid deposition associated with decreased hippocampal activation during encoding and memory performance in asymptomatic older controls

POSTER ABSTRACT

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Recent studies suggest successful memory formation requires integrated activity between the precuneus and hippocampus, but the role of amyloid burden within this distributed memory network in asymptomatic normal controls is not well understood. In this study, we investigated the relationship between precuneus fibrillar amyloid deposition and hippocampal activation during associative memory encoding task. Twenty-three cognitively normal older individuals (CDR 0, age 73.4+9.2) were imaged with PiB-PET, and fMRI during a paradigm consisting of three encoding trials for each face-name pair with subsequent recognition trial. PET datasets were corrected for partial-volume effect, and PiB distribution volume ratios (DVR) were calculated using individual anatomic regions defined on the high-resolution MP-RAGE sequence. Whole brain fMRI contrast maps for All Encoding *vs* Fixation were generated in SPM2, and MR signal response for each subject was pulled from a functionally defined region of interest with a peak at [–24 –27 –9]. Across the whole group, a negative correlation was found between hippocampal activation during the third encoding trial and both precuneus PiB (r=-0.482; p=0.020) and global PiB (r=-0.547; p=0.007). When subjects were divided into two groups based on global PiB values, only the "high" PiB group (n=12) demonstrated a significant association between activation and global PiB (r=-0.66; p=0.020), and a trend with precuneus PiB (r=-0.55; p=0.064). Similarly, the high PiB group demonstrated a negative correlation between recall performance and precuneus PiB (r=-0.775; p=0.009), while no association was found within either whole group or low PiB group. In contrast, hippocampal PiB levels did not show a significant relationship with either activation or performance in any group. These findings suggest that among cognitively normal controls with high amyloid burden, hippocampal activation and memory performance is related to precuneus but not hippocampal amyloid load.

Age and amyloid burden in healthy controls, subjects with mild cognitive impairment and patients with Alzheimer's disease as assessed with the PET tracer florpiramine F18 (^{18}F-AV-45)

POSTER ABSTRACT

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In three trials, at more than 20 centers, 96 healthy controls (HC) distributed among age ranges 35-49, 50-59, 60-69, 70-79 and 80+, 63 patients with a clinical diagnosis of AD, and 60 subjects with mild cognitive impairment (MCI) received a 10-min PET scan, 50 min after 370 MBq florpiramine F18. Images were evaluated visually, by readers blind to the subject's diagnostic and demographic characteristics and quantitatively via a semiautomated algorithm that calculated the ratio of tracer uptake (SUVR) in cortex relative to the cerebellum. The cortical average SUVR, and the proportion of subjects rated as having high tracer amyloid burden on visual read, were greater for patients with AD than for HC. However, approximately 20-25% of subjects with a clinical diagnosis of AD had low amyloid burden by both measures, and 15-30% of healthy controls had high amyloid burden. Subjects with MCI produced intermediate results, with 40-50% showing high amyloid burden. Amyloid levels in subjects with a clinical diagnosis of AD were independent of age. However, in HC the cortical average SUVR and the proportion of subjects rated as having high tracer uptake/amyloid burden increased monotonically with age. Importantly, none of the HC younger than 50 years of age showed evidence of increased amyloid burden.

The findings are consistent with previous studies showing that approximately 20% of subjects clinically diagnosed with AD do not meet neuropathological criteria for AD, and 25% or more of cognitively normal elderly show AD pathology at autopsy. The low tracer uptake on the PET scans from young controls, who almost never show evidence of amyloid pathology on autopsy, is consistent the low affinity of florpiramine F18 for known CNS/CV binding sites, and the expectation that florpiramine F18 PET imaging will have a high specificity for amyloid.

Aβ amyloid and glucose metabolism in posterior cortical atrophy

POSTER ABSTRACT

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Objective: To compare the regional distribution of amyloid deposition and glucose metabolism in patients with posterior cortical atrophy (PCA) and Alzheimer's disease (AD).

Methods: Patients meeting criteria for PCA (McMonagle 2006, n=5, mean age 63.5±4.5, MMSE 21.2±5.9) and matched patients with AD (n=9, NINCDS-ADRDA, mean age 66.3±8.0, MMSE 23.8±4.3) underwent PET imaging with ^{11}C-PiB and ^{18}F-FDG PET. PiB DVR (Logan, cerebellar reference) and FDG (pons-averaged) images were normalized to the PET MNI template and mean regional tracer activities were extracted utilizing the Automated Anatomical Labeling atlas. An "Occipital Index" (OI) was calculated to compare frontal versus occipital activity in each group:

Occipital Index=(occipital – frontal) / (mean [occipital + frontal]).

Results: Mean cortical DVRs were higher in AD (1.76±0.22) than in PCA (1.49±0.12, p<0.02). In AD, there was a non-significant trend towards higher DVRs in frontal (1.80±0.22), parietal (1.78±0.26) and lateral temporal (1.82±0.26) cortex compared to occipital cortex (1.64±0.24), while in PCA frontal (1.51±0.11), parietal (1.49±0.16) and lateral temporal (1.50±0.14) DVRs were comparable to occipital values (1.45±0.21). The Occipital Index for PiB did not differ between PCA (-0.05±0.18) and AD (-0.08±0.07, p=0.19). In contrast, FDG uptake patterns differed between the syndromes, with relative frontal sparing in PCA (normalized frontal uptake 1.58±0.32 for PCA versus 1.46±0.16 for AD), and relative occipital sparing in AD (normalized occipital uptake 1.37±.37 for PCA versus 1.58±.31 for AD). Mean Occipital Index for FDG was significantly lower in PCA (-0.18±0.10) than in AD (-0.04±0.13, p<0.02)

Conclusions: Amyloid deposition in PCA equally involved anterior and posterior brain regions, similar to the deposition pattern seen in AD. Glucose hypometabolism in PCA prominently involved occipital cortex, in distinction from AD and in concordance with the clinical syndrome. Further studies are needed to determine the mechanisms of selective network degeneration in focal variants of AD.

Amyloid deposition is associated with increased posterior cingulate activity during memory recall in asymptomatic older adults

POSTER ABSTRACT

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Cortical β-amyloid deposition is a major histopathological finding in Alzheimer's disease (AD) and a likely contributor to the observed memory impairment. The medial parietal regions may be specifically vulnerable to early AD amyloid pathology, and are also thought to play a key role in memory retrieval. In this study, we used *in vivo* amyloid imaging to investigate the impact of fibrillar amyloid burden on functional MRI (fMRI) activity during cued recall, in clinically normal older individuals.

Twenty-one older subjects (age=72.8±2.3; CDR=0) were scanned (GE 3T) while performing a face-name associative memory task. During retrieval runs, subjects were shown the face from previously learned face-name pairs, and asked to indicate if they knew the name associated with the face (cued recall). Posterior cingulate PiB DVR, age and performance (% recalled stimuli) were entered as regressors into whole brain SPM2 activation maps for cued recall ($p<0.001$). β-amyloid deposition was quantified using PiB distribution volume ratios (DVR) in anatomic regions of interest (ROI) delineated from 3-D MP-RAGE images using FreeSurfer. FreeSurfer ROI analyses allowed the direct comparison of PiB retention and fMRI activity within the identical anatomically defined regions.

Whole brain (SPM2) multiple regression analysis demonstrated a positive correlation between PiB DVR and fMRI activity during cued recall in the medial parietal lobe with a global maxima found in the right posterior cingulate region [x=6, y=-30, z=30] ($r=0.63$, $p=0.003$). FreeSurfer ROI analysis confirmed a positive correlation between the fMRI activation and PiB DVR in the right posterior cingulate after controlling for age and performance ($r=0.51$, $p=0.03$).

These findings demonstrate that high levels of amyloid deposition, regardless of age and test performance, are associated with increased activation in brain regions supporting memory retrieval. It remains unclear whether the increased activation during successful retrieval is compensatory or is related to local amyloid toxicity resulting in hyperactivity.

Phase I [^{18}F] AV-45 safety and initial quantification for amyloid imaging

POSTER ABSTRACT

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We present here phase I imaging of [^{18}F]AV-45 which assessed the brain pharmacokinetics, safety and initial modeling in 16 healthy controls (HC) and 16 patients with Alzheimer's disease (AD).

Methods: Brain imaging was carried out for up to 180 minutes total. PET images were co-registered to MRI and re-sliced to create a mean image by SPM and then were spatially normalized to Talairach space. Images were segmented to identify grey and white matter, CSF and skull. High flow areas were determined and compared to the previously segmented grey matter dataset (from the first 10 min). Volumes of interest (VOI) were created in orbitofrontal, temporal, parietal, occipital, cingulate, and precuneus. Cerebellar grey matter and centrum semiovale white matter were used as reference regions. The VOIs were then overlaid on the spatially normalized images for each subject to provide the standardized uptake value (SUV) for each imaging time point using above VOIs plus frontal and average cortex.

In a subgroup, subjects were studied using a kinetic modeling (Zhou *et al* 2007) employing the cerebellum as a reference for distribution/volume ratios (DVR).

Results: Cortical to cerebellar SUVs peaked ~50-90 minutes. Plasma metabolites rose to 80% in 10 minutes, but were more polar. SUV of AD were generally greater than control, but 2 HC showed similar pattern to AD. Spatially normalized DVR images for the AD ranged from 1.34 to 1.42 in multiple cortical regions with 1.6 (cingulate) and 1.5 (putamen). DVR were negligible (1.0 to 1.3) for the same regions on HC. Multiple T tests showed significant increases in DVR for AD in all except subcortical, pons, white matter and cerebellar regions.

Conclusions: ^{18}F-AV45 has a favorable safety and shows significant discrimination between AD and HC with promising characteristics for quantification, with either SUV or kinetic modeling.

Human amyloid PET imaging with a novel dedicated high-sensitivity 3D PET brain scanner

POSTER ABSTRACT

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Background: Human amyloid PET imaging agents, particularly ^{18}F-labelled agents which allow distribution and potentially widespread use, are rapidly becoming more validated and available. In this context, dedicated high-sensitivity instrumentation in support of human PET amyloid imaging has the potential to provide several benefits. Specifically, it can provide performance meeting or exceeding that of general-purpose PET scanners, with reduced site and cost requirements, and at lower dose to patient and staff. Further, it's high-sensitivity may allow for amyloid imaging at later time windows.

Methods: We have developed and manufacture a compact, dedicated 3D PET brain scanner (NeuroPET, not yet 510k cleared as of this writing 3/6/2009). As part of this submission we have performed standardized NEMA (National Electrical Manufacturers Association), ACR, and Hoffman phantom-based testing of this new instrumentation, which can be used to compare its performance with existing general-purpose scanners. We have also generated human amyloid radiotracer PET images and have compared these with those of the same subjects on conventional general-purpose PET scanners.

Results: We have demonstrated that our dedicated device is capable of generating 3D PET brain images with sub-milliCurie patient doses, for human amyloid imaging agents. A subject injected with 9.2mCi C11 PiB was imaged on an HR+ (at 45 min post-inj, 2.0mCi, 15-min scan, FBP) and then on NeuroPET (at 70 min post-inj, 0.8mCi, 16-min scan, MLEM). The regional distribution of PiB retention in the left temporal lobe was similar in each case, but with qualitatively improved tissue contrast and lower noise using the higher sensitivity camera. SUV-based contrast values from the two cameras were within 11% for left temporal and reference regions. Our phantom test results are consistent with these results, closely tracking the performance of modern whole-body general-purpose PET scanners in terms of spatial resolution (4.3mm) and measured image quality. Because of its reduced (30cm aperture) bore diameter and its extended (24cm) axial extent, the system shows more than a factor of 2 increase in system sensitivity (20 kHz/MBq) relative to existing general-purpose PET scanners.

Conclusions: Dedicated high-sensitivity 3D PET brain instrumentation can provide high image quality at lower doses and demonstrates the potential for achieving better images of specific/non-specific amyloid binding at later time windows. These capabilities may enable safe multiple repeat scans of the same patient for longitudinal studies or measurement of therapy response.

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