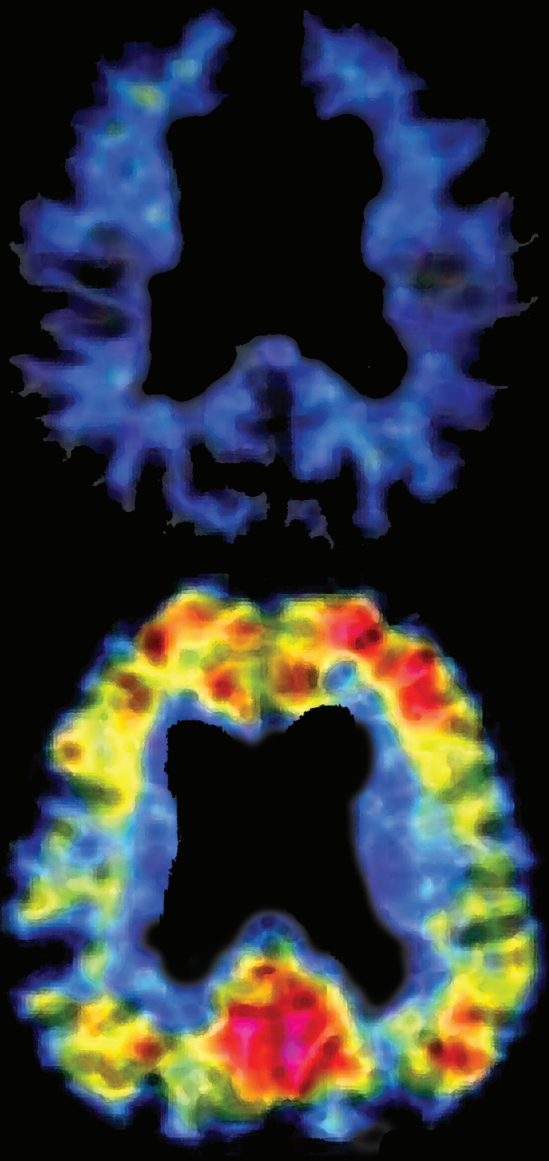

Human Amyloid Imaging

Toronto 2010

Friday, April 9th 2010

The Novotel Toronto Centre

Schedule & Abstract Book

Schedule - Human Amyloid Imaging Meeting - 9th April 2010
The Novotel Toronto Centre, Toronto

07:30 – 08:00	**Registration and Continental Breakfast**
08:00 – 08:15	**Introduction**
08:15 – 09:30	**Session 1: Pathologic Correlations, Amyloid Positivity** **Chester Mathis, Agneta Nordberg (Chairs)**
08:15 – 08:30	Comparison of PiB distribution on PET with beta-amyloid deposits at autopsy *VJ Lowe, Mayo Clinic, Rochester, MN, USA*
08:30 – 08:45	Update on florbetapir F 18 (^{18}F-AV-45) PET clinical studies *AS Fleisher, Banner Alzheimer's Institute, Phoenix, AZ, USA and University of California, San Diego, CA, USA*
08:45 – 09:00	Prevalence and incidence of beta-amyloid accumulation from cross-sectional and longitudinal [^{11}C] PIB PET imaging *MA Mintun, Washington University School of Medicine, St. Louis, MO, USA*
09:00 – 09:15	Not quite PIB-positive, not quite PIB-negative: low levels of beta-amyloid deposition in elderly normal control subjects may precede AD-like changes *EC Mormino, University of California Berkeley, Berkeley, CA, USA*
09:15 – 09:30	Comparison of approaches for establishing cut-offs for [C-11] Pittsburgh Compound B *AD Cohen, University of Pittsburgh, Pittsburgh, PA, USA*
09:30 – 10:00	**General Discussion (Chairs and Speakers)**
10:00 – 10:15	**Morning Break**
10:15 – 11:00	**Session 2: F18 agents, Clinical Correlations** **William Jagust, Christopher Rowe (Chairs)**
10:15 – 10:30	Multicenter phase 2 trial to test florbetaben for β-amyloid (Aβ) brain PET in Alzheimer's disease (AD) *O Sabri, University of Leipzig, Leipzig, Saxony, Germany*
10:30 – 10:45	Primary outcome analysis of the multicentre phase II trial of 18F-flutemetamol, a Pittsburgh Compound B derivative for *in vivo* beta amyloid imaging *R Vandenberghe, University Hospitals Leuven, Leuven, Belgium*
10:45 – 11:00	Amyloid deposition detected with ^{18}F-AV-45 is related to decreased memory performance in clinically normal older individuals *RA Sperling, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
11:00 – 11:15	**General Discussion (Chairs and Speakers)**
11:15 – 12:00	**Keynote presentation by Marcus Raichle, Professor of Radiology, Neurology, Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, USA**

12:00 – 13:00	**Sit-down Buffet Lunch and Poster Viewing**
13:00 – 14:00	**Session 3: Metabolism, J-ADNI** **William Klunk, Mark Mintun (Chairs)**
13:00 – 13:15	A comparison of imaging, cognitive and blood biomarkers for prediction of cognitive decline *CC Rowe, Austin Hospital, Melbourne, VIC, Australia*
13:15 – 13:30	Relation between hypometabolism, impaired functional connectivity and ß-amyloid load in pre-dementia stages of Alzheimer's disease *A Drzezga, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA and Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA*
13:30 – 13:45	Amyloid deposition and FDG metabolism in relation to age in APOE4 carriers *JA Becker, Massachusetts General Hospital, Boston, MA, USA*
13:45 – 14:00	The status and the first preliminary results of amyloid imaging in Japanese Alzheimer's disease neuroimaging initiative (J-ADNI) study *K Ishii, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan*
14:00 – 14:15	**General Discussion (Chairs and Speakers)**
14:15 – 15:00	**Keynote presentation by Karen Ashe, Director, N. Bud Grossman Center for Memory Research and Care, Edmund Wallace and Anne Marie Tulloch Chairs in Neurology and Neuroscience, Professor of Neurology, University of Minnesota Medical School, Minneapolis, MN, USA**
15:00 – 15:15	**Afternoon Break**
15:15 – 16:00	**Session 4: Biomarkers** **Keith Johnson, Reisa Sperling (Chairs)**
15:15 – 15:30	Brain Aβ amyloid measures and MRI are complimentary predictors of progression from MCI to AD *CR Jack Jr, Neurology Mayo Clinic and Foundation, Rochester, MN, USA*
15:30 – 15:45	PET imaging of fibrillar amyloid in brain more sensitive diagnostic marker than CSF Aß42? *A Nordberg, Karolinska Institute, Stockholm, Sweden*
15:45 – 16:00	PIB imaging and CSF biomarkers predict cognitive impairment and dementia of the Alzheimer type (DAT) *JC Morris, Washington University School of Medicine, St. Louis, MO, USA*
16:00 – 16:30	**General Discussion (Chairs and Speakers)**
16:30 – 18:00	**Poster Session: 24 Posters - Wine and Cheese** Presentation of the HAI Young Investigator Award

Comparison of PiB distribution on PET with beta-amyloid deposits at autopsy

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Background: A comparison of the distribution of PiB accumulation as seen on PET with the distribution of amyloid pathology seen on autopsy is of great interest in understanding PiB binding *in vivo*. Very limited autopsy/PiB correlative data exists in the literature. In this report we describe the findings of PiB scans as compared to autopsy findings on 5 subjects.

Methods: Five subjects (4 male, 1 female) who underwent antemortem PiB PET scans subsequently came to autopsy. Diagnoses were of AD (CDR global = 2), naMCI (CDR global = 1.0), aMCI (CDR global = 0.5), LBD (CDR global = 0.5), and normal control (CDR global = 0.0). They expired 9, 17, 16, 32 and 24 months after their PiB scans, respectively. The quantitative distribution of PiB on PET imaging was compared in the frontal (Fr), parietal (Par), temporal (Tem), occipital (Occ) and hippocampal (Hip) regions to the distribution of diffuse plaques, cored plaques and vascular amyloid, evaluated with beta-amyloid immunohistochemistry (Novacastra, NCL-B-amyloid; clone 6F/3D) at autopsy.

Results: PiB scans showed increased PiB binding in the subjects with AD, aMCI and LBD (global PiB cerebellar ratios = 2.7, 1.7 and 1.5) but not in the naMCI or control subjects (global PiB cerebellar ratios = 1.3 and 1.4). At autopsy, the AD, aMCI and LBD subjects showed frequent numbers of diffuse and cored amyloid plaques in neocortical areas and variable amyloid angiopathty. In the naMCI and control subjects there was a conspicuous absence of amyloid deposits (diffuse and compact plaques) and amyloid angiopathy in all areas sampled.

Conclusions: These results are consistent with the expected finding that PiB accumulation occurs in subjects with AD, aMCI, and LBD although with some variability and reflects the frequency of microscopic amyloid deposits at autopsy. The findings are also consistent with the idea that subjects with naMCI are less likely to have AD-like pathological substrate, and more likely to have prodromal, non-AD dementia.

Grant support: National Institute on Aging [P50 AG16574, U01 AG06786, K23 AG030935 and R01 AG11378]; the Robert H and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program; and the Alexander Family Alzheimer’s Disease Research Professorship of the Mayo Foundation, USA.

Update on florbetapir F 18 (^{18}F-AV-45) PET clinical studies

AS Fleisher, JA Schneider, TG Beach, BJ Bedell, SP Zehntner, CM Clark, MP Krautkramer, MJ Pontecorvo, A Joshi, MA Mintun, M Flitter, F Hefti, DM Skovronsky.

Banner Alzheimer's Institute, Phoenix, Arizona, USA, University of California, San Diego, California, USA, Rush University, Chicago, Illinois, USA, Banner Sun Health Research Institute, Sun City, Arizona, USA, Biospective Inc, Montreal, Canada, Montreal Neurological Institute, McGill University, Montreal, Canada, University of Pennsylvania, Philadelphia, Pennsylvania, USA, Avid Radiopharmaceuticals, Philadelphia, Pennsylvania, USA, Washington University, St. Louis, USA.

Abstract: Avid Radiopharmaceuticals is currently conducting a phase III clinical study of subjects at the end of life with and without neurodegenerative dementia. A planned interim analysis of the first six subjects brought to autopsy has been performed comparing histopathology to quantitative and qualitative assessments of amyloid PET imaging.

Subjects who were ≥18 years old and willing to consent to a brain autopsy were admitted to the study if they had a life expectancy of <6 months. Florbetapir F 18 PET imaging was performed at the time of enrollment. Blinded raters scored the PET images for overall ligand retention in cortical grey matter using a semi-qualitative (0-4) scale. Mean cortical to cerebellar standard uptake value ratios (SUVr) were also determined across six predefined regions of interest. The mean interval from imaging to time of death was 43 days (range 1-158). Neuropathologic studies were performed blinded to the clinical and PET data. At the time of death, 6 micron paraffin-embedded tissue sections corresponding to the PET regions of interest were evaluated for density of β-amyloid deposition using immunohistochemistry (Signet 4G8, 100% sampling) and semi-quantitative estimates of plaque density as determined by a Bielschowsky silver stain of the same regions (modified CERAD scoring: none, sparse, moderate or frequent).

Of the six subjects, 4 had a clinical diagnosis at the time of imaging of AD, one had a clinical diagnosis of Parkinson's disease with dementia (PDD), and one had no clinical evidence of dementia. The mean age was 76 (range 47-86). Histopathology, CERAD neuritic plaque scores, florbetapir PET SUVr values, and visual ratings of grey matter retention will be presented and compared for the six autopsy cases.

Prevalence and incidence of beta-amyloid accumulation from cross-sectional and longitudinal [^{11}C] PIB PET imaging

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Background: We performed PET [^{11}C] PIB scans on cognitive normal subjects in both a cross-sectional and longitudinal design to estimate the prevalence and incidence of Aβ plaques, as well as the rate of accumulation.

Methods: Cognitively normal (CDR 0) subjects (45 to 88 yrs) underwent one (n=241) or two (n=129; separated by 2.5±1.1 years) PET [^{11}C] PIB scans. Binding Potential (BP) values and a global estimate of Aβ plaque deposition, the mean cortical BP (MCBP), were estimated in MRI-derived regions. The rate of Aβ accumulation was estimated from the change in BP per year.

Results: Using a threshold of MCBP >0.18, prevalence of Aβ plaques were seen to increase with age from 4.4% in the 50-59 decade to 30% in the 80-89 decade. Longitudinal analysis showed that 8 of the 110 subjects (7.3%) with a negative initial scan became positive on the second PIB scan yielding an incidence of 2.9%/yr. Subjects with at least one abnormal PIB scan (n=29) had a significantly higher rate of Aβ accumulation compared to the remaining subjects (0.034 BP/yr *vs* 0.008 BP/yr; $p<0.001$). Using a simple decay model and the estimated incidence of 2.9%/yr, the observed prevalence of Aβ plaques in each decade was predicted with surprising accuracy using a mean time between appearance of Aβ plaques to dementia of 10.8 years.

Conclusions: [^{11}C] PIB can detect accumulation of Aβ in cognitively normal subjects. These results suggest that combining longitudinal and cross-sectional Aβ imaging may characterize the onset and progression of a preclinical AD state to dementia.

Not quite PIB-positive, not quite PIB-negative: low levels of beta-amyloid deposition in elderly, normal control subjects may precede AD-like changes

EC Mormino, AO Hayenga, IV Yen, GD Rabinovici, SL Baker, WJ Jagust.

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

Objective: To compare approaches for defining PIB positivity, and investigate the relevance of elevated PIB in elderly normal controls.

Methods: Seven young normal controls (yNC), 52 elderly normal controls (eNC) and 23 Alzheimer's disease (AD) subjects underwent PIB-PET scanning (mean age: yNC=25.2[3.5]; eNC=74.1[6.0]; AD=66.3[10.7]). Distribution volume ratios (DVRs) were extracted using Logan plotting (35-90 min post-injection, cerebellum reference region) and PIB index values were extracted (average DVR across prefrontal, lateral temporal, parietal, and cingulate). Two methods were employed to determine a PIB positivity cut-off: Aizenstein 2008 iterative outlier approach using eNC PIB indices and 2 standard deviations (SDs) above the yNC PIB index mean. Resulting cut-offs were applied to eNC and AD. Based on classification results, eNC subjects were further divided into 3 groups (PIB-: PIB- with both approaches; PIB+: PIB+ with both approaches; "ambiguous": classified differently). Age, hippocampus volume (HV), episodic memory (EM) and APOE were investigated in these 3 eNC groups.

Results: PIB index values were highest in AD and lowest in yNC (yNC=1.025[0.024]; eNC=1.096[0.167]; AD=1.528[0.165]). The Aizenstein approach cut-off of 1.123 labeled 8/52 eNC and all AD cases as PIB+. Two SDs above the young NC mean was 1.074 and classified 15/52 eNC and all AD cases as PIB+. Compared to the PIB- group, the PIB+ group showed higher age (p=0.08), smaller HV (p=0.05), reduced EM (p=0.10) and more APOE4 carriers (p=0.19). Differences were not detected between ambiguous and PIB- groups, however, the ambiguous group was younger than the PIB+ group (p=0.01).

Conclusions: A more conservative cut-off had no effect on AD classification, and isolated eNC that were more similar to AD subjects. Longitudinal follow up is needed to determine the biological relevance of "ambiguous" eNC subjects. It is possible that these subjects show early amyloid deposition before downstream atrophy and cognitive deficits are present.

Comparison of approaches for establishing cut-offs for [C-11] Pittsburgh Compound B

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Background: Amyloid deposition can be detected using PET imaging with [C-11] Pittsburgh Compound-B (PiB). Several methods have been used to identify cut-off values to determine PiB(+) and PiB(-) status. To date, there has been little discussion of the advantages and disadvantages of the various methods used to determine these cut-offs.

Methods: Sixty-two normal controls were screened for normal cognition using a neuropsychological test battery. PiB PET scanning (90 min) was performed and regional PiB retention measures were determined (DVR (40-90 min) and SUVR (50-70 min): cerebellum reference). These measures were then corrected for cerebrospinal fluid (CSF) using co-registered MRIs. Cut-offs were created using an iterative approach removing "mild" outliers to identify a residual amyloid-negative group. This method was used to compare cut-offs generated for CSF corrected *vs* non-CSF corrected data, DVR *vs* SUVR data, and global *vs* cortical regional PiB measures.

Results: Comparisons of regional and global PiB measures used for calculation of cut-offs demonstrated that use of regional PiB values identified a greater or equal number of PiB(+) subjects than did cut-offs calculated from a global PiB value. Cut-offs calculated using CSF corrected data *vs* non-CSF corrected data or from DVR *vs* SUVR analyses yielded variable results depending on the methods used.

Conclusions: Differences in the number of PiB(+) subjects classified using cut-offs calculated from regional or global PiB measures may be a result of focal early amyloid deposition, with cortical regional measures more readily detecting focal deposition than single global average measures. The variations observed in cut-offs calculated with CSF *vs* non-CSF corrected data and with DVR *vs* SUVR data are not as well understood, but may be a result of variations within the inter-quartile ranges for each data set. Ongoing studies will explore cut-offs calculated with other measures using the iterative approach and cut-offs calculated using an ROC approach.

Multicenter phase 2 trial to test florbetaben for b-amyloid (Aβ) brain PET in Alzheimer's disease (AD)

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In AD, PET imaging to detect Aβ has a great potential for early and accurate diagnosis. Florbetaben is currently under clinical development as a promising tracer candidate for this purpose. The aim of this multicenter, phase 2 trial was to determine the diagnostic efficacy of florbetaben in differentiating ADs from healthy controls (HCs).

In 18 centers, 150 subjects were recruited/imaged with florbetaben PET: 81 patients with probable AD (DSM-IV-TR and NINCDS-ADRDA criteria, age ≥55 yrs, MMSE=18-26, CDR=0.5-2) and 69 age-matched HCs (MMSE≥28, CDR=0). The PET data were visually analyzed by 3 blinded readers. Further, semi-quantitative analysis was done by adapting a modified AAL volume of interest (VOI) template and obtaining SUV-ratios (SUVRs, reference: cerebellar cortex). To optimize this VOI method, grey matter was automatically segmented on the MRIs.

According to visual analysis, the 90-110 min p.i. PET data were 80% sensitive and 90% specific in discriminating ADs from HCs. VOI analysis of the 90-110 min p.i. PET data revealed significantly ($p<0.0001$) higher SUVRs for ADs versus HCs, in particular in frontal, laterotemporal, parietal, and cingulate cortices. Grey matter segmentation led to 10-22% improved SUVR discrimination between AD and HCs ($p<0.0001$) for cortical regions compared to the non-segmented approach. In AD patients, APOE4 alleles were found more frequently for PET-positives as compared to PET-negatives (65 *vs* 22%, $p=0.027$). There were significant correlations of SUVRs to APOE4 status (number of APOE4 alleles) in gyrus rectus, temporal and cingulated cortices for the AD group ($p<0.05$, all $r\geq0.3$) but not for HCs (all $p>0.1$).

Florbetaben brain PET is accurate in differentiating clinically diagnosed ADs from HCs. The correlations observed between PET data and APOE4 genotypes confirm preclinical data showing that florbetaben binds to Aβ. Further development of florbetaben PET as a visual adjunct for improved AD diagnosis is encouraged.

This trial was supported by Bayer Healthcare.

Primary outcome analysis of the multicentre phase II trial of ^{18}F-flutemetamol, a Pittsburgh Compound B derivative for *in vivo* beta amyloid imaging

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Objective: 1. Primary: To determine the efficacy of visual assessment of ^{18}F-flutemetamol scans in assigning patients with clinically probable Alzheimer's disease (AD) and cognitively intact healthy volunteers (HV) to a 'raised' versus 'normal' uptake category, with the clinical diagnosis as standard of truth (SOT). 2. To compare visual assignment of ^{18}F-flutemetamol scans in AD and amnestic mild cognitive impairment (MCI) with visual assignment based on ^{11}C-PIB scans. 3. To compare the visual reads with categorization based on quantitative measures.

Methods: 27 patients with early-stage AD, 20 with MCI, 15 HV above and 10 HV below 55 years, underwent an ^{18}F-flutemetamol PET scan (max target activity 185 MBq, acquisition window 85-115 min post-injection). 20 of the AD and 20 of the MCI cases also underwent a ^{11}C-PIB PET (max target activity 370 MBq, acquisition window 40-70 min post-injection). Five independent readers assigned the 18F-flutemetamol scans to either 'raised' or 'normal' uptake category in a binary way. Inter-rater agreement was expressed by Fleis' kappa coefficient. In a separate session 3 months later, the same readers classified the 40 ^{11}C-PIB scans. Quantitative analysis was based on Standardized Uptake Value Ratios (SUVR) in a composite cortical region with cerebellum as reference region.

Results: 25/27 ^{18}F-flutemetamol scans from the AD subjects and 1 scan from the 15 elderly HVs were visually assigned to the raised uptake category (sensitivity and specificity of 93.1% and 93.3%, respectively). Nine MCI cases were assigned to the raised uptake category. Across all groups, kappa was 0.96. Visual assignment based on ^{18}F-flutemetamol strictly matched that based on ^{11}C-PIB. In AD and HV, visual and SUVR-based classifications were strictly concordant. In 2 MCI subjects, SUVR values were just above threshold while they were read as negative by all 5 readers.

Conclusion: This phase II study met its primary objective.

Amyloid deposition detected with ^{18}F-AV-45 is related to decreased memory performance in clinically normal older individuals

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Background: Converging evidence from autopsy, cerebrospinal fluid, and PET amyloid imaging studies suggests that a substantial proportion of clinically normal, older individuals harbor amyloid-β pathology. The clinical relevance of amyloid deposition in healthy older individuals remains to be fully elucidated, as neuropsychological studies in amyloid-positive older individuals have yielded variable results to date. In this study, we evaluated the relationship of amyloid burden and cognition in healthy control (HC) subjects recruited in a multicenter study of florbetapir F18 (^{18}F-AV-45) PET amyloid imaging.

Methods: Seventy-eight HC subjects (CDR=0, MMSE>29, mean age 69.5±11.1) were assessed with a brief cognitive test battery, including the Weschler memory immediate and delayed recall, digit-symbol substitution, verbal fluency and ADAS-Cog. Subjects underwent PET amyloid imaging during a 10 min acquisition, 50 min following i.v. injection of 10 mCi (370 MBq) of ^{18}F-AV-45. SUVr were calculated from a combined set of 6 cortical regions. Scans were also visually scored as amyloid+ or amyloid- by 3 blinded readers.

Results: Among the 78 HC subjects, SUVr was significantly related to both lower immediate (partial r=-0.33; p=0.003) and delayed recall scores (partial r=-0.28; p=0.017), controlling for both age and education. Digit-symbol substitution also demonstrated a relationship with SUVr (p=0.035), but this was no longer significant with age included in the model. On visual inspection, 11/78 (14%) of the HCs were rated as amyloid+. Performance on immediate recall was significantly lower in the amyloid+ (11.9±3.99) compared with amyloid- HCs (14.0±2.94, p=0.04); with a similar trend observed in delayed recall (p=0.061).

Conclusions: These results indicate that high amyloid burden is associated with decreased memory performance, even within the range seen in clinically normal older subjects. Longitudinal follow-up is ongoing to determine if ^{18}F-AV-45 is predictive of progressive cognitive decline in these individuals.

A comparison of imaging, cognitive and blood biomarkers for prediction of cognitive decline

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Background: Longitudinal studies including both structural and amyloid neuroimaging as well as cognitive, genetic and biochemical biomarkers are allowing a better understanding of the role of brain Aβ deposition in cognitive decline. The purpose of this study was to compare the accuracy of different biomarkers to predict cognitive decline and conversion to Alzheimer's disease (AD).

Methods: Follow-up was obtained 20±3 months after biochemical (plasma $A\beta_{42}/A\beta_{40}$), genetic (ApoE), cognitive (memory and non-memory scores) and neuroimaging (3D MRI, FDG and PiB-PET) evaluation in 57 subjects with mild cognitive impairment (MCI) (79% amnestic) and 97 age-matched healthy controls (HC) (73±7 years of age).

Results: At follow-up, progression to AD occurred in 47% of MCI, while 4% were re-classified as HC. Comparison of converters to non-converters showed a significant difference in episodic memory scores, prevalence of ApoE-ε4 allele, PiB retention, hippocampal volume (HV) and posterior cingulate glucose metabolism. There were no differences in plasma $A\beta_{42}/A\beta_{40}$ and non-memory scores. The accuracy in predicting conversion from MCI to AD based on cut-off values was 81% for PiB, 78% for memory, 77% for ApoE-ε4, 72% for HV, 68% for FDG, and 61% for plasma Aβ. Combining PiB and memory, the predictive accuracy increased to 87%. Of the high PiB HC, 14% developed MCI or AD by 20 months and at least 21% by 3 years. One (2%) low PiB HC developed MCI. Of PiB, HV, FDG, age, memory score and non-memory cognitive score, only PiB SUVR ($p<0.001$) and memory score ($p=0.003$) survived as significant predictors of decline in MMSE in the combined MCI and HC cohort using step-wise regression.

Conclusions: PiB binding and cognitive measures were the best predictors of cognitive decline and conversion to AD over 20 months. These findings may have application in early diagnosis of AD and subject selection for therapeutic trials.

Relation between hypometabolism, impaired functional connectivity and ß-amyloid load in pre-dementia stages of Alzheimer's disease

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Objectives: In Alzheimer's disease (AD) and mild cognitive impairment (MCI), specific patterns of cerebral hypometabolism and disrupted functional connectivity have been reported. New functional MRI-methods allow the identification of cortical hubs, i.e. regions with high functional, whole-brain connectivity (WBC), without restriction to specific networks. Aim of this study was to assess changes in cerebral metabolism and WBC in relation to β-amyloid load in pre-dementia-stages of AD.

Methods: Thirty-seven older subjects underwent resting state BOLD-fMRI to measure WBC, [18F]FDG PET for assessment of cerebral glucose metabolism and [11C]PIB PET for evaluation of amyloid-plaque load. PIB-uptake ratios were calculated within a ROI including frontal, temporoparietal, and retrosplenial cortices (FLR-ROI), using the cerebellum as reference region. Based on a FLR-threshold of 1.15, subjects were divided into PIB-positive(+) and -negative(-). Three age-matched groups were studied: A) 12 PIB(-) controls, B) 12 PIB(+) controls, C) 13 PIB(+) MCI patients. Voxel-based and ROI-based statistical analyses were performed. The overlap between hypometabolism and WBC abnormalities in MCI was used to define a ROI to extract values for correlation analysis between different modalities.

Results: Group comparison between MCI and PIB(-) controls revealed significant hypometabolism and regionally overlapping WBC-reductions in MCI in posterior cingulate and parietal cortex (typical cortical hubs). PIB-FLR values were negatively correlated with FDG (r=-0.67) and WBC values (r=-0.42), and a linear positive correlation was found between FDG and WBC-values (r=0.51) across the entire population (groups A, B and C). These results survived correction for age and grey matter density.

Conclusions: In MCI, reduced WBC was found in cortical hub regions regionally overlapping with local hypometabolism, suggesting that these abnormalities may be interrelated. Across all subjects, both metabolic and functional changes demonstrated a significant relationship with amyloid-load, indicating that they reflect early neurodegenerative changes in AD, progressively evolving prior to symptomatic onset of dementia.

Amyloid deposition and FDG metabolism in relation to age in APOE4 carriers

JA Becker, J Carmasin, J Maye, DR Rentz, RL Buckner, RA Sperling, KA Johnson.

Background: APOE4 carrier status in normal individuals has been associated with both altered glucose metabolism and higher levels of amyloid deposition.

Objective: To evaluate the impact of APOE-ε4 carrier status on FDG metabolism considering the effects of PiB retention, cortical thickness and age in cognitively normal (CN) older individuals.

Methods: Forty-three CN subjects, mean age ± SD = 75.6 ± 7.0 (11 ε4 carriers, mean age = 73.4 ± 7.6, and 32 ε4 non-carriers, mean age = 76.4 ± 6.8) underwent PiB (DVR, cerebellar cortex reference region) and FDG (SUV, covariance adjusted for cerebellar cortex SUV) PET and MR imaging; image data was processed using Freesurfer. FDG analyses were performed vertex-wise controlling for precuneus PiB retention, cortical thickness local to each vertex, and age, in order to isolate APOE-ε4 effects on metabolism.

Results: Compared to non-carriers, ε4 carriers had similar precuneus, parietal, frontal and global amyloid deposition, but exhibited hypometabolism in default network areas and hypermetabolism in prefrontal, inferomedial temporal and caudal anterior cingulate regions (cluster-wise corrected $p<0.001$). In addition, compared to non-carriers, the relationship of FDG metabolism to age in ε4 carriers was significantly steeper: greater age was associated with lower FDG metabolism (interaction term peak vertex $p<0.005$, right-hemisphere superior frontal cortex, Talairach xyz = 16,54,16; cluster-wise $p<0.043$ corrected for multiple comparisons).

Conclusions: These preliminary results in 43 CN subjects suggest that certain frontal and anterior cingulate regions of relative hypermetabolism may mark an important intermediate step along a trajectory of prodromal AD.

The status and the first preliminary results of amyloid imaging in the Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) study

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The Alzheimer's Disease Neuroimaging Initiative in Japan (J-ADNI) project has been launched enacting a harmonized protocol with US and worldwide ADNI studies. Thirty-eight clinical sites recruited a total of 600 subjects: 300 mild cognitive impairment (MCI), 150 Alzheimer's disease (AD) and 150 cognitively normal (CN), and candidates of surrogate markers such as MRI, FDG-PET, PiB-PET, BF227-PET and CSF biomarkers are being accumulated. Among the registered 311 subjects, as of February 2010, amyloid PET was acquired in 45%, and FDG-PET was obtained in 75% of the total participants.

The first 75 baseline PiB scans from 9 PET centers were analyzed with demographic information including APOE genotype. A bolus injection of [C-11] PiB (537±70 MBq) was followed by a 70-min 3D dynamic scan. A sum image of 50-70 min and a parametric image of distribution volume by Logan graphical analysis were created in each subject, and evaluated in reference to the cerebellar cortex measures, that is SUVR and DVR, for both visual diagnosis and quantitative measurements of neocortical regions.

We estimated an optimal cut-off value for SUVR as 1.47, with which the discrimination well corresponds to the visual diagnosis. The prevalence of PiB positivity was 93% in AD (age and ratio of APOE4 carrier; 73±5.3, 50.0%), 70% of MCI (71±5.6, 57.9%), and 32% of CN (67±5.1, 43.8%). The PiB positive ratio in APOE4 carrier in AD, MCI and CN groups were 100%, 100%, and 54%, whereas those in non-carriers remain 88%, 40%, and 22%. A significant positive effect of APOE4 for PiB accumulation was observed even in early 60s. Among 3 cases out of 33 subjects diagnosed as PiB-negative with SUVR images, we found distinct cortical deposition of PiB in DVR images, but none of the reverse.

We observed a PiB positive ratio in the Japanese population equivalent to the US, Australia and EU studies. A significant APOE4 effect was found to push up amyloid-beta deposition even in young-old subjects. A dynamic PiB-PET analysis may give us more sensitive assessment for a small amount of amyloid deposition.

Brain Aβ amyloid measures and MRI are complimentary predictors of progression from MCI to AD

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Introduction: Biomarkers of brain Aβ amyloid deposition, measured either by CSF or PIB PET imaging, are significant predictors of future progression from MCI to AD, as are MRI measures of brain atrophy. Our objective was to compare these two classes of biomarkers to predict time to progression and evaluate their effect on the hazard of progressing.

Methods: A total of 218 MCI subjects were identified from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The primary outcome was time to conversion from a diagnosis of MCI to AD. Hippocampal volume was measured from FreeSurfer and adjusted for total intracranial volume. We used a new method of converting CSF Aβ42 into PIB PET units and combining CSF and PIB PET imaging data to produce equivalent measures of "brain Aβ amyloid load" from either biomarker source.

Results: Over a median progression-free follow-up time of 1.7 years, 86 subjects progressed from MCI to AD. The overall hazard ratio [(HR); 95% CI] for progression based on comparing the upper vs the lower quartiles was 2.5 (1.4 to 4.3) for Aβ amyloid load and 2.6 (1.9 to 3.6) for comparing the lower to the upper quartile for hippocampal volume. The relationship between hazard of progressing and increasingly abnormal hippocampal volume (functional form) was linear. In contrast, there was evidence of non-linearity for Aβ amyloid load in the form of a plateau in terms of risk. MRI and Aβ amyloid load remained significant in models that included both biomarkers as predictors.

Conclusions: Biomarkers of neurodegeneration (i.e. atrophy on MRI) and brain Aβ amyloid deposition predict conversion from MCI to AD independently and also provide complimentary predictive information. However, the functional form of these two classes of biomarkers differs such that at some point additional amyloid load does not confer additional risk.

PET imaging of fibrillar amyloid in brain more sensitive diagnostic marker than CSF Aß42?

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There is a rapid increasing knowledge of the molecular pathogenesis of Alzheimer's disease (AD). Early diagnostic markers are needed for identifying subjects at risk for developing AD as well as for outcome measures in clinical trials of new disease modifying drugs. Amyloid (Aß) imaging offers possibilities to further understand the influence of amyloid deposition on functional changes during development of clinical AD. High amyloid PIB retention is observed in prodromal AD. The CSF biomarkers Aß42, tau and ptau have in large, multicentre studies shown high predictive value as clinical diagnostic tools in AD.

A cohort of patients (age range 51-83 years), who underwent routine clinical assessment for cognitive problems at the Department of Geriatric Medicine, Karolinska University Hospital Huddinge (including MRI, CSF biomarkers and neuropsychology testing) and diagnosed as mild cognitive impairment (MCI) and mild AD, also underwent PET scans with ^{11}C-PIB and ^{18}F-FDG. A comparison was made been the percentage of patients who showed high PIB retention (PIB+) compared to those who showed pathological CSF Aß42, tau and ptau levels, respectively.

When the patients underwent PIB PET scans, 82% of the AD and MCI patients showed high amyloid load in the brain (PIB+). Forty-six% of the patients showed pathological low Aß42 values, 63% high tau values and 81% high levels of ptau in CSF. We and others have previously reported a reverse correlation between brain PIB retention and Aß42 levels in CSF. Although this relationship was noticed, we observed patients with high PIB retention (PIB+), normal Aß42 levels but elevated CSF ptau levels. It is important to further study the time course of brain fibrillar Aß levels and CSF biomarkers in prodromal AD to obtain a deeper insight into the disease mechanisms. In these ongoing studies, we now also include PET tracers for studies of activated astrocytes as a component of inflammatory processes.

PIB Imaging and CSF biomarkers predict cognitive impairment and dementia of the Alzheimer type (DAT)

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Background: We reported that preclinical AD as detected by the amyloid-imaging agent PIB is associated with progression to symptomatic AD in cognitively normal persons. Here, we update the predictive power of PET PIB imaging for symptomatic AD and cognitive impairment and explore whether PIB uptake and cerebrospinal fluid (CSF) biomarker measures concomitantly predict time to cognitive impairment.

Methods: Participants (n=195; mean age 71.6 years) were CDR=0 at time of baseline PET PIB scan and were assessed annually for a mean of 2.9 years. A subsample (n=114) had CSF within 1 year of PET/PIB imaging. Cox proportional hazards models were used to examine time to cognitive impairment (CDR>0) in both samples and to DAT in the larger sample as a function of the mean cortical binding potential (MCBP) for PIB at baseline scan.

Results: In the entire sample, 28 participants developed cognitive impairment over the follow-up period, 11 of whom were diagnosed with DAT. Higher baseline MCBP (p=0.02) predicted a faster time to a DAT diagnosis (p=0.02) and also predicted time to cognitive impairment generally (p=0.001). In the subsample with CSF data, 12 participants developed cognitive impairment. When considered alone, MCBP (p=0.0257), $A\beta_{42}$ (p=0.0163), and the ratios of tau/$A\beta_{42}$ (p=0.0026) and $ptau_{181}$/$A\beta_{42}$ (p=0.0016) predicted time to cognitive impairment. When MCBP was paired with each of the CSF variables in a series of Cox proportional hazards models, either MCBP or the CSF variable, but not both, significantly predicted incident cognitive impairment.

Conclusions: Preclinical AD, as detected either by PET PIB or by CSF biomarkers, is a harbinger of both cognitive impairment generally and symptomatic AD specifically. Incorporating both MCBP and CSF biomarkers in the models does not add to the predictive power of using either biomarker alone.

Patterns of amyloid deposition distinguish non-demented Parkinson's disease from normal aging

POSTER ABSTRACT

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In a previous study, we found that non-demented patients with Parkinson's disease (PD) did not differ from normal controls (NC) in average global PiB binding, but focal cortical PiB retention was observed in many PD subjects and in all demented patients with PD. In this study, we tested whether the overall burden and spatial distribution of amyloid deposits differed in non-demented PD compared to healthy controls.

Twenty non-demented PD patients (age 70±7 years) and 70 NC (aged 74±8 years) underwent PiB PET, high-resolution MR imaging, Freesurfer processing, and partial volume correction. Cortical PiB DVR values in ROI were left-right averaged. A linear stepwise discriminant analysis initially identified a subset of 7 ROIs from a pool of 35, a linear combination of which significantly discriminated the two groups ($p<0.0001$; 63% of variance of the function accounted for by the group classification). A parallel logistic regression analysis produced a similar linear combination of ROI predictors, which discriminated the PD from NC ($p<0.0001$); the ROC analysis area under the curve (AUC) was 0.976. Cross-validation was by the leave-one-out method (AUC=0.953; for 1000 bootstrap re-samples 95% CI=0.92-0.98) and by 1000 random split-half re-samples (AUC CI=0.65-0.94).

The discriminant coefficients indicated higher DVR values in parahippocampal, post-central and rostral anterior cingulate ROIs reflecting PD status, whereas higher DVR values in posterior cingulate, lateral occipital, temporal pole and amygdala were indicative of NC status. Non-partial volume-corrected PET data yielded slightly weaker results though still significant. We also found significant relations of discriminant scores to measures of motor impairment in PD (Hoehn & Yahr, UPDRS). These results suggest that PD patients and NC subjects can be reliably distinguished by different patterns of amyloid accumulation.

Overestimation of memory performance in normal elderly subjects is associated with amyloid burden in the temporal lobe

POSTER ABSTRACT

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Anosognosia, a defect in self-awareness of cognitive deficit, is frequently observed in Alzheimer's disease (AD), and has been linked to temporal lobe pathology. Since amyloid deposition in AD begins many years prior to clinical dementia, we hypothesized that early alterations in awareness of memory performance might be associated with occult amyloid deposition in clinically normal older subjects.

Thirty-six cognitively normal (CDR 0) subjects underwent neuropsychological assessment and PiB PET imaging. The Memory Function Questionnaire "Frequency of Forgetting" (FoF) variable was used as a measure of self-awareness of memory functioning, and actual memory performance was measured with the 12-word Selective Reminding Test "Delayed Recall" (DR) variable. We calculated an Anosognosia Ratio (AR) for each subject as [self-assessment – actual performance] divided by [self-assessment + actual performance] (range -1.0 to 1.0). More positive scores indicate an overestimation of memory performance, similar to anosognosia, while more negative scores indicate an underestimation of memory performance. A score of 0 is an accurate estimation of performance.

Higher AR score was associated voxel-wise with greater PiB retention (DVR) in the inferior temporal lobe ($Z=4.33$, voxel-level corrected $p=0.03$; cluster-level corrected $p=0.02$). AAL ROI analyses confirmed that subjects who overestimated performance ($n=20$) had greater PiB retention in medial and lateral temporal cortex, hippocampus, fusiform and amygdala compared to those who did not overestimate performance ($n=16$; $p<0.05$). Lower DR score was also associated voxel-wise with greater PiB retention in the inferior temporal lobe ($Z=4.24$, voxel-level corrected $p=0.04$; cluster-level corrected $p=0.10$).

We conclude that clinically normal older adults who overestimated their own memory performance had greater amyloid burden in multiple temporal regions. In addition, amyloid was related to mild memory impairment in the full sample. Clinical follow-up will be required to determine whether these individuals develop memory impairment, signs of anosognosia, or AD.

Pharmacokinetics and pharmacodynamics of ^{18}F-AV-45 (florbetapir F 18) PET imaging in Alzheimer's disease (AD) and healthy control subjects: results of a phase II trial: ^{18}F-AV-45-A03

POSTER ABSTRACT

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The primary objectives of this study were to: 1) obtain additional information regarding the safety of the administration of ^{18}F-AV-45 in healthy volunteers and subjects with AD; 2) evaluate two dose levels of ^{18}F AV 45: 111 MBq (3 mCi) and 370 MBq (10 mCi) in healthy volunteers and subjects with AD, and; 3) obtain data regarding the metabolism and clearance of ^{18}F-AV-45.

20 subjects were enrolled in this study: 9 subjects (5 with AD and 4 control subjects) received a single injection of 111 MBq (3 mCi) and 11 (4 with AD and 7 control subjects) received 370 MBq (10 mCi) of ^{18}F-AV-45.

Blood clearance and metabolite results showed that ^{18}F-AV-45 is rapidly eliminated from circulation, with less than 5% of the injected ^{18}F-radioactivity remaining by 20 minutes post-injection. Most of the ^{18}F remaining in circulation was in the form of polar metabolites of ^{18}F-AV-45. The blood clearance of ^{18}F, following administration of ^{18}F-AV-45, was found to be similar for healthy control subjects and AD subjects.

Visual assessments of the PET image quality for the 370 MBq dose group were slightly better than the 111 MBq dose group, however, there was no difference in blinded reader ability to identify high and low amyloid burden at the two dose levels. For both the 111 MBq and 370 MBq doses, subjects with AD showed a clear separation between cortical and cerebellar activity within 15 minutes of dose administration; cognitively normal controls did not show separation of cortical and cerebellar time activity curves. There were no significant differences in SUVR results for images acquired between 30 and 90 minutes post-injection for either dose group for AD and control subjects. The numerical optimum timeframe for cortical SUVR results in AD subjects was reached by 40 minutes post-injection and was constant for the remainder of the imaging session.

Evaluation of metabolites of [^{18}F]flutemetamol, an amyloid imaging agent in human and rat *in vitro* and rat *in vivo* models

POSTER ABSTRACT

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[^{18}F]flutemetamol is an ^{18}F-labeled derivative of PIB that shows affinity for beta-amyloid, a characteristic of the pathology in Alzheimer's disease (AD) that develops before clinical manifestation of AD. [^{18}F]flutemetamol in AD patients shows significantly greater uptake in neocortical and striatum regions compared with healthy volunteers (HV) and distributes in a comparable manner to the [^{11}C]PIB tracer, but has the advantage of a longer half-life. [^{18}F]flutemetamol is a small lipophillic tracer with good brain uptake of 4% injected dose (id) at 2 minutes post-injection (pi).

Metabolites identified in pre-clinical work are primarily more hydrophilic than flutemetamol itself. Human, dog, mouse and rat hepatic S9 incubations have been carried out on ^{18}F and ^{14}C-radiolabelled flutemetamol compounds for up to 180 minutes. Small quantities of two to four metabolites were observed in these *in vitro* assays. N-demethylation was considered the main metabolic pathway and the resulting metabolite was present in both the rat and human systems.

In vivo evaluation of [^{11}C]flutemetamol in baboons and rats resulted in two hydrophilic metabolites in both species. [^{3}H]flutemetamol was also tested in human and rat plasma *in vitro* studies, generating small quantities of two metabolites.

Analysis of arterial blood samples from subjects in the ALZ103 clinical trials, showed rapid metabolism of [^{18}F] flutemetamol at 20 minutes pi. These data are compared with *in vivo* rat studies to establish if any metabolites formed cross the blood-brain barrier (BBB).

An understanding of metabolism in preclinical and human subjects is important so that any transfer of metabolites across the BBB can be assessed with regards to appropriate kinetic modelling. In the case of imaging amyloid, this could be valuable in potentially improving the accuracy of image interpretation, especially in subjects close to the threshold of normality and abnormality.

Using FDG PET and PIB (Pittsburgh B) PET imaging to distinguish atypical Alzheimer's disease and fronto-temporal dementia cases

POSTER ABSTRACT

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Background: Many cases of progressive dementia are not clinically typical for Alzheimer's disease (AD). Fronto-temporal dementia (FTD) or variants are often considered, but are by no means certain clinical diagnoses. More precise diagnosis is needed.

Methods: 35 patients were studied; 12 meeting criteria for "probable AD", and 6 judged to be FTD or one of its variants with "high probability". The other 17 were judged to be "atypical/possible AD/possibly FTD, and the degree of diagnostic certainly was rated as medium to low. All were studied with FDG PET, and PET amyloid imaging with PIB (Pittsburgh B Compound).

Results: Of those 12 subjects meeting criteria for "probable AD", 11 remained classified as such after multi-modal imaging, but one was reclassified as FTD. Of the 6 patients judged to be FTD with "high certainty", four remained as such, while two were reclassified as AD. Of the 17 rated clinically with medium to low diagnostic certainty, all were reclassified, 15 as AD, and 2 as FTD.

Conclusions: Multi-modal imaging was successful in classifying all medium and low certainty cases in a convergent manner.

Can we use pons as a reference region for the analysis of [11C]PIB PET?

POSTER ABSTRACT

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Aim: To validate the pons as a reference region for the analysis of [11C]PIB PET.

Background: [11C]PIB PET is a marker of amyloid in dementia. The majority of studies have either used Logan analysis to generate relative distribution volumes (DVR) with cerebellar uptake as a reference of non-specific binding or target to cerebellar ratios as the preferred methods of analysis. However, cerebellar amyloid may be present in genetic Alzheimer's disease (AD) and prion diseases. In this study we assess whether the pons can be used as a reliable reference region for the analysis of [11C]PIB PET.

Methods: 12 AD subjects age 65±4.5 yrs and MMSE 21.4±4 and 10 control subjects had [11C]PIB PET with arterial blood sampling. Object maps were created by segmenting individual MRIs and spatially transforming the grey matter images into standard stereotaxic MNI space and then superimposing a probabilistic atlas. Cortical [11C]PIB uptake was assessed by ROI (region of interest) analysis. Regional DVRs were generated with the Logan method. Additionally, 60-90 min target to cerebellar ratios ($RATIO_{CER}$) and 60-90 min target to pons ratios ($RATIO_{PONS}$) were computed. Using SPSS we calculated T-scores, p values, percentage increases and intraclass correlations (ICC) for the different regions.

Results: All the analytical methods were able to differentiate AD from controls ($p<0.001$). $RATIO_{CER}$ and $RATIO_{PONS}$ showed increased [11C]PIB uptake in AD compared to controls that was higher than seen using an arterial input function. All methods had a very high ICC; $RATIO_{CER}$ performed best closely followed by $RATIO_{PONS}$.

Conclusions: This study shows that 60-90 min target to pons RATIOs can be used as a reliable method of analysis in [11C]PIB studies where cerebellum is not appropriate without the use of invasive arterial input measurements in clinical studies.

Evaluation of inositol and benzothiazole derivatives for amyloid-β peptide inhibition and amyloid imaging

POSTER ABSTRACT

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Despite numerous recent advances, Alzheimer's disease continues to pose a challenge both for diagnostic and treatment strategies. We have recently evaluated two compounds for potential use both as amyloid imaging agents and as therapeutic agents.

Multiple lines of evidence suggest that the accumulation of neurotoxic oligomeric aggregates of amyloid-beta (Aβ) may be a central event in the pathogenesis of Alzheimer's disease. It is possible that inhibitors of Aβ aggregation and toxicity may be effective in blocking this pathogenic cascade. Here, we report the development of a compound that could have both diagnostic and therapeutic roles by binding to oligomers. In an effort to combine bioavailability and dual function we have tethered scyllo-inositol, known to bind and neutralize oligomers into soluble complexes, to 2-ethyl-8-methyl-2,8-diazospiro-4,5-decan-1,3-dione, a muscarinic receptor agonist which improves neurotransmitter function. These derivatives have recently been evaluated for Aβ peptide polymerization inhibition.

In addition, F-18 labeled N-2-[fluoropropyl]-2-(4'-(methylamino)phenyl)-6-hydroxybenzothiazole (FMHT) was prepared as a potential imaging agent for Alzheimer's disease. Brain activity for F-18MHT was pronounced within 2 minutes (4%ID/g) and washed out quickly; brain activity was 1.2%ID/g at 45 minutes and right and left hemispheres were clearly visualized. Initial brain uptake of F-18MHT was higher than that of PIB. Interestingly, *in vitro* Aβ studies showed cold FMHT had a 25-fold inhibition of Aβ polymerization, suggesting that FMHT could be a promising candidate for Alzheimer's treatment.

Regional burden of Aβ-amyloid relates to cognitive function in Parkinson's disease

POSTER ABSTRACT

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Isolated cognitive impairments and dementia are common in Parkinson's disease (PD). In this study, we evaluated the extent of Aβ accumulation in non-demented PD individuals and the relation of global and regional Aβ to cognitive impairment.

35 non-demented PD subjects underwent neurological examination, cognitive testing, and PiB PET. To assess regional amyloid burden, 20 subjects also underwent high resolution MRI for Freesurfer processing and partial volume correction. 16 cortical ROIs that are associated with high amyloid deposition in Alzheimer's disease were selected for analysis. PiB DVR values in ROI were left-right averaged. The 35 PD subjects (men/women = 26/9) had a mean age of 69 years, education of 16.5 years and Hoehn & Yahr stage of 2.3; the mean MMSE was 28.

Global, non-partial volume corrected PiB DVR (with cerebellar reference) ranged from 0.98 to 1.57 (mean±SD: 1.18±0.14), and did not differentiate those with (n=15) and without (n=20) specific cognitive impairments (defined as CDR-sum of boxes score [CDR-SOB]>0). Across 11/16 ROIs, partial volume corrected regional amyloid burden correlated with increased impairment on CDR-SOB ($p<0.04$ for each correlation, covarying for age). A multiple regression analysis revealed a linear combination of 5 ROIs that significantly predicted the CDR-SOB ($p<0.0001$). In addition, amyloid deposition in medial temporal lobe structures (the hippocampus, parahippocampus, and entorhinal cortex), significantly correlated with short term memory impairment (logical memory IIa and the free recall component of the selective reminding test, covarying for age). When three subjects with PD dementia were included in this analysis, these correlations grew stronger and PiB DVR in the anterior cingulate also correlated significantly with memory impairment.

These results suggest that Aβ-amyloid accumulation is a frequent finding in non-demented PD patients and that regional amyloid burden relates to cognitive performance in PD, supporting the possibility that Aβ may be a risk factor in PD for developing dementia.

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Progression of MCI associated with amyloid deposition using PIB PET imaging

POSTER ABSTRACT

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Objective: We investigate amyloid deposition in patients with mild cognitive impairment (MCI) over time by carbon 11-labeled Pittsburgh Compound B ([11C]-PIB) PET, and determine whether cortical PIB uptake is predictive of development of Alzheimer's disease (AD).

Methods: 34 patients with MCI, 21 with AD, and 24 healthy controls (HC) were included. All subjects underwent cognitive testing, ApoE genotype and 60-min dynamic [11C]-PIB PET. [11C]-PIB data was acquired from 35-60 min after injection. Distribution volume ratios (DVR) were calculated for 18 cortical regions using Logan graphical analysis. The patients were clinically followed up for 1-2 years after baseline and re-examined.

Results: Eleven (32%) of the 34 patients with MCI developed AD during the follow-up period (20.50±6.35 months). All of these converters had an increase in PIB retention at baseline, and mean DVR value in whole cortical regions was 2.31±0.29, similar to that of AD patients. The DVR value after baseline did not increase significantly in any cortical region. In contrast, 11 PIB positive patients with MCI remained relatively stable during this period although the mean cortical DVR did not significantly differ from MCI converters (2.09±0.32, n=11). None of the 6 MCI patients with an intermediate level of PIB retention and 6 MCI patients without increased PIB retention converted to AD. ApoEε4 was present in 13 (38%) of 34 patients with MCI. Ten (45%) of 22 PIB positive patients with MCI were ApoEε4 carriers, who did not have higher PIB retention. Seven (64%) of 11 converting MCI patients carried the ApoEε4 ($p<0.05$, chi-square), compared with 6 (26%) of 23 MCI non-converters.

Conclusions: The PIB-positive patients with MCI, who are ApoEε4 carriers, are more likely to faster develop AD. The cortical amyloid deposition associated with ApoE-ε4 allele may be a predicting biomarker of faster progression to AD.

Kinetic modeling of florbetaben PET data to quantify β-amyloid binding in the human brain

POSTER ABSTRACT

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Objectives: Florbetaben is a promising PET tracer for imaging of human β-amyloid deposits. This ^{18}F-ligand is rapidly metabolized *in vivo*, producing a low molecular weight, polar metabolite, which appears to enter the brain. We modeled the presence of the metabolite in the brain in quantifying β-amyloid binding.

Methods: PET data and multiple arterial samples were collected over 260 min after i.v. injection of florbetaben (300 MBq) for 10 Alzheimer's disease (AD) and 10 healthy controls (HC). PET data were analyzed by 1) "full" two input (parent and metabolite) model (2F) with 6 and 4 kinetic parameters in target and reference tissue (cerebellar cortex), respectively, 2) "simplified" two input model (2S) in which the metabolite delivery rate constant was fixed, 3) one input (parent) model (1), and 4) reference tissue model, to estimate the β-amyloid binding parameters, BP_P (2F), BP_P (2S), BP_P (1) and BP_{ND}, respectively. Target-to-cerebellar cortex ratio (R_T) at 90 min was also calculated. To evaluate the impact of the metabolite, these 5-binding parameters were compared.

Results: There were no differences between BP_P (2F) (2.65±1.82) and BP_P (2S) (2.67±2.22) (p=0.7). BP_P (1) (3.80±2.55) and R_T (0.57±0.37) were 44% and 32% higher than BP_P (2F) and BP_{ND}, respectively (n=20). There were strong correlations between BP_P (1) or R_T and BP_P (2F) (r^2=0.82 and 0.89, $p<10^{-4}$). BP_{ND} (0.43±0.28) also correlated highly with BP_P (2F) (r^2=0.79, $p<10^{-4}$). All binding parameters discriminated well between amyloid positive (8 ADs) and negative (9 HCs) scans, consistent with the visual assessment (effect size (Cohen's d): 4.0 (BP_{ND}), 3.4 (R_T), 2.7 (BP_P (2F)), 2.5 (BP_P (2S)) and 2.2 (BP_P (1)).

Conclusion: The florbetaben metabolite effect can be modeled in quantifying β-amyloid binding. However, the binding parameters that ignore the metabolite correlate very well with those that account for it and all binding parameters discriminate effectively between amyloid positive and negative scans.

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Histological comparison of neocortical β-amyloid plaque labeling using fluorescent derivatives of flutemetamol (3'-F-PiB) and PiB

POSTER ABSTRACT

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Background: The 3'-F analog of Pittsburgh Compound-B (3'-F-PiB; flutemetamol) is a new promising [F-18]-labeled amyloid binding agent for *in vivo* imaging of β-amyloid (Aβ) deposits in brains of subjects with Alzheimer's disease (AD). Preliminary imaging data demonstrated that compared to [C-11]PiB, [F-18]flutemetamol has similar uptake and retention characteristics although somewhat higher, non-specific retention in white matter (Mathis *et al*. *J Nucl Med* 2007; **48**: (Supplement 2): 56P). Whether the two tracers have comparable ability to identify cortical Aβ deposits is unknown.

Methods: Consecutive 12 μm paraffin sections of frontal and temporal cortical autopsy tissues from two AD patients were processed for histofluorescence analyses using highly fluorescent derivatives of flutemetamol (6-CN-flutemetamol) and PiB (6-CN-PiB), as well as for Aβ immunohistochemistry (clone 4G8 mab) and Bielschowsky silver staining. The pattern of plaque labeling and the extent of overlap with Aβ-immunoreactive deposits and Bielschowsky positive neuritic plaques were compared between 6-CN-flutemetamol and 6-CN-PiB. *In vitro* binding characteristics of 6-CN-PiB and 6-CN-flutemetamol, compared to PiB and flutemetamol, were determined in homogenates of frozen AD frontal cortex.

Results: 6-CN-flutemetamol and 6-CN-PiB labeled parenchymal amyloid plaques and cerebral vascular amyloid deposits in cortical regions, while no labeling of neurofibrillary tangles was detectable. Aβ-immunoreactive plaques were labeled with both compounds; a more intense fluorescence signal was detected in compact/cored Aβ plaques, while diffuse Aβ plaques were less intensely labeled. Bielschowsky positive neuritic plaques were prominently labeled with 6-CN-flutemetamol and 6-CN-PiB. The Ki values of the tested compounds were 8.6 nM (6-CN-PiB) and 9.3 nM (6-CN-flutemetamol), versus 4.3 nM (PiB) and 5.9 nM (flutemetamol).

Conclusions: Our data demonstrate that 6-CN-flutemetamol and 6-CN-PiB have comparable patterns of binding to Aβ plaque deposits in postmortem neocortical tissue sections and in tissue homogenates from AD brains. This suggests that *in vivo* PET retention of flutemetamol in AD brains reflects neocortical Aβ plaque load in a manner similar to PiB binding.

Comparison of longitudinal changes in amyloid deposition and cerebral metabolism in early-onset familial AD

POSTER ABSTRACT

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Background: We have previously reported a focal, striatal-dominant pattern of Aβ deposition in early-onset, familial Alzheimer's disease (eFAD). We also have found that striatal amyloid may reach a peak early in the disease process and then decline. Metabolic changes similar to those in sporadic, late-onset AD have previously been reported in eFAD.

Objective: Compare changes in amyloid deposition with changes in cerebral metabolism over time in carriers of eFAD mutations.

Methods: Thirteen carriers of mutations in presenilin-1 (n=9), presenilin-2 (n=1) or APP (n=3) received at least two PiB-PET and FDG-PET scans (15 mCi PiB; 7 mCi FDG, 40-60 min; ECAT HR+). We included mutation carriers with normal cognition (n=4), mild cognitive impairment (n=4) and AD (n=5). The delta-SUVR (follow-up minus baseline SUVR) was calculated for both PiB and FDG (using cerebellum as reference and atrophy correction). These values were then compared by Pearson's correlation as well as a comparison of statistically significant individual changes using the "Reliable Change Index (RCI)". The longest inter-scan interval was used for each subject (the interval varied from 2-5 years). Regions of interest (ROIs) analyzed included anterior cingulate, precuneus and striatum. We also explored larger composite ROIs.

Results: At baseline, there was a trend for a negative correlation between PiB retention and metabolism in the eFAD subjects ($r=-0.45$, $p=0.06$). However, we found no relationship between changes in PiB retention and metabolism in the eFAD subjects over time in any single or composite ROI. Depending on the ROI, 4-5 of the eFAD subjects showed increased PiB retention over time and 1-3 subjects showed decreased metabolism. Only one subject (an APP mutation carrier with AD) showed both. Although the striatum had heavy Aβ deposition, there was no significant decrease in striatal glucose metabolism in any subject by the RCI method.

Conclusions: Although Aβ deposition and cerebral metabolism were weakly related at baseline in eFAD mutation carriers, the changes in these parameters did not appear to be tightly coupled – except, perhaps, in the later stages of the illness. The heavy Aβ deposition in the striatum did not appear to lead to a progressive disruption in cerebral metabolism. The number of subjects in this study is small and confirmation from larger longitudinal studies will be necessary.

Association between pulse pressure and fibrillar amyloid-beta burden in cognitively normal, late middle-aged people at three levels of genetic risk for Alzheimer's disease

POSTER ABSTRACT

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Background: Epidemiological studies suggest an association between cardiovascular disease risk factors in mid-life and Alzheimer's disease (AD) in late-life. In the present study we used Pittsburgh Compound-B (PiB) positron emission tomography (PET) to examine the relationship between blood pressure (BP) measures and this brain imaging measurement of pre-symptomatic AD in a cohort of cognitively normal, late middle-aged APOE ε4 homozygotes (HM), heterozygotes (HT) and non-carriers (NC).

Methods: Mean systolic and diastolic BP was computed from three supine measurements. SPM5 was used to characterize relationships between systolic BP (SBP), diastolic BP (DBP) and peripheral pulse pressure (PP) with regional-to-cerebellar PiB PET distribution volume ratios (DVR) in 32 cognitively normal persons (mean age 65.5±4.5), including 8 HM, 11 HT, and 13 NC.

Results: The APOE ε4 groups did not differ significantly in demographic characteristics, clinical ratings or neuropsychological test scores. 19% of the participants' BP measurements met criteria for hypertension and 34% reported using anti-hypertensive medications. SBP was positively correlated and DBP negatively correlated with PiB DVR bilaterally in frontal, temporal and precuneus regions ($p<0.005$-0.05, uncorrected). Higher PP was associated with increased PiB DVR bilaterally in frontal and posterior cingulate-precuneus regions ($p<0.005$-0.05, uncorrected). Controlling for APOE ε4 did not significantly alter these findings. The PP PiB DVR correlations were significantly greater than the SBP or DBP correlations. Restricting the PP analysis to only normotensive individuals who did not report using anti-hypertensive medications, higher PP was associated with increased PiB DVR bilaterally in frontal, posterior cingulate, precuneus and medial temporal brain regions ($p<0.005$-0.05, uncorrected), with no correlations in the opposite direction.

Conclusions: These findings provide additional evidence that increases in pulse pressure in mid-life may be associated with increased risk of AD pathology. This study provides a rationale for using brain imaging to rapidly evaluate the efficacy of anti-hypertensive medications for the pre-symptomatic treatment of AD.

Hippocampal substructural volume in relation to amyloid deposition

POSTER ABSTRACT

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Background: A link has been postulated between brain amyloid deposition in the preclinical stages of Alzheimer's disease (AD) and early downstream processes of neurodegeneration. With recent advances in brain volumetry using high field MRI, we can quantify substructural volumes within the hippocampus, a major target of degeneration in AD.

Objective: We tested the hypothesis that amyloid deposition was related to an AD-like pattern of hippocampal degeneration involving the subiculum and CA1 subfields.

Methods: PiB PET and MRI were acquired in 117 subjects: 74 unimpaired control subjects (CS; CDR=0; mean ± SD age 70±6), 28 subjects with mild cognitive impairment (MCI; CDR=0.5; age 74±8), and 15 patients with AD (CDR=1; age 71±8 years). Hippocampal substructural volumes were calculated (Van Leemput *et al* 2009) in presubiculum, subiculum, CA1, CA2-3, CA4-dentate, fimbria, and the hippocampal fissure and adjusted for intracranial volume.

Results: Group volume differences (CS>MCI>AD; ANOVA) were highly significant ($p<10^{-6}$) for presubiculum, subiculum, CA2-3, and CA4-dentate; precuneus PiB retention also differed by group (CS<MCI<AD) ($p<10^{-13}$). Across the full sample, reduced volume was related to age in presubiculum ($p<0.001$), subiculum ($p<0.006$), and fimbria ($p<0.001$) and to precuneus PiB retention (covarying age) in presubiculum ($p<0.006$), subiculum ($p<0.001$), CA2-3 ($p<0.001$), and fimbria (0.001). However, these associations were driven by between-group differences. Analyzed separately, each group had a significant relation of substructural volumes to age, but only marginally significant associations with PiB retention. Within the CS group, associations of subfields with PiB retention were at the trend level for subiculum and CA4-dentate, but non-significant in other subfields.

Conclusions: These preliminary results suggest that hippocampal substructure volumes differ according to diagnostic group and are age-related. Although amyloid is strongly associated with reduced volumes across the full spectrum of normal to AD, it is not clear that the association holds within groups.

Maternal history of dementia is associated with amyloid deposition in clinically normal older individuals

POSTER ABSTRACT

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Positive family history of dementia (FH+) is a significant risk factor for clinical Alzheimer's disease (AD), particularly when there is a maternal history. Recent studies of clinically normal (CN) adult offspring have linked maternal history of AD to reduced gray matter volume and FDG hypometabolism. However, little is known about the relationship of family history to amyloid pathology, particularly in the absence of clinical symptomatology. We tested whether FH+ CN subjects had greater amyloid deposition and whether this was more evident in those with a maternal history.

We evaluated PiB PET data from a total of 58 CN (CDR 0) individuals (mean age 72±8) who stated that they knew the cognitive status of their parents after the age of 63. Of these, 29 (mean age 70±7) reported they were FH+ and 29 (mean age 75±8) were FH-. Within the FH+ group, 21 subjects reported maternal histories of dementia (mFH+), 5 reported paternal histories (pFH+), and 3 reported dementia in both parents. We evaluated our hypothesis in 12 ROIs, covarying age.

Compared to FH-, FH+ subjects had greater cortical PiB retention in widespread frontal lateral, frontal, and parietal ROIs ($p<0.05$). The subset of mFH+ subjects had increased PIB retention in frontal ROIs ($p<0.05$), whereas pFH+ did not differ from FH- CN. When the presence of the APOE4 allele was added to the model, the association of PiB retention with mFH+ remained significant. ($p<0.05$).

Self-reported parental history of dementia is associated with increased amyloid deposition in clinically normal individuals. The association appears to be driven by maternal history of dementia, and it is observed independently of APOE status. These findings are consistent with the hypothesis that amyloid deposition occurs prior to any clinical symptoms, and that family history is a significant risk factor for the development of AD pathology.

Amyloid burden in normal aging: The Dallas Lifespan Brain Study

POSTER ABSTRACT

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Beta-amyloid (Aβ) plaques have been well-documented in the brains of persons with Alzheimer's disease. The precise effect of this deposition on the disruption of human brain function/structure is unclear. Notably, how this protein accumulation is related to the course of normal aging is unknown. Approximately a third of older adults have levels of amyloid on par with those individuals diagnosed with AD, yet are cognitively normal. Examining the time-course of Aβ deposition and its neural and cognitive consequences in normal and healthy aging populations is an important step in disentangling healthy from pathological aging. Our goal is to characterize the distribution of Aβ in a normally aging population across the adult lifespan.

The Dallas Lifespan Brain Study (DLBS) is an ongoing large study of brain structural and functional aging and the impact on cognitive performance that will enroll 350 individuals aged 20-89 (n = 50 per decade). We are now PET scanning a subset of these individuals (n = 260) to quantify amyloid deposition using AV-45 (^{18}F-florpiramine). To date, we have scanned 50 individuals ranging in age from 45-89 (m = 63.95; 20 men, 37 women) with a mean education level of 16.18 years (range = 12-21) and MMSE = 29 (26-30). The ultimate goal of the study is to not only characterize when in the age span beta-amyloid deposition begins to occur but also to examine if earlier deposition in middle-age is associated with brain structural decline (e.g., regional volumes, white matter integrity) and age-related differences in patterns of functional neural activation, as well as cognitive performance. We expect that the DLBS will greatly expand the existing knowledge of the time course and neural/cognitive consequences of amyloid deposition in normal aging. We will report the DLBS amyloid findings to date.

Contribution of amyloid and cerebrovascular disease to cognitive impairment in individuals with high vascular risk

POSTER ABSTRACT

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Objective: To evaluate the relationship of amyloid and cerebrovascular disease (CVD) to cognitive state in a population with high vascular risk.

Methods: Subjects enrolled in two vascular-focused studies of cognition underwent PIB-PET and MRI (n=23, mean age 79.8±7.8 years, 91% with vascular risk factors). PIB DVR images (Logan, cerebellar reference) were classified as positive (PIB+) or negative (PIB-) based on visual reads and MRI scans were rated for the presence of infarcts, all blinded to clinical data. Subjects were classified as having cerebrovascular disease (CVD+) if there was a clinical history of stroke/TIA or an infarct on MRI. Patients with a CDR≥0.5 were considered cognitively impaired (n=14/23, median CDR=0.5).

Results: 10/23 subjects had PIB+ scans (mean PIB Index 1.31±0.30, versus 0.95±0.05 in PIB- scans, $p<0.001$). Highest regional uptake in PIB+ scans was in the precuneus (mean DVR 1.40±0.35). 16/23 subjects were CVD+ (50% with lacunar infarcts, 25% with cortical infarcts and 25% with both). Cognitive impairment was found in 1/6 CVD-/PIB-, 5/7 CVD+/PIB-, 0/1 CVD-/PIB+ and 8/9 CVD+/PIB+ subjects ($\chi^2=9.77$, $p=0.02$). In a logistic regression that included cognitive impairment as the outcome and PIB, CVD, age and education as predictors, cognitive impairment was associated with CVD+ (odds ratio=32, 95% confidence interval 1.5-694, $p=0.03$) but not with PIB+ status ($p=0.78$). A trend for an association between CVD+ and cognitive impairment remained after excluding subjects with cortical infarcts ($p=0.08$).

Conclusions: In this small, mildly impaired, elderly cohort enriched for vascular disease, CVD was more strongly linked to cognition than was amyloid. CVD is often viewed as a secondary factor in cognitive impairment, but this data suggests it is not infrequently the primary cause of mild impairment. Further studies are needed to determine the relative contributions of amyloid and CVD to changes in cognition and brain structure, and function.

Potential conflicts of interest: Nothing to report.

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Amyloid imaging in presenilin 1 mutation carriers with 11C-PiB PET

POSTER ABSTRACT

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Objective: *In vivo* investigation of amyloid distribution in pre-symptomatic and mildly affected carriers of mutated presenilin 1 (*PSEN1*) using 11C-PIB PET.

Background: Mutations of the *PSEN1* gene are linked to the early onset of dementia. Post mortem studies have revealed increased amyloid deposition within the brains of these subjects. The distribution of amyloid appears to be distinct from sporadic AD (SAD).

We aim to investigate a range of pre-symptomatic and mildly affected mutation carriers to confirm the presence of amyloid and to identify patterns of deposition that may be distinctive to *PSEN1*.

Method: Seven mutation carriers (5 cognitively normal and 2 mildly affected (MMSE≥20)), 10 SAD and 10 healthy controls were studied. 11C-PiB-PET was performed on all subjects. All PET images were co-registered to T1-weighted MRIs and regions of interest were generated using an in-house atlas. Pontine ratios were generated of the following regions: anterior and posterior cingulated, thalamus, striatum and the frontal, temporal, parietal occipital and cerebellar cortices.

Results: SAD subjects had significantly higher 11C-PIB binding compared to controls and *PSEN1* carriers. *PSEN1* carriers had significantly higher levels of 11C-PIB binding when compared to controls. Two patterns of amyloid distribution emerged. Firstly, emphasis on the striatum occurring in E184D and intron 4 mutations and secondly, increased cerebellar and thalamic uptake in M1461 and Y115C mutations.

Conclusions: PSEN1 gene carriers represent a distinctive group of patients. To date 185 mutations of *PSEN1* gene have been published. In this study we have demonstrated the importance of investigating a range of *PSEN1* mutations as different patterns of amyloid deposition have emerged. We also confirmed the presence of amyloid in the cerebellum of these subjects supporting the use of the pons as the reference region for this cohort.

A challenging test of name retrieval may be sensitive to early amyloid deposition in normals

POSTER ABSTRACT

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We recently reported that precuneus amyloid deposition is associated with lower memory performance in normal older individuals, but that a challenging test of memory may be required to overcome the effect of cognitive reserve. Here, we tested whether a highly demanding test of face/name retrieval (FNAME) was able to detect evidence of subtle impairment in performance related to amyloid burden, particularly to deposition in both memory and executive function networks.

Methods: We studied 45 normal subjects (mean age = 71.7±8.7, education = 16.6±2.7; AMNART IQ = 123.5±7.1) with clinical dementia rating (CDR) scores = 0 and MMSE≥28. Using multiple linear regression analysis, we related PiB retention (DVR, cerebellar reference) as a continuous variable in frontal, lateral temporal, lateral and medial parietal cortices, co-varying for age and AMNART IQ, to NP test scores. We transformed NP scores into composites representing traditional memory measures (all subtests of the Selective Reminding Test) and executive functions [Trails B, FAS, digits backward) as well as name retrieval on the FNAME.

Results: We found a significant inverse relationship for FNAME name retrieval with amyloid deposition in frontal (R^2=0.28, β=-2.1, p=0.02), lateral temporal cortices (R^2=0.270, β=-2.5, p=0.03), lateral and medial parietal cortices (R^2=0.27, β=-2.4, p=0.05), that was not modified by IQ. Traditional memory measures did not show a significant relationship with amyloid deposition in these regions, except for frontal (R^2=0.20, β=-0.30 p=0.04) and medial temporal regions (R^2=0.26, β=-0.57 p=0.02) and only when IQ was included in the model. We did not observe any significant inverse relationship between frontal amyloid deposition and tests of executive function.

Conclusions: Performance on a demanding test of face/name retrieval, a common complaint of many normal older individuals, was associated with amyloid burden in brain regions critical for both executive function and memory systems, including frontal, temporal and parietal cortices. Challenging tests of associative memory retrieval in clinically, normal older individuals may prove to be sensitive markers for detecting early effects of amyloid deposition, regardless of cognitive reserve.

PET imaging of amyloid deposition in patients with mild cognitive impairment: A two year follow-up study

POSTER ABSTRACT

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Background: Because of the ongoing development of disease modifying therapies, it is potentially of great clinical value to identify subjects at a high risk of developing Alzheimer's disease (AD). Patients with amnestic mild cognitive impairment (MCI) represent a group of individuals with greater risk of conversion to AD. Increased brain amyloid burden in AD and MCI has been demonstrated with PET using [^{11}C]PIB.

Objective: To compare levels of beta-amyloid deposition during an approximately 24-month (range 16-39) follow-up period in 29 MCI patients, 12 of whom remained MCI and 17 of whom converted to AD, and in 13 healthy elderly control individuals.

Method: Patients with MCI and controls were studied with [^{11}C]PIB PET, MRI and neuropsychometry at baseline. These investigations were repeated in MCI patients after follow-up for 24 months.

Results: At group level, patients with MCI had increased [^{11}C]PIB uptake in several cortical regions. Those MCI patients converting to AD had greater [^{11}C]PIB retention in the posterior cingulate ($p=0.020$), in the lateral frontal cortex ($p=0.006$), in the temporal cortex ($p=0.022$), in the putamen ($p=0.041$) and in the caudate nucleus ($p=0.025$) as compared to non-converters. In the MCI converters, there was no significant change in [^{11}C]PIB uptake during the follow-up, whereas [^{11}C]PIB uptake increased as compared to baseline in the MCI non-converters in the anterior and posterior cingulates, temporal and parietal cortices and in the putamen. Hippocampal atrophy was greater in MCI converters at baseline than in non-converters, but increased significantly in both groups during follow-up.

Conclusions: Hippocampal atrophy and amyloid deposition seem to dissociate during the evolution of MCI, the atrophy increasing clearly and [^{11}C]PIB retention changing modestly when conversion to AD occurs. Future studies will determine whether the increased [^{11}C]PIB uptake and hippocampal atrophy in MCI non-converts will predict conversion to AD during longer follow-up.

Effects of acquisition time in [^{11}C]PIB PET dynamic studies of non-demented older adults

POSTER ABSTRACT

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A simplified reference tissue model with linear regression and spatial constraint (SRTM-LRSC; Zhou *et al. Neuroimage* 2007) is a sensitive method for detection of subtle changes in distribution volume ratios in non-demented older adults using a 90 min dynamic acquisition. As a shorter scan time is an important consideration in PET studies of older adults, we investigate whether 70 min dynamic data acquisition provides an acceptable alternative to 90 minutes using SRTM-LRSC.

Methods: Sixty-five non-demented participants in the Baltimore Longitudinal Study of Aging (age 78.2±6.6 years; 6 with CDR=0.5, 26 with follow-up [^{11}C]PIB study) had dynamic [^{11}C]PIB PET scans analyzed for (0,90 min; DVR90) and (0,70 min; DVR70) timeframes. Fifteen regions of interest were defined on co-registered MRIs, and cerebellum was used as a reference tissue. Regional DVRs were obtained via SRTM-LRSC using (0,90 min) and (0,70 min) data. The mean cortical DVR (mcDVR) of 8 cortical regions was calculated for both timeframes. Correlations between DVR70 and DVR90, possible systematic differences in mcDVRs for the two measures, as well as changes in DVR over time for DVR70 and DVR90, were evaluated.

Results: DVR70 is highly correlated with DVR90 (DVR70=0.0155+0.953 * DVR90, r=0.998). DVR70 is lower than DVR90 by 3.3% with mean difference of 0.04 (SD 0.02) DVR. DVR70 for posterior cingulate showed the greatest underestimation (4.1%). The difference between DVR70 and DVR90 was not related to mcDVR in older adults with elevated mcDVR (mcDVR>1.1, p=0.51). Changes in mcDVR over time differ by 0.002 (SD=0.013).

Conclusions: DVR obtained using 70 min data is highly correlated with the DVR obtained using 90 min data. Underestimation of mcDVR obtained using 70 min data is within the test-retest variability of [^{11}C]PIB and does not increase with increasing DVR, providing an alternative timeframe for dynamic [^{11}C]PIB studies analyzed by SRTM.

Support: This research was supported by the Intramural Research Program of the NIH, National Institute on Aging N01-AG-3-2124 and K24 DA000412(DFW).

Proteome-based identification of plasma biomarkers for brain amyloid burden

POSTER ABSTRACT

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We have employed a novel strategy combining ^{11}C-PiB PET imaging of the brain with mass spectrometry-based proteomic analyses of plasma to identify peripheral biomarkers associated with brain amyloid burden in non-demented older individuals.

Using plasma samples from participants in the neuroimaging sub-study of the Baltimore Longitudinal Study of Aging (BLSA), we have identified a robust peripheral signature associated with brain amyloid deposition. Several of these plasma proteins, including apolipoprotein-E (ApoE) have established roles in amyloid clearance pathways. In another approach, we first used proteomic analyses of plasma to demonstrate that the concentration of clusterin (also known as apolipoprotein-J/ApoJ) is associated with atrophy of the entorhinal cortex as well as with faster cognitive decline in patients with established Alzheimer's disease (AD). We then tested whether plasma clusterin concentration was also associated with extent of brain amyloid deposition in normal aging. Using a commercially available ELISA assay, we showed that clusterin, measured in plasma samples collected 10 years prior to the ^{11}C-PiB PET scans, is associated with greater amyloid deposition within the medial temporal lobe.

Taken together with recent genome wide association studies demonstrating that polymorphic variation in the clusterin gene is associated with a risk of AD, these results suggest a key role of this amyloid chaperone protein in AD pathogenesis. Our strategy combining ^{11}C-PiB PET imaging of the brain with proteomic analyses of plasma holds promise for the discovery of biologically relevant peripheral biomarkers for AD.

Acknowledgement: This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging.

Amyloid-ß burden and neuropsychological test performance in cognitively normal first-degree relatives at varying genetic risk for Alzheimer's disease

POSTER ABSTRACT

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In Alzheimer's disease (AD) there is strong evidence that brain amyloid deposition precedes the emergence of dementia by many years. In addition, a greater accumulation of amyloid in the postmortem brain has been demonstrated in people who carry the major genetic risk factor for AD – APOE-ε4. This study investigated the relationship between APOE-ε4 genotype, amyloid deposition, and neuropsychological test performance in pre-symptomatic individuals at varying genetic risk for AD.

Methods: Cognitively normal subjects (n=270) aged 50-69, with a first-degree family history for AD, were genetically screened to select three groups: APOE genotype ε4ε4 (n=9), ε3ε4 (n=10), and ε3ε3 (n=10), matched for age, sex, and education. Subjects were then studied with ([^{11}C]PiB) PET, MRI, and neuropsychological testing. PET and MR images were co-registered for application of an ROI template (AAL for SPM2) to generate regional time-activity curves with cerebellum as reference region. Parametric BP_{ND} images are then generated using SRTM2 such that BP_{ND}=0 reflects no specific binding. BP_{ND} was computed for a mean cortical ROI consisting of frontal, posterior cingulate-precuneus, and lateral temporal ROIs.

Results: APOE-ε4 carriers demonstrated significantly greater BP_{ND} (0.37±0.20) in comparison to non-carriers (0.21±0.09; t=2.37, p=0.025), with no dosage effect between ε4ε4 and ε3ε4 groups. There was no significant effect of APOE genotype on neuropsychological test performance. When associations between mean cortical [^{11}C]PiB BP_{ND} and neuropsychological test performance were examined, there was some tendency for [^{11}C]PiB binding to be correlated with measures of episodic memory: CVLT recognition hits (r=-0.47, p=0.02), CVLT free-delayed recall (r=-0.38, p=0.07), Visual Reproductions I (r=0.52, p=0.01).

Conclusions: These results confirm and extend observations by Reiman *et al*, 2009, but in a somewhat younger sample (mean age 60 *vs* 65). Additional research is necessary to determine the predictive value and functional consequences of brain amyloid deposition in asymptomatic individuals at risk for AD.

Comparison between cerebellum and pons as reference regions for quantification of the amyloid imaging agents [^{18}F]flutemetamol and [^{11}C]PIB

POSTER ABSTRACT

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Background: Amyloid imaging data is often quantified using a simplified method where target region to cerebellum reference region uptake ratios (SUVR) are computed. In this study, we investigate the use of pons as an alternative reference region.

Methods: Data from the previously reported [^{18}F]flutemetamol phase II study was used. 27 patients with early-stage AD, 20 with MCI and 25 healthy volunteers (HV) underwent an [^{18}F]flutemetamol PET scan (acquisition window 85-115 min post-injection). Five of the AD subjects had a second (retest) scan performed within 1-2 weeks and 20 of the AD and the 20 MCI subjects also underwent a [^{11}C]PIB scan (acquisition window 40-70 min post-injection). The "30-min PET sum" images were co-registered with the subject's MRI and all data was spatially normalized to MNI space where a volume of interest (VOI) atlas was applied. SUVRs were computed for VOIs corresponding to frontal, lateral temporal and parietal cortices, and anterior cingulated and posterior cingulate/precuneus. In addition, SUVR for a composite region (COM) was computed by averaging SUVRs for the individual VOIs. SUVRs were computed using the cerebellar cortex ($SUVR_{CER}$) and pons ($SUVR_{PON}$) as reference regions. We compared the different reference methods by investigating discrimination between the AD and HV subject groups, test-retest variability and the correlation between [^{18}F]flutemetamol and [^{11}C]PIB.

Results: Both methods showed similar capability in discriminating between AD and HV (p-value $SUVR_{CER}$=1.54E^{-11}, p-value $SUVR_{PON}$=1.11E^{-9} for the COM region). The average [^{18}F]flutemetamol test-retest variability for the COM region was 1.7±0.7% for $SUVR_{CER}$ and 1.1±0.9% for $SUVR_{PON}$. Correlations between [^{18}F]flutemetamol and [^{11}C]PIB in the 20 AD and 20 MCI subjects were high in all cortical regions using $SUVR_{CER}$ values (Pearson R=0.91 for COM) and very high using $SUVR_{PON}$ values (Pearson R=0.99 for COM).

Conclusion: The results show that pons is a suitable alternative reference region to the cerebellar cortex for computation of SUVR values, with similar discrimination capability and test-retest variability and with high correlation between [^{18}F]flutemetamol and [^{11}C]PIB.

NOTES

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