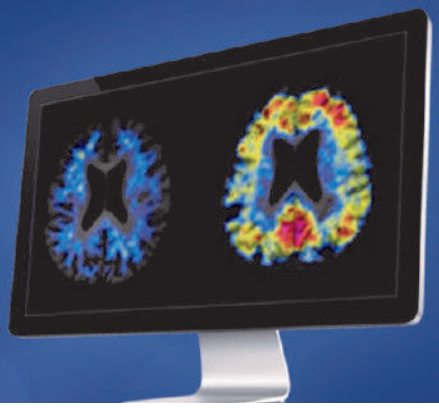
7th Human Amyloid Imaging

January 16-18, 2013
Miami, Florida



Co-Organizers:
Keith A. Johnson, MD • William J. Jagust, MD • William E. Klunk, MD, PhD • Chester Mathis, PhD

Schedule and Abstract Book

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HAI Program Abstracts

Oral Presentations

Session 1: The Curves that Jack Built

CHAIRS:

Keith A. Johnson, MD, ***Massachusetts General Hospital***

William J. Jagust, MD, ***University of California, Berkeley***

Conversion to MCI and Amyloid-Positivity in Normal Controls

William Klunk, Ann Cohen, Beth Snitz, Howard Aizenstein, Edythe Halligan, Lisa Weissfeld, Chet Mathis, Julie Price, Robert Nebes

University of Pittsburgh

Background: Several studies have shown that MCI subjects with brain Aß are more likely to progress to Alzheimer's disease. Few studies have followed the clinical outcome of normal controls. Here we report the effects of Aß deposition on controls followed ~4 yrs.

Methods: Sixty-three cognitively normal subjects (age 74.7±5.4 yrs) were followed between 1 and 6 years (average 43±15 months) with an ADRC clinical assessment and PiB PET at 1-2 year intervals.

Results: 17/63 (27%) were PiB(+) at baseline and an additional 13 [30 total;(48%)] became PiB(+) by their last evaluation 36±17 months later (1 conversion/10.5 person-yrs). Baseline global PiB retention was associated with conversion to PiB-positivity [point biserial correlation coefficient r(pb)=+0.35;p=0.01] but age [r(pb)=-0.24;p=0.11] and time of follow-up [r(pb)=+0.08;p=0.60] were not. Of those PiB(+) at baseline, 6/17 progressed to MCI, while only 5/46 baseline PiB(-) cases progressed (Odds Ratio=4.47;95% CI=1.15-17.4;p=0.031). Subjects who were ever PiB(+) had an OR of 3.64 (0.86-15.3) of converting to MCI (8/30 vs. 3/33), but this was not significant (p=0.078). Within the PiB(+) group, time of PiB-positivity was positively, but non-significantly associated with progression to MCI [r(pb) = +0.24;p=0.21]. Across all 63 subjects, global cortical PiB retention was significantly associated with progression to MCI [r(pb) = +0.27;p=0.034];and was most significant in the parietal/precuneus [r(pb) = +0.4;p=0.001]. Stroop was the only cognitive test associated with conversion to MCI [r(pb)=0.31;p=0.014]. Progression to MCI was not associated with FDG [r(pb)=-.09;p=0.51], ApoE4 (chi^2=0.0032;p=0.96) or age [r(pb)=+0.17;p=0.17].

Conclusions: The prevalence of PiB-positivity increased at a rate of ~10%/year. Being PiB(+) increased the odds of progressing to MCI. Time spent PiB(+) was associated with increased risk of conversion, but this variable may be better represented by the level of PiB retention since the time spent PiB(+) before baseline is unknown.

Keywords: *controls, MCI, PiB, progression, conversion*

Presented by: Klunk, William

The Curves that Jack Built: the Natural History of Abeta Deposition, Neurodegeneration and Cognitive Decline in Sporadic Alzheimer's Disease

Victor L Villemagne [1], Samantha Burnham [2], Pierrick Bourgeat [3], Belinda Brown [4], Kathryn A Ellis [5], Olivier Salvado [3], Ralph Martins [4], Paul Maruff [6], David Ames [7], Christoper C Rowe [1], Colin L Masters [8]

[1] *Centre for PET, Austin Health, Melbourne, Australia*
[2] *CSIRO Preventative Health Flagship: Mathematics, Informatics and Statistics, Floreat, WA, Australia*
[3] *CSIRO Preventative Health Flagship: The Australian e-Health Research Centre - Brisbane, QLD, Australia*
[4] *Edith Cowan University, School of Exercise, Biomedical and Health Sciences, Perth, WA, Australia*
[5] *Dept of Psychiatry, The University of Melbourne, Melbourne, VIC, Australia*
[6] *CogState Ltd., Melbourne, Melbourne, VIC, Australia*
[7] *National Ageing Research Institute, Melbourne, VIC, Australia*
[8] *The Mental Health Research Institute, The University of Melbourne, VIC, Australia*

Background: Like most chronic diseases, Alzheimer's disease (AD) develops slowly from a preclinical phase as it evolves into a fully expressed clinical syndrome. We used longitudinal data to calculate the rates of Abeta deposition, cerebral atrophy and cognitive decline in healthy controls (HC), mild cognitive impairment (MCI) and AD patients.

Methods: Two hundred participants (145 HC; 36 MCI; and 19 AD) were evaluated at enrolment and 1.5 and 3 years later. On each visit, participants underwent neuropsychological examination, MRI and a PiB PET scan. Rates of change for Abeta deposition, MRI volumetrics and cognition were derived from the slope of the regression plots over 3-5 years and used in the analysis. Those with a positive rate of Abeta deposition were used to calculate the trajectory of each parameter over time.

Results: Abeta deposition follows sigmoidal kinetics where it takes 19 years to reach the levels observed in fully developed AD (average increase 0.043 SUVR/yr). As AD progresses, the rate of Abeta deposition slows, trending towards a plateau. Five years before the onset of dementia (CDR 1), hippocampal and cortical atrophy and cognitive impairment sequentially become abnormal and rapidly progress. Thus the preclinical phase of AD is approximately 15 years.

Conclusions: Abeta deposition is a slow and protracted process that extends for more than two decades. Predicting the rate of evolution of preclinical changes and the onset of clinical phase of AD are essential for the design and timing of therapeutic interventions aimed at modifying the course of this illness.

Keywords: *Alzheimer's disease; Abeta; cognitive decline, cerebral atrophy; PiB; positron emission tomography*

Presented by: Rowe, Christopher

Agreement and Disagreement between PET Imaging and CSF Measurements of Aß

Susan Landau [1], Ming Lu [2], Abhinay Joshi [2], Michael Pontecorvo [2], Mark Mintun [2], John Trojanowski [3], Leslie Shaw [3], William Jagust [1]

[1] *University of California, Berkeley*
[2] *Avid Radiopharmaceuticals*
[3] *University of Pennsylvania*

We examined agreement and disagreement between two biomarkers of Aß deposition (amyloid PET and CSF $Aß_{1-42}$) in normal, MCI, and AD participants (N=374) from the Alzheimer's disease neuroimaging initiative (ADNI). Additional neuroimaging, genetic, and cognitive data allowed us to further examine biomarker profiles of discordant cases. Florbetapir and CSF Aß measures were inversely correlated across all diagnostic groups (Figure 1), and the majority of subjects (84-89%, depending on diagnosis) were either abnormal on both markers or normal on both. 11-16% of subjects had discordant measurements (florbetapir+/CSF Aß- or florbetapir-/CSF Aß+). The direction of discordance was not related to diagnostic status, ApoE4 status or other biomarkers. While both abnormal florbetapir and abnormal CSF Aß were associated with poor episodic memory performance, there was some evidence that the association was more robust for CSF Aß.

In a separate sample that had serial CSF measurements over 3.1 +/- 0.8 yrs (N=60) that preceded a single florbetapir scanning session, we observed both stable and fluctuating CSF Aß trajectories (Figure 2). We observed several individuals who had CSF Aß measurements that were normal at baseline and declined steadily over the course of followup, resulting in ultimately abnormal CSF Aß that was consistent with the subsequently measured abnormal florbetapir retention.

Overall, CSF and amyloid-PET measurements of Aß were in good agreement. Furthermore, analysis of individuals who had discordant measurements did not provide any evidence that abnormal CSF Aß consistently precedes abnormal florbetapir measurements or vice versa. Finally, we observed longitudinal CSF Aß trajectories in active transition from normal to abnormal, but regardless of the preceding CSF trajectory, the final CSF Aß was generally consistent with florbetapir cortical retention.

Keywords: *amyloid, CSF, florbetapir, longitudinal*

Presented by: Landau, Susan

Characteristics of Incident Amyloid PET Positivity

Clifford Jack, Heather Wiste, Stephen Weigand, David Jones, Prashanthi Vemuri, Val Lowe, Vernon Pankratz, Michelle Mielke, David Knopman, Ronald Petersen

Mayo Clinic Rochester

Purpose: To characterize the incidence of, and imaging findings associated with, incident amyloid PET positivity.

Methods: Two-hundred thirteen cognitively normal (CN) participants in the Mayo Clinic Study of Aging, age 70 to 90 plus years, had 2 or more serial amyloid PET studies using PIB. Of these, 126 were PIB negative at baseline. PIB quantification was done by normalizing a set of AD-signature cortical ROIs to cerebellar uptake (SUVR). Our threshold for a positive PIB scan was 1.4. To qualify for incident PIB positivity, a subject must have changed from PIB negative to PIB positive (>1.4) over their series of scans and increase by more than 0.04 SUVR (which represents a change greater than noise). Twenty-seven subjects met this criterion for incident PIB positivity and were compared to 70 CN subjects from the MCSA that remained PIB negative over their entire series of scans and did not increase by more than 0.04 SUVR. All subjects underwent serial MRI and FDG PET at the same time points as PIB PET.

Results: Based on 202 person-years of follow up, the annual incidence of PIB positivity was approximately 13%. Compared to the stable PIB negative group, subjects with incident PIB positivity had greater baseline PIB SUVR ($p < .001$) but similar FDG PET uptake and hippocampal volumes at baseline. Subjects with incident PIB positivity also had greater rates of change in PIB SUVR over time ($p < .001$) (as expected), compared to the PIB negative group, but no difference in rates of change in FDG PET uptake or hippocampal volumes.

Conclusions: The annual incidence of PIB positivity is approximately 13% among CN participants over age 70 from a population-based sample. Incident PIB positivity seems to occur prior to changes in FDG PET and hippocampal volume.

Keywords: *Alzheimer's disease, Amyloid PET, PIB, MRI, FDG PET*

Presented by: Jack, Clifford

Session 2: Amyloidosis, Neuro-Degeneration, White Matter Integrity

CHAIRS:

Michelle M. Mielke, MD, ***Mayo Clinic***

Victor Villemagne, MD, ***Austin Health***

Beta-amyloid Influences the Relationship between Hippocampus Volume and Episodic Memory in Aging

Elizabeth Mormino [1], Trey Hedden [1], Dorene Rentz [1], Alex Becker [1], Andrew Ward [1], Aaron Schultz [1], Gad Marshall [1], Brendon Boot [1], Randy Buckner [2], Keith Johnson [1], Reisa Sperling [1]

[1] *Massachusetts General Hospital*
[2] *Harvard University*

Advanced aging is associated with increases in beta-amyloid plaque deposition, a pathology central to Alzheimer's disease (AD), as well as reductions in hippocampus volume and episodic memory performance. Although these changes are consistently observed in studies of aging, the degree to which beta-amyloid, hippocampus volume and episodic memory are directly related and influence each other within cognitively normal aging cohorts remains unclear. One hundred eighteen cognitively normal older individuals from the Harvard Aging Brain study were scanned with PIB-PET amyloid imaging and volumetric MRI. The association between age and hippocampus volume was 2-3 times greater than the association between beta-amyloid and hippocampus volume. A relationship between hippocampus volume and episodic memory was absent among beta-amyloid negative individuals, but emerged when subjects with slightly elevated PIB values were introduced into the sample. Thus, although age and beta-amyloid are related to hippocampus volume, hippocampus volume was only associated with episodic memory amongst beta-amyloid+ individuals. These results suggest that the earliest stages of AD-related volumetric changes may be present in cognitively normal samples at a level of amyloid burden that is lower than the level traditionally considered biologically relevant. Furthermore, the observation that the link with episodic memory in cognitively normal samples may be predominantly associated with beta-amyloid burden despite large age-related changes in hippocampal volume suggest that AD-independent mechanisms of hippocampal volume loss minimally influence episodic memory in aging.

Keywords: *preclinical AD, aging, hippocampus volume, episodic memory, PIB cut offs*

Presented by: Mormino, Elizabeth

Increased Beta-Amyloid Deposition is Associated with Decreased White Matter Integrity in Healthy Adults

Kristen M. Kennedy [1], Karen M. Rodrigue [1], Michael D. Devous Sr. [2], Jennifer R. Rieck [1], Patrick Evans [1], Denise C. Park [1]

[1] *University of Texas at Dallas, School of Behavioral and Brain Sciences and Center for Vital Longevity*
[2] *University of Texas Southwestern Medical Center, Department of Radiology*

The integrity of the white matter degrades with age, even in normally aging individuals. Beta-amyloid deposition increases with age and may instigate a cascade of other neuropathological effects across the brain. The current study examined the association of regional beta-amyloid deposition on the integrity of white matter connectivity in the brains of healthy adults across the lifespan using Diffusion Tensor Imaging (DTI) and beta-amyloid imaging using Florbetapir PET. We hypothesized that beta-amyloid deposition would exert a local rather than global effect on white matter degradation. Participants were individuals from the Dallas Lifespan Brain Study who had complete data on these two scans (N=141, aged 30-89 years). Regional SUVR was computed from the PET scans in precuneus and anterior cingulate ROIs. DTI data were used to compute diffusion properties from ROI analyses in the genu and the splenium of the corpus callosum and probabilistic tractography was computed to assess the inferior longitudinal fasciculi (bilaterally), the superior longitudinal fasciculi (bilaterally), and the uncinate fasciculi (bilaterally). Measures of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were computed. We found that, beyond the effects of aging, increased beta-amyloid in the precuneus was associated with poorer white matter integrity in the splenium of the corpus callosum, suggesting a potential local effect of beta-amyloid on white matter integrity. Further, increased beta-amyloid in the anterior cingulate was associated with poorer white matter integrity in the nearby uncinate fasciculus (again after correcting for age effects). In both cases, the dominant (although not exclusive) impact of beta-amyloid on white matter was evidenced as increased RD, a putative marker of myelin damage. This pattern of results suggests that beta-amyloid deposits may exert local detrimental effects on the health of the white matter and the integrity of its connections.

This study was supported in part by NIH grants R-37-AG-06265-27, 5-K99-AG-036818-3, and Alzheimer's Association grant IIRG-09-135-087. Radiotracer was provided by Avid RadioPharmaceuticals.

Keywords: *beta-amyloid, white matter, normal aging, Diffusion Tensor Imaging, Florbetapir*

Presented by: Kennedy, Kristen M.

The Impact of Amyloid Deposition and Cerebrovascular Risk Factors on Cortical Thickness

Sylvia Villeneuve [1], Bruce Reed [2], Cindee Madison [1], Miranka Wirth [1], Stephen Kriger [3], Charles deCarli [2], Helena Chui [4], Michael Weiner [3], William Jagust [1]

[1] *University of California, Berkeley*
[2] *University of California, Davis*
[3] *University of California, San Francisco*
[4] *University of Southern California*

Background: Cerebrovascular risk factors are risk factors for Alzheimer disease and are associated with amyloid deposition and reduction of gray matter integrity.

Objective: To investigate how brain beta-amyloid affects the relationships between cerebrovascular risk and brain structure and to examine their association with cognition.

Methods: The study included 67 persons from the Aging Brain cohort; a study recruiting cognitively normal and mild cognitive impairment (MCI) patients at increased risk of vascular disease. Subjects were categorized as PIB+ (n=22; age=80±5.9; MCI=14) or PIB- (n=45; age=78±6.9; MCI=18) based on their cortical PIB uptake (DVRs values; cerebellar reference region). Cortical thickness and hippocampal volume were measured using Freesurfer and 3T MRI data. Cerebrovascular risk factors were measured with the Framingham Coronary Risk Profile (FCRP) index and a MANCOVA was conducted to assess the individual contribution of each factor (age, gender, LDL cholesterol, HDL cholesterol, systolic blood pressure, diabetes and smoking) on cortical thickness/volume. Cognition was evaluated using standardized composite scores of memory and executive functions.

Results: Higher vascular burden (FCRP total score) was associated with lower frontal, parietal and temporal thickness. Higher vascular burden was also associated with lower memory performance. Among the FCRP factors, age (p=.014) and HDL cholesterol (p=.021) were related to cortical thickness and hippocampal volume. Both increased age and lower HDL cholesterol were associated with thinner temporal cortex and smaller hippocampal volumes; low HDL was also associated with thinner frontal and parietal cortex. The association between cerebrovascular risk factors and cortical thickness was stronger among PIB+ (Fig.). Cortical thickness mediated the effect of amyloid and FCRP on memory.

Conclusions: These data extend previous findings by showing that lower HDL cholesterol and higher vascular burden are related to thinner cortex and smaller hippocampal volume. This effect is greater in those with high amyloid burden and mediates memory function.

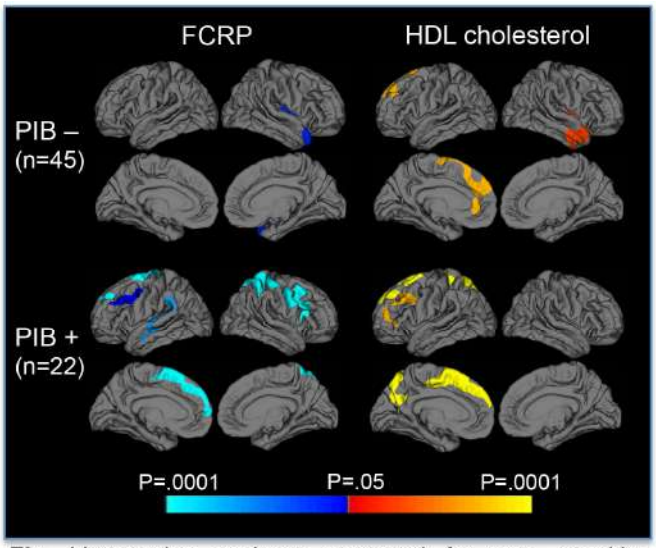


Fig. Vertex-wise analyses corrected for age, cognitive status and multiple comparisons assessing the impact of FCRP (total score) and HDL cholesterol on cortical thickness.

Keywords: *vascular burden, HDL cholesterol, beta-amyloid, cortical thickness, memory*

Presented by: Villeneuve, Sylvia

Alzheimer's Disease Neurodegenerative Biomarkers Are Associated with Decreased Cognitive Functions but not Beta-amyloid in Cognitively Normal Older Individuals

Miranka Wirth [1], Cindee Madison [1], Gil D. Rabinovici [2], Hwamee Oh [1], Susan M. Landau [1], William J. Jagust [1]

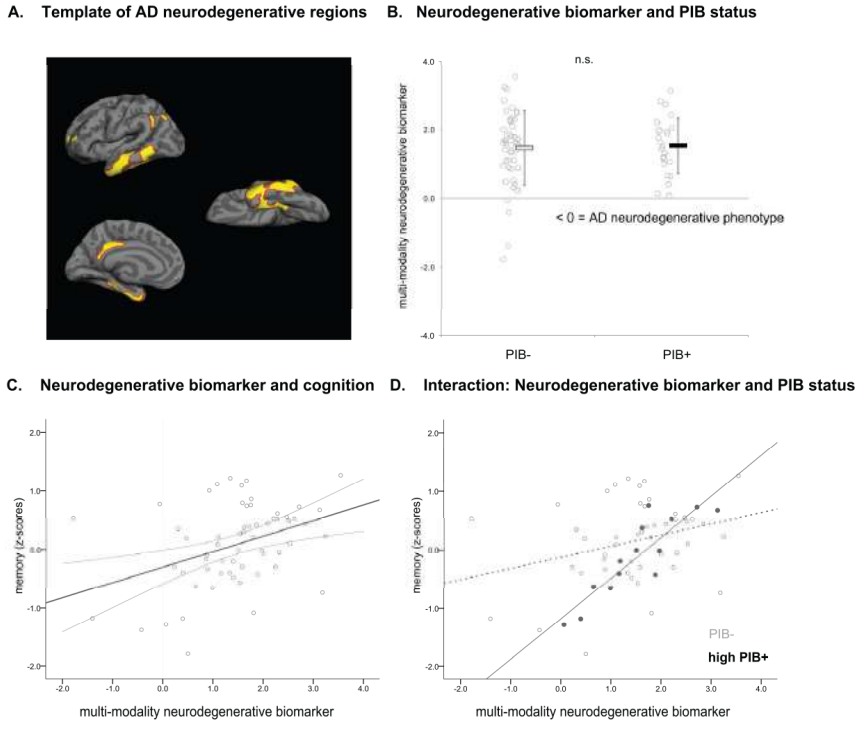
[1] *Helen Wills Neuroscience Institute, UC Berkeley*

[2] *Memory and Aging Center, Department of Neurology, UCSF*

Objective: The Alzheimer's disease (AD) pathobiological phenotype of beta-amyloid (Abeta) deposition and neurodegeneration occurs in cognitively normal older individuals and has been included in preclinical AD criteria. Yet, it remains uncertain whether Abeta and neurodegenerative biomarkers are invariably associated in the normal elderly. This study examined relationships between biomarkers of Abeta and AD-sensitive neurodegeneration as well as cognitive abilities in normal older individuals.

Methods: Abeta burden was quantified in 72 normal older people from the Berkeley Aging Cohort (BAC) using [11C] Pittsburgh compound B (PIB) PET. In the same individuals, neurodegeneration was evaluated within AD-sensitive regions using three biomarkers: hippocampal volume, glucose metabolism (measured with [18F] Fluorodeoxyglucose [FDG] PET) and cortical thickness, both extracted from a template of AD neurodegenerative regions that was developed in a separate cohort (ADNI, Figure 1A). These functional and structural markers were merged into a highly AD-sensitive multi-modality biomarker (classification accuracy (AUC = 0.97) and related to PIB uptake and cognitive functions.

Results: There was no association between Abeta deposition (indicated by a positive PIB status) and the multi-modality neurodegenerative biomarkers (Figure 1B) in cognitively normal older individuals. Lower brain integrity within AD-affected and a control region, but not PIB positivity, was related to poorer cognitive functions (depicted for memory, Figure 1C). There was a significant interaction for the AD region, such that the biomarker-cognition relationship was stronger in individuals with the highest PIB uptake (Figure 1D).



Conclusions: Our findings indicate that neurodegeneration occurs within AD-affected regions irrespective of fibrillar Abeta and accounts for reduced cognitive ability in cognitively normal older people. The impact of neurodegeneration on cognition is, however, enhanced in the presence of high Aβ burden for regions that arevulnerable to AD pathology.

Keywords: *aging, cognition, amyloid, neurodegeneration*

Presented by: Wirth, Miranka

Keynote Lecture

The Amyloid Cascade Hypothesis is Not a Hypothesis (and How to Fix It)

Karl Herrup

Division of Life Science, Hong Kong University of Science & Technology

The amyloid cascade hypothesis has been, and continues to be, a galvanizing conceptualization of the cognitive, behavioral and histopathological symptoms of the condition we recognize as Alzheimer's disease (AD). Originally proposed during the period in which the three major familial AD genes were identified, it interconnects the pathology, genetics and biochemistry of the disease in a compelling and testable scheme. Serious problems with the hypothesis have appeared, however, as its various predictions have been tested. The failure of these tests could and should have led to a re-statement of the hypothesis and to a certain extent this has happened. Unfortunately, the more prominent response has been instead to re-define the disease. As a result, the amyloid cascade hypothesis can no longer be disproven and, therefore, it is no longer a useful hypothesis. It has instead become a "model" of AD. This may seem like a minor semantic distinction, but at stake is the central question of how we are to diagnose AD and measure the effectiveness of new prevention and treatment regimens. The following 'fixes' to the address the weakness in the model are proposed: 1) amyloid burden should define AD risk, not disease; 2) amyloid, in any stage of aggregation, should be considered as correlated with, but mechanistically distinct from, the biological processes that produce the dementia we call Alzheimer's and 3) other measures and markers (e.g., inflammation, oxidation, neuronal cell cycle activity) should be incorporated into our diagnostic schemes as equal partners to amyloid and tau.

Presented by: Herrup, Karl

Session 3: Amyloid Correlates: Fluoro-Deoxyglucose; Memory; Non-Tremor-Onset PD

CHAIRS:

Denise C. Park, PhD, ***The University of Texas at Dallas***

Dorene Rentz, PsyD, ***Brigham and Women's Hospital***

Hypometabolic Findings in PiB Positive, Cognitively Normal Subjects in the Mayo Clinic Study of Aging

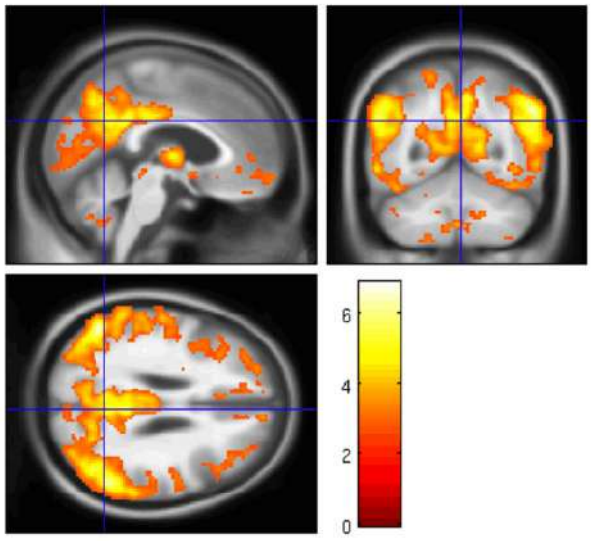
Val Lowe, Stephen Weigand, Matthew Senjem, Kejal Kantarci, David Knopman, Bradley Boeve, Ronald Petersen, Clifford Jack

Mayo Clinic

Background: Pittsburgh compound B (PiB) accumulation occurs in about a third of cognitively normal (CN) subjects. The relationship of neurodegenerative biomarkers, namely FDG PET, and PiB positivity in CN subjects is not well understood. We hypothesized that subtle hypometabolism may occur in close temporal association with the early findings of PiB positivity. Therefore, we assessed hypometabolism in different stages of PiB positivity in CN subjects.

Methods: 617 CN subjects in the Mayo Clinic Study of Aging were analyzed. We used two methods to identify any hypometabolic changes in PiB positive subjects. First, we used penalized logistic regression and cross-validation to develop a parsimonious multivariable region of interest model of "optimal" cortical brain regions of hypometabolism associated with PiB positivity. This method was first validated in our CN and AD populations and then employed in CN PiB negative and positive subjects. Second, we used a voxel-wise approach (SPM) to look at hypometabolism in various PiB-value subsets (dose-finding approach) namely those CN subjects with PiB values < 1.4 (n=351), >1.4 to 1.48(n=66), >1.48 to 1.73(n=66), >1.73 to 205(n=66), and >2.05(n=66).

Figure 1. Pattern of hypometabolism seen in CN PiB positive subjects vs. CN PiB negative subjects by SPM analysis.



Results: Our penalized logistic regression model demonstrated hypometabolism in signature AD regions, namely the angular gyrus and posterior cingulate, in a cross-validated multivariable ROI model (AUC=0.65) in the CN PiB positive subjects. SPM analysis demonstrated a trend (non-FDR, P=0.005) for hypometabolism in these same regions beginning at the 1.48-1.73 PiB-value subset that became most significant in these regions but with additional, more diffuse cortical regional hypometabolism in the >2.05 subset (non-FDR, P=0.001 and FDR of P=0.05). (Figure #1)

Conclusions: Hypometabolism is seen in PiB positive, CN subjects in AD-signature cortical regions. The hypometabolism can be seen early in the development of PiB positivity in these subjects suggesting that hypometabolism, and related neurodegeneration, likely occurs early in the amyloid deposition process.

Keywords: *PET, PiB, FDG, Normal Cognition*

Presented by: Lowe, Val

Correlation Analysis of FDG PET Images from Amyloid-Low and Amyloid-High ADNI MCI Subjects

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Background: Correlation analysis of structural and functional brain images has the potential to provide unique insights into the natural evolution of Alzheimer's disease, as well as facilitate the assessment of therapeutic intervention. In order to determine the effects of beta-amyloid deposition on brain functional architecture at the early disease stage, we have performed cortical correlation analysis of FDG PET images from amyloid-low and amyloid-high MCI subjects in the ADNI study.

Methods: T1-weighted MRI, [18F]florbetapir (AV-45) PET, and [18F]FDG PET images were obtained from ADNI-GO/-2 MCI subjects. PET volumes were registered to a customized MRI template in MNI stereotaxic space, and SUVR images were generated and projected onto each subject's cortical surface using Biospective's fully-automated PIANO™ pipeline. Subjects were classified into amyloid-low and amyloid-high groups using lower and upper florbetapir SUVR thresholds based on a composite ROI. For each group, we computed vertexwise Cortical Correlation Strength (CCS) measures, defined as the average correlation value between a vertex and all other cortical vertices. The thresholded CCS maps revealed hubs, defined as the vertices that were most highly correlated with all other cortical vertices, which were subsequently utilized for a hub-based correlation analysis (HBCA).

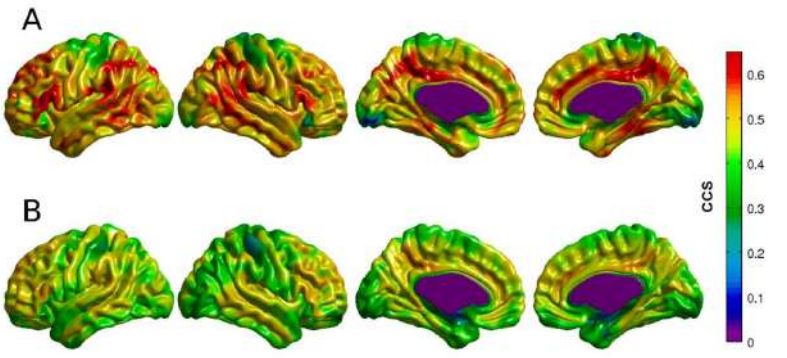

Figure 1. Cortical Correlation Strength (CCS) maps for the amyloid-low (A) and amyloid-high (B) groups.

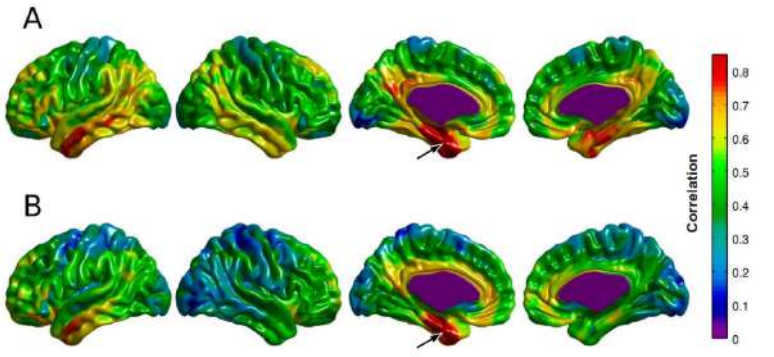

Figure 2. Hub-based cross-correlation maps with left entorhinal cortex (*arrow*) as the hub for the amyloid-low (A) and amyloid-high (B) groups.

Results/Conclusions: The amyloid-low group had stronger overall CCS measures compared to the amyloid-high group (Figure 1). We performed HBCA in several regions and identified statistically significant differences between amyloid-low and amyloid-high groups. A striking feature was reduction in CCS between homologous regions in the left and right cerebral hemispheres of the amyloid-high subjects (Figure 2). While this study examined functional correlations based on glucose utilization, future studies could evaluate and compare similar properties derived from resting-state BOLD and ASL perfusion MRI data. Based on this study, correlation analysis of functional imaging data may serve as a sensitive imaging biomarker for the assessment of therapeutic intervention in early disease studies.

Keywords: *Amyloid PET, FDG PET, Correlation Analysis, MCI, ADNI*

Presented by: Bedell, Barry

Longitudinal FDG Change in CN and MCI: Relation to Aβ Status and Cognitive Change

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Objective: To evaluate within-subject change in FDG metabolism in relation to change in clinical outcomes (CO)(CDR Sum of Boxes (SB) and MMSE) in cognitively normal (CN) and Mild Cognitive Impairment (MCI) subjects with known amyloid status.

Methods: A total of 1438 longitudinal FDG PET data sets from the ADNI and Harvard Again Brain samples were assessed in CN (n=295) and MCI (n=227) subjects whose amyloid status was determined by CSF Aβ or PiB data. Mixed-effects models were constructed for CO as a function of baseline age, education, baseline FDG in a precuneus/posterior cingulate ROI (MNI space normalized), time since baseline, and FDG change since baseline. FDG change was separately modeled with mixed-effects at vertices (Freesurfer) using baseline age, time since baseline, amyloid status and Aβ-by-time interaction as predictors.

Results: A portion of the CO decline was age dependent and independent of FDG decline, and was greater in Ab+ than Ab- in both CN and MCI ($p<0.03$). MMSE and SB decline that was FDG-dependent was significant in Ab- and Ab+ MCI, respectively. Within-subject FDG decline in AD-associated cortical regions (lateral parietal and temporal, medial temporal, and precuneus/posterior cingulate) was seen in both Ab- and Ab+ CN and MCI subjects, however, FDG decline was greater in Ab+ subjects in both groups ($p<0.05$).

Conclusions: Cerebral glucose metabolism declines with time in AD-associated regions in CN and MCI. FDG decline is more rapid in Ab+ compared to Ab- subjects, and is related to clinical decline independent of aging. FDG may prove effective in tracking the impact of anti-amyloid therapy in preclinical and prodromal stages of AD.

Keywords: *FDG, PiB, Longitudinal, ADNI*

Presented by: Becker, J. Alex

Amyloid Deposition and Cognition in Older Adults: The Effects of Premorbid Intellect

Kevin Duff [1], Norman Foster, Kathryn Dennett, Dustin Hammers, Lauren Zollinger, Paul Christian, Regan Butterfield, Britney Beardmore, Angela Wang, Kathryn Morton, John Hoffman

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Background: Although amyloid deposition remains a marker of the development of Alzheimer's disease, results linking amyloid and cognition have been equivocal.

Methods: Twenty-two community-dwelling non-demented older adults were examined with ^{18}F-flutemetamol, an amyloid imaging agent, and a cognitive battery (premorbid intellect and Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]).

Results: In the first model, ^{18}F-flutemetamol uptake significantly correlated with the Delayed Memory Index of the RBANS (r=-0.51, p=0.02). In the second model, the relationship between ^{18}F-flutemetamol and cognition was notably stronger when controlling for premorbid intellect (e.g., 3 of the 5 RBANS Indexes and its Total score significantly correlated with ^{18}F-flutemetamol).

Conclusions: Associations were found between amyloid-binding ^{18}F-flutemetamol and cognitive functioning in non-demented older adults. These associations were greatest with delayed memory and stronger when premorbid intellect was considered, suggesting cognitive reserve partly compensates for symptomatic expression of amyloid pathology in community-dwelling elderly.

Keywords: *amyloid, flutemetamol, memory, cognition, pre-morbid IQ, elderly*

Presented by: Duff, Kevin

Different PIB Binding between Patients with Tremor-onset and Non-tremor-onset Parkinson's Disease

Anna Brück, Joseph Locascio, Stephen Gomperts, Dorene Rentz, Alex Becker, Laura Memole, Jeremy Carmasin, Reisa Sperling, John Growdon, Keith Johnson

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Bradykinesia, rigidity and falls have been associated with higher risk for developing dementia in Parkinson's disease (PD). Post-mortem data has indicated that patients with non-tremor onset of the disease have more amyloid pathology than patients with tremor as the initial motor symptom. The aim of this study was to investigate whether patients with different initial motor symptoms of PD differed in cortical PIB binding. Twenty-three patients with PD or PDD (18 PD, 2 PD-MCI, 3 PDD) and 93 healthy volunteers (men/women, 32/61, age mean±SD, 73.7±8.1years) underwent PIB PET, high-resolution MR imaging, Freesurfer processing, and partial volume correction. PD subjects did not differ significantly from controls in global or regional PIB retention ($p>0.1$). The patients were divided into two groups based on the first motor symptom: subjects with tremor (n=16; M/W, 7/9; mean±SD, age 70.3±7.3, H&Y 2.2±0.5, UPDRS 19.7±5.9, MMSE 28.1±2.3, CDR 0.2±0.3) and subjects with slowness or gait problem as the first symptom (non-tremor group, n=7; M/W, 5/2; mean±SD, age 69.7±6.1, H&Y 2.9±0.2, UPDRS 22.6±7.5, MMSE 28.1±2.2, CDR 0.4±0.5). The two groups did not differ in age, gender, H&Y, UPDRS, MMSE or CDR ($p>0.1$). The non-tremor group had higher global PIB DVR (mean±SD, 1.62±0.29) than the tremor group (1.38±0.29) when adjusted for age and gender ($p<0.05$). Similar differences were also found in caudal anterior cingulate and occipital region ($p<0.05$) and borderline significant in precuneus and rostral anterior cingulate ($p<0.1$). When PDD and PD-MCI subjects were pre-excluded from the analyses there was still a significant ($p<0.05$) or borderline significant ($p<0.1$) difference between the groups. In conclusion this study shows in vivo for the first time that patients with non-tremor-onset PD have more cortical amyloid than patients with tremor-onset PD. These data support previous epidemiological and post-mortem studies suggesting that bradykinesia and difficulties with gait are associated with higher risk for dementia.

Keywords: *PET, [11C]PIB, Parkinson's disease*

Presented by: Brück, Anna

Session 4: Tau PET

CHAIRS:

Charles Duyckaerts, MD, PhD, ***Salpêtrière Hospital/University of Paris VI***

John Seybil, MD, ***The Institute for Neurodegenerative Disorders***

In Vivo Tau Imaging in Alzheimer's Disease

Victor L Villemagne [1], Shozo Furumoto [2], Michelle Fodero-Tavoletti [3], Rachel Mulligan [1], John Hodges [4], Ryuichi Harada [2], Paul Yates [1], Svetlana Pejoska [1], Yukitsuka Kudo [5], Colin L Masters [3], Kazuhiko Yanai [2], Christopher C Rowe [1], Nobuyuki Okamura [2]

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[2] *Dept Pharmacology, Tohoku University School of Medicine, Sendai, Japan*
[3] *The Mental Health Research Institute, Melbourne, Australia*
[4] *Neuroscience Research Australia, Sydney, Australia*
[5] *Innovation of New Biomedical Engineering Center, Tohoku University, Sendai, Japan*

Objectives: Definitive diagnosis of tauopathies such as Alzheimer's disease (AD), is still reliant upon post-mortem examination of the human brain. ^{18}F-THK523, a novel tau imaging ligand developed at Tohoku University in Sendai, Japan, that displayed high selectivity and specificity for PHF-tau pathology both *in vitro* and *in vivo*, was evaluated in humans with PET.

Methods: Twenty-one participants -10 elderly healthy controls (HC), 8 Alzheimer's disease (AD) and 3 semantic dementia (SD) patients underwent neuropsychological examination, MRI, ^{18}F-THK523 and ^{11}C-PiB PET. Standard uptake value ratios (SUVR) at 60-90 min and 40-70 min post injection were calculated for ^{18}F-THK523 and ^{11}C-PiB, respectively, using the cerebellar cortex as the reference region. Images were corrected for partial volume effects.

Results: Significantly higher ^{18}F-THK523 cortical retention was observed in the temporal, parietal, orbitofrontal and hippocampus of AD patients when compared to healthy controls and SD patients. The pattern of ^{18}F-THK523 retention followed the known distribution of PHF-tau in the AD brain (higher in posterior areas than frontal) and it did not correlate with the cortical retention of ^{11}C-PiB. Furthermore, unlike ^{11}C-PiB, ^{18}F-THK523 hippocampal retention was correlated with episodic memory impairment ($r = -0.75$; $p = 0.0003$) and with hippocampal volume ($r = -0.78$; $p = 0.0002$), even when HC ($r = -0.69$; $p = 0.03$) and AD patients ($r = -0..79$; $p = 0.02$) were considered separately.

Conclusions: ^{18}F-THK523 does not bind to Abeta in vivo, while following the known distribution of PHF-tau in the brain. Significant higher cortical ^{18}F-THK523 retention in AD patients, along its association with cognitive parameters and hippocampal atrophy suggests ^{18}F-THK523 selectively binds to PHF-tau in the AD brain. Further studies are needed to confirm these initial findings.

Research Support: Supported in part by ADDF Research Grant (20101208 AFTD)

Keywords: *Alzheimer's disease, tau imaging, Aβ imaging, positron emission tomography*

Presented by: Villemagne, Victor L

Early Clinical PET Imaging Results with the Novel PHF-Tau Radioligand [18F]-T807

Hartmuth Kolb, David Chien, A. Katrin Szardenings, Joseph C. Walsh, Arkadij Elizarov, et al.

Siemens MI

The PET imaging results of the first 6 human subjects (2 AD, 1 MCI, 3 healthy controls) will be presented.

The subjects underwent a dynamic PET/CT scan for the first 60 minutes post injection and a static scan from 80-100 minutes. Volumes of interest (VOI) of the frontal lobes (FL), parietal lobes (PL), lateral temporal lobes (LTL), mesial temporal lobes (MTL), occipital lobes, cerebellum, and white matter were defined by manual contouring of the CT images and then applying the VOIs to the PET images. The mean standardized uptake value (SUV) and SUV ratio relative to the cerebellum (SUVR) were generated for each VOI.

The mean MMSE for the HCs was 29, the MMSE for the MCI case was 26, the MMSE for the mild AD case was 21 and for the severe case 7.

There was rapid tracer distribution to the brain in all subjects that cleared from all cortical regions at similar rates for the HCs. AD subjects had significantly slower clearance in cortical regions where abnormal PHF-Tau is expected to accumulate. There was minimal tracer retention by the white matter in all subjects.

The pattern of cortical retention in the mild and severe AD subject correlated with the pattern of PHF-Tau deposition described by Braak. In the mild AD subject, the highest SUVR is in the LTL (1.83) and MTL (1.73), followed by PL (1.37) and FL (1.27), corresponding to Braak stage III-IV. In the severe AD subject, the PL (2.06) had the highest SUVR, followed by LTL (2.03), FL (1.95), and MTL (1.47), corresponding to Braak stage V-VI.

References:

Zhang W, Arteaga J, Cashion DK, Chen G, Gangadharmath U, Gomez LF, Kasi D, Lam C, Liang Q, Liu C, Mocharla VP, Mu F, Sinha A, Szardenings AK, Wang E, Walsh JC, Xia C, Yu C, Zhao T, Kolb HC (2012) A Highly Selective and Specific PET Tracer for Imaging of Tau Pathologies J Alzheimers Dis. 31 601-612.

Keywords: *PHF-Tau Alzheimer's Disease Braak Stage Tau PET Imaging*

Presented by: Kolb, Hartmuth

Session 5: Technical Emphasis Session

CHAIR:

Chester A. Mathis, PhD, *University of Pittsburgh*

Regional Correspondence Between [11C]PiB PET and Post-mortem Measures of Amyloid Load: Consideration of Partial Volume Averaging

Julie Price [1], Davneet Minhas [1], Charles Laymon [1], Eric Abrahamson [2], Lisa Weissfeld [3], Oscar Lopez [2], Manik Debnath [4], Li Shao [4], Ronald Hamilton [5], Carl Becker [1], William Klunk [6], Chester Mathis [1], Milos Ikonomovic [6]

[1] *Department of Radiology, University of Pittsburgh School of Medicine*
[2] *Department of Neurology, University of Pittsburgh School of Medicine*
[3] *Department of Biostatistics, University of Pittsburgh School of Medicine*
[4] *Department of Psychiatry, University of Pittsburgh School of Medicine*
[5] *Department of Neuropathology, University of Pittsburgh School of Medicine*
[6] *Departments of Psychiatry and Neurology, University of Pittsburgh School of Medicine*

Objectives: To better understand the impact of partial volume (PV) correction on the regional correspondence between in vivo PET measures of fibrillar amyloid-β (Aβ) plaque deposition and postmortem assessments of Aβ-load.

Methods: [11C]PiB PET was performed for 8 subjects (S1-S8) with dementia over 90 min (n=7) or 60 min (n=1*), with a maximum interval of 42 months before death. PiB retention was measured using SUVR50-70 or SUVR50-60*. Post-mortem Aβ plaque load was assessed using a highly fluorescent derivative of PiB (6-CN-PiB) applied to 12-μm paraffin sections of multiple regions. Region-labeled images of postmortem brain guided region generation on the corresponding ante-mortem MR and sampling of the co-registered PET (e.g., anterior cingulate (ACG), frontal cortex (FRC), precuneus (PRC)). PiB SUVR was corrected for atrophy-related PV effects using two methods with different segmentation algorithms: (1) two-compartment (GM+WM, CSF) CSF-dilution correction and (2) three-compartment (GM, WM, CSF) least squares fit for extraction of GM+WM concentration. PiB SUVR and 6-CN-PiB correlations were assessed using Spearman's rho (2-sided, **$p<0.05$**)

Results: Uncorrected SUVR values ranged from minimal-to-high (PRC: 1.1 (S3) to 2.7 (S1*)). Corrected PRC SUVR ranged from 1.2 (S3) to 3.4 (S1*) for Method-1 and 1.3 (S3) to 3.1 (S5) for Method-2. Relationships between uncorrected PiB SUVR and 6-CN-PiB measures appeared more linear at lower fibrillar Aβ load and somewhat asymptotic at higher load. Linearity was often more apparent throughout the pathology-load range after PV-related corrections. Correlations for ACG, FRC, and PRC were, respectively: 0.571, 0.619, **0.905** (Uncorrected); **0.762**, 0.667, **0.952** (Method-1); **0.810, 0.738**, **0.976** (Method-2).

Conclusion: Correction for PV effects can improve correspondence of regional antemortem PiB retention and post-mortem amyloid-load measures. This is consistent with the exclusion of CSF spaces from post-mortem plaque-load analyses. A larger and more variable sample is needed to characterize the PV-related corrections and segmentation algorithms for ante-mortem/post-mortem correlations.

Keywords: *PiB, postmortem, amyloid-beta, partial volume correction*

Presented by: Price, Julie

Scanner Resolution Effects on Quantitative Amyloid Measurements

Gregory Klein [1], David Scott [1], Vahan Sharoyon [1], Joonmi Oh [1], Robert Koeppe [2], Joyce Suhy [1]

[1] *Synarc, Inc*
[2] *University of Michigan*

Introduction: Quantitative amyloid Standard Uptake Value Ratio (SUVr) assessments are used for longitudinal efficacy endpoints in clinical trials, and potentially for cross-sectional evaluation of patient amyloid burden, yet the effect of differing spatial resolution from PET scanners in a multi-center study remains unclear. Peak spatial resolutions of scanners now in clinical use vary by more than 5mm FWHM, and reconstruction parameters are often selected that increase this variability.

Methods: We analyzed florbetapir PET data from a subset of normal, MCI and AD subjects that were scanned using the highest resolution scanners in the ADNI study. Differences in global cortical SUVrs were compared as data were increasingly smoothed. Each scanner's resolution was calibrated from Hoffman phantom acquisition data, and reconstructed images were smoothed to values representing effective resolutions between 5.5mm and 9.0mm FWHM. SUVrs were calculated in four cortical meta-regions in MRI patient space using Freesurfer. SUVrs were computed separately using whole cerebellum and the cerebellar grey regions as the reference region, and a global cortical amyloid index was obtained as described by the ADNI PET core lab.

Results: Compared with SUVrs computed at the highest spatial resolution in the ADNI dataset, SUVrs at 9mm FWHM resolution changed between -5% and 8% using whole cerebellar reference, and between -5% and 4% using cerebellar grey reference. Low SUVrs tended to shift higher with increasing smoothing for amyloid negative patients, but lower for amyloid positive patients.

Conclusions: Quantitative SUVr thresholds used for cross-sectional analysis require attention to spatial resolution to compensate for effects of different scanner resolutions, suggesting caution for how longitudinal SUVrs should be compared different scanner types. White matter hyperintensity partial volume effects may increase SUVrs following smoothing in amyloid negative patients, while CSF partial volume effects may decrease SUVrs in amyloid positive patients, especially in cases with atrophy.

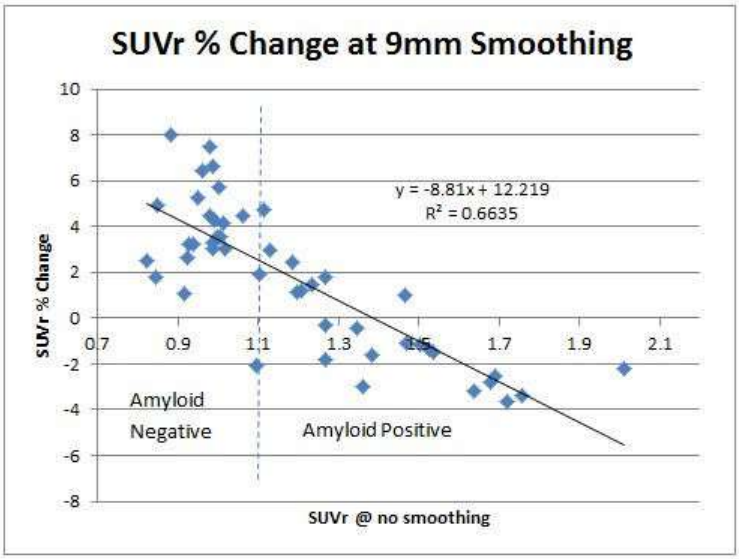
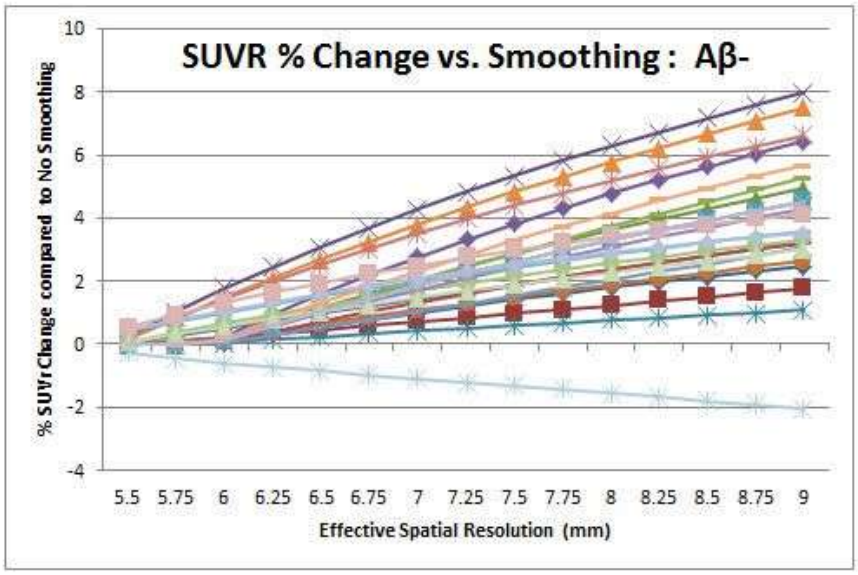


Fig 1. Percent change of composite SUVr for AV-45 ADNI images analyzed at native spatial resolution compared to images smoothed to 9mm effective resolution. A trend is seen where increasingly amyloid negative values show increasing SUVr due to smoothing, and conversely, increasingly amyloid positive values show decreasing SUVr due to smoothing.



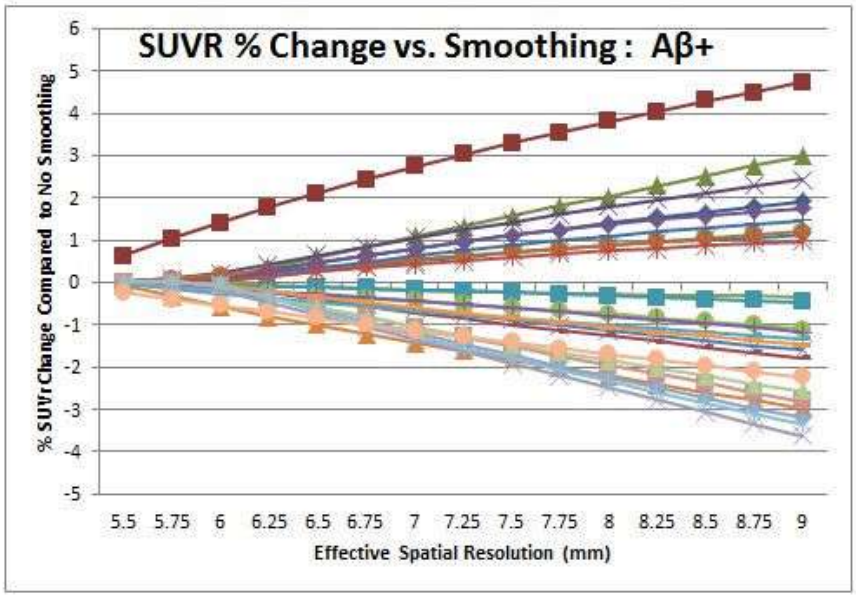


Fig 2. Percent change of composite SUVr versus scanner effective resolution. Clear differences are seen in changes of SUVr values due to smoothing in amyloid positive compared to negative subjects. Data are referenced to analysis of images using the unsmoothed data available from the ADNI dataset.

Keywords: *SUVr, florbetapir, smoothing*

Presented by: Klein, Gregory

Data Analysis for Amyloid PET Imaging: Longitudinal Studies

Robert A. Koeppe

University of Michigan

Key issues in analysis of amyloid PET images will be discussed, with a particular focus on longitudinal studies. In cross-sectional studies differences in amyloid load across subjects can be very large and the research and/or clinical questions being are varied. Is this subject amyloid positive or negative? Does this diagnostic group have higher amyloid loads than another diagnostic group? Is the pattern of amyloid load different between groups? This is in contrast with longitudinal studies where the question is almost always: Did the amyloid load, as measured by PET, change over time? In such studies, one is looking for small changes on the order of a few percent, and on top of this, in drug efficacy trials, the question is: Does this drug alter the magnitude of this change over time? In order to achieve reliable results, one look very carefully at the methods and procedures used to extract the amyloid measures in order to minimize all sources of variance other than true change over time. Effects of differences in 1) methods to extract target region values; 2) selection of and methods to extract reference region values; 3) time of scan relative to injection; 4) shape of tracer input curve; 5) use of co-registered MR vs. PET-only methods are explored.

Presented by: Koeppe, Robert A.

Standardization of Quantitative Amyloid Imaging Data: the Centiloid Project

William E. Klunk

University of Pittsburgh

Although amyloid imaging with PiB-PET, and now with F-18-labelled traces, has produced remarkably consistent qualitative findings across a large number of centers, there has been considerable variability in the specific numbers reported as quantitative outcome measures of tracer retention. In some cases this is as trivial as the choice of units (e.g., BP vs. SUVR), in some cases it is scanner dependent, and of course, different tracers yield different numbers. A suggestion was made at the AAIC-2012 to standardize quantitative amyloid imaging measures by simply scaling the outcome of each particular analysis method or tracer to a 0 to 100 scale, the units of which have come to be called "Centiloids." A working group was formed and met by weekly teleconferences to develop this standardization procedure. The specifics will be outlined, but basically, a standard method of analyzing PiB PET data for a specified set of young controls (≤45 yrs) and typical AD patients was proposed. These two groups will define the 0 and 100 points on the scale (which can extend well-above, and perhaps slightly below these anchors). The second phase of this procedure outlines a recommended method for scaling any method of PiB PET analysis other than the "standard" approach to the Centiloid scale or scaling any other tracer to this scale. It is expected that all de-identified data used in the initial scaling of a tracer be uploaded to a publically-accessible website, so sites choosing to express results in Centiloid units can download this data and test the analysis pipeline at their site to ensure reproducibility of the approach before proceeding to use the pipeline for scaling of their own data to the Centiloid scale. Some preliminary scaling analyses across PiB and several F-18 tracers will be presented.

Presented by: Klunk, William E.

Session 6: Neuropathology

CHAIRS:

Susan Resnick, PhD, ***National Institute on Aging***

Juha Rinne, MD, PhD, ***University of Turku***

Evaluation of the Histopathology Burden Underlying [18F]flutemetamol PET Imaging

Adrian Smith [1], Chris Buckley [1], Paul Sherwin [1], Kerstin Heurling [1], Milos Ikonomovic [2], Chet Mathis [2], Bill Klunk [2], Gill Farrar [1]

[1] *GE Healthcare*
[2] *University of Pittsburgh Medical Center*

Background: Postmortem brain histopathology analyses were compared to region-matched antemortem visual PET image assessments in 68 cases from the GE067-007 [^{18}F]flutemetamol end of life amyloid imaging trial. The *a priori* standard of truth (SOT) was dichotomous Bielschowsky silver stain (BSS) assessment of neuritic plaques based on CERAD criteria, while additional reference standards included percentage area covered by amyloid beta immunoreactive plaques and neuropathological diagnosis of Alzheimer's disease (AD) based on the NIA-Reagan criteria. The main goals were to examine the criteria set *a priori*, identify histopathology thresholds for positive [^{18}F]flutemetamol PET scan, demonstrate diagnostic relevance of these thresholds, and determine causes of any disparity between PET imaging and histopathology findings.

Results: 43 brains (63%) were AD pathology positive by the BSS SOT, with a broad and continuous spectrum of amyloid pathology burden. There was a high concordance between [^{18}F]flutemetamol PET retention and the *a priori* criteria for pathology determined postmortem. No cases of PET positivity were observed in the absence of amyloid pathology. Two cases of tangle-predominant pathology were PET negative. In some late-stage AD cases cortical atrophy complicated PET image reading but was mitigated by coronal assessment of inferior parietal which was less frequently atrophied than other cortical regions. Four equivocal cases were PET positive, three of which had neuritic plaque amounts just below the *a priori* threshold between sparse and moderate. All four cases had heavy cortical diffuse plaque burden; in one case this was accompanied by significant deposits of Aβ in cerebral vasculature.

Conclusions: The antemortem [^{18}F]flutemetamol amyloid imaging data are in agreement with the *a priori* histopathology thresholds of neuritic plaques. [^{18}F]flutemetamol retention is not influenced by tangle pathology, however, diffuse fibrillar deposits of amyloid-beta in non-neuritic plaques may contribute to flutemetamol PET imaging.

Keywords: *Flutemetamol, PET, autopsy, histopathology, Bielschowsky*

Presented by: Smith, Adrian

Differential Regional Amyloid Load in Familial and Sporadic Alzheimer's Disease: Implications for Interpreting In Vivo PiB PET Signal

Milos Ikonomovic, Julie Price, Eric Abrahamson, Chester Mathis, William Klunk

University of Pittsburgh

Objectives: To quantify postmortem histopathology measures of regional Aβ burden and PiB binding in familial (FAD) and sporadic (SAD) AD cases and examine their relationship to antemortem [C-11]PiB PET retention levels.

Methods: [C-11]PiB PET scans were performed on two SAD subjects (PiB-positive); one FAD subject (PiB-positive), and a DLB subject (PiB-negative); another FAD subject (cousin of scanned FAD subject) in the study was not scanned. Caudate nucleus (CD), temporal cortex (TC), frontal cortex (FC), primary visual cortex (PVC), and the precuneus (PreC) were processed to quantify pathology burdens (% area) detectable by PiB (6-CN-PiB, a highly fluorescent derivative of PiB), Aβ immunohistochemistry (4G8 antibody), and a pan-amyloid marker (X-34, a highly fluorescent derivative of Congo red).

Results: The PiB-negative DLB case had the lowest amyloid burden, consisting mainly of diffuse 4G8 plaques with <1% 6-CN-PiB and X-34 plaque burden in neocortical areas and no plaques in the CD. SAD cases had up to fifteen times greater neocortical amyloid burden than the PiB-negative DLB case, and substantial amyloid deposits in the CD. FAD cases had highest amyloid burden in the CD (eight times greater than SAD) and FC (2-3 times greater than SAD). [C-11]PiB PET data mirrored neuropathological observations, with CD showing highest retention levels among all regions in FAD, but not in SAD cases.

Conclusions: Amyloid pathology and [C-11]PiB PET retention in the CD and FC is more extensive in FAD than in SAD, despite the predominance of diffuse Aβ plaques which are generally considered to bind PiB poorly. Diffuse Aβ plaques were also predominant in the neocortex of the DLB case, however this pathology was essentially undetectable with PiB. These observations reveal differential regional binding of PiB to diffuse plaques in FAD compared to other cases with amyloid pathology. The extent of contribution of diffuse Aβ plaques to PiB PET signal warrants further examination.

Keywords: *amyloid, PiB, PET, neuropathology*

Presented by: Ikonomovic, Milos

Cerebral Amyloid Angiopathy Can Produce a "False Positive" PIB Scan -A Case Study

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Dept. of Neurology, McGill University

Amyloid is one of the morphologic hallmarks of Alzheimer disease (AD). According to most recent results, PIB is positive in Alzheimer's subjects in 85-95% of subjects. Cerebral amyloid angiopathy (CAA)= congophilic angiopathy demonstrates deposition of β -amyloid in the media and adventitia of small- and mid-sized arteries of the cerebral cortex and the leptomeninges. CAA may lead to dementia, intracranial hemorrhage (ICH), or transient neurologic events.

We present a single case study in which CAA presented clinically as a progressive cortical dementia and was clinically diagnosed as probable AD.This 83 year old man had progressive memory loss, along with mild diabetes. CT scan was read as showing "Moderate diffuse atrophy, periventricular white matter lucency due to chronic small vessel arteriolar occlusive disease" compatible with AD, in the absence of clinical strokes or TIAs. As part of an ongoing research project, he underwent MRI, and PIB PET imaging. He sustained a sudden collapse with left hemiparesis 6 months later, and CT scan revealed a massive and fatal right intracerebral hemorrhage.

His imaging showed PIB positive amyloid deposition in a typical AD distribution, SUVR 1.98. HIs MRI showed confluent white matter hyperintensities on T2.

Brain autopsy was carried out. There was a large right cerebral intracerebral hemorrhage. On microscopy, there were no senile plaques or neurofi brillary tangles to be found anywhere. There was diffuse amyloid angiopathy, severe, in anterior as well as posterior brain regions. The conclusion was that the dementia as well as the hemorrhage were related to cerebral amyloid angiopathy without Alzheimer's Disease. What is striking is that, despite the white matter changes on MRI, this man appeared clinically as probable AD, and had a supporting PIB PET scan typical for AD.

It appears that CAA can masquerade as AD both clinically and on PIB scanning. This might be termed a "false positive" PIB.

Research Support: *The Canadian Institutes for Health Research (CIHR)*

Keywords: *PIB, diagnosis, autopsy AD*

Presented by: Chertkow, Howard

Microbleeds Are Associated with Increased Permeability of the Blood Brain Barrier: a Quantitative [11C]PIB PET Study

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Introduction: MBs have been related to high [^{11}C]PIB PET retention, suggesting increased amyloid binding due to cerebral amyloid angiopathie (CAA). However, increased retention of [^{11}C]PIB may also be caused by altered blood-brain barrier (BBB) permeability and does not necessarily mean increased specific binding e.q. amyloid load. Therefore, in this methodological case-control study we assessed the relation between MBs, BBB permeability and specific binding using quantitative [^{11}C]PIB PET.

Methods: We included 8 AD patients with MBs (Group I) and 5 AD patients without MBs (Group II). Dynamic 90 minute [^{11}C]PIB PET scans were acquired on the HR+ PET camera with arterial blood sampling to generate a metabolite corrected input curve. Data were analysed with a previously validated two tissue compartment model. We assessed the non-displaceable binding potential ($BP_{ND)}$ as a marker of specific binding as well as the K1/k2 ratio, reflecting BBB permeability. BP_{ND} and K1/k2 were assessed in regional volumes of interest (VOI)as well as in a total cortical VOI. In addition, VOI were drawn manually around the MB regions and copied contra laterally which served as control regions.

Results Eighteen MB VOIs were identified and, when compared to the contra lateral control VOIs, K1/k2 ratios were found to be higher in the grey matter surrounding the MB (2.19±0.63 and 1.98±0.53, respectively $p<0.05$), while BP_{ND} did not differ significantly. In addition, the MB K1/k2 ratios in the grey matter correlated with size of the VOI (Spearman's Rho 0.80, p=0.002) while this was not the case in the control region (Rho 0.49, p=0.12). None of the larger regions, or global cortical ROIs showed a difference in BP_{ND} (global: group I 3.29±2.5 group II 3.01±1.4, p=0.82) or K1/k2 ratio (global: group I 2.15±0.4, group II 2.21±0.4, p=0.83).

Conclusion: At the MB level, local K1/k2 ratio was higher and associated with MB VOI size. This indicates that MB are associated with increased permeability of the BBB. This has important implications for the use of [^{11}C]PIB scans in the diagnosis of CAA.

Keywords: *microbleeds, amyloid, CAA, blood brain barrier*

Presented by: van Berckel, Bart

Keynote Lecture

Type and Progression of ABeta Pathology

Charles Duyckaerts, Vincent Lebon, Véronique Sazdovitch, Danielle Seilhean

Laboratoire de Neuropathologie Escourolle, Alzheimer-Prion Team, ICM

Aβ deposition may take various aspects in the human brain. The diffuse, focal, subpial, or stellate amyloid deposits have different time course and are variously connected with the symptoms. Amyloid angiopathy may affect capillaries (frequently in patients bearing the ApoE4 allele) or spare them. Thal phases describe the progression of Aβ pathology: starting in the neocortex, it involves successively the hippocampus, the basal ganglia, the mesencephalon and finally the rest of the brainstem and the cerebellum. Progression of tau pathology has a different topography starting in the transento- and ento- rhinal cortex (Braak stages I and II, or entorhinal stages), secondarily reaching the hippocampus (Braak stages three and four-hippocampal stages) and the isocortex (five and six). Taking tau pathology as a chronological baseline, we recently reviewed Aβ pathology in thirty post mortem cases with low Braak stages (up to IV) collected in the last ten years in this laboratory. Forty four percent of the cases were at Thal 0 phase (no Aβ deposit); eighty percent of these Thal 0 cases were at Braak stages I or II. At Thal phase 1 or above, sixty percent were at Braak stages III or IV. When amyloid pathology was present in one of the cortical samples, all the studied samples were generally involved; *discontinuity* was exceptional. At Thal phase 1, the great majority of the deposits were of the diffuse type; *heterogeneity* of the deposits was observed only at later phases in the cortex, while in the basal ganglia all the deposits remained of the diffuse type. Focal deposits were associated with microglia, which were lacking in diffuse deposits. Neurites were observed only around focal deposits but focal deposits could be devoid of neurites. In conclusions, tau pathology may be observed in the absence of Aβ deposits. To explain why discontinuity is so rarely observed, we hypothesize that cortical Aβ pathology develops within a short time. The connection between tau au Aβ pathology suggests a link – tau pathology in our observational study being a condition to the development of Aβ pathology. Neurites are attracted in the plaque by other factors than Aβ, possibly secreted by macrophages. The term senile plaque, being used with too many different meanings should be abandoned or qualified.

Presented by: Duyckaerts, Charles

Session 7: Lessons Learned from Recent Clinical Trials and Implications for Prevention Trials

CHAIRS:

Reisa A. Sperling, MD, *Brigham and Women's Hospital*

Clifford R. Jack Jr., MD, *Mayo Clinic*

Relationship between Solanezumab Treatment and Amyloid Burden in Mild to Moderate AD Patients

Michael Pontecorvo [1], Abhinay Joshi [1], Ming Lu [1], Ann Marie Hake [2], Joel Raskin [2], Eric Siemers [2], Daniel Skovronsky [1], Mark Mintun [1]

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Background: Solanezumab is a humanized monoclonal antibody developed for the treatment of Alzheimer's disease (AD). It binds to the mid-domain of soluble amyloid beta peptide but not to deposited amyloid plaques. Florbetapir F18 is a PET imaging agent that estimates the burden of amyloid neuritic plaque pathology.

Methods: Subjects with mild to moderate stage AD (as determined using NINCDS/ADRDA criteria and baseline MMSE scores of 16-26) were enrolled in two Phase 3 trials of solanezumab (EXPEDITION and EXPEDITION2) between May 2009 and December 2010. Participants were randomized to 400 mg solanezumab IV or placebo once every 4 weeks for 80 weeks. Cognition and daily functioning as well as safety and tolerability measures were assessed. Allparticipants underwent structural and volumetric magnetic resonance imaging at baseline and at Weeks 12, 28, 52 and 80. A subset of participants underwent florbetapir PET amyloid imaging at baseline and endpoint. Images were analyzed quantitatively, using different regions of interest and different methods for coregistration and normalization, to calculate cortical target to reference region SUVr.

Results: A total of 243 of 2052 (11.8%) randomized participants had florbetapir PET data. Among participants who had imaging, approximately 20-30% had evidence of low density of neuritic amyloid plaque at entry. These amyloid-negative subjects showed a slower rate of cognitive deterioration than subjects with elevated neuritic plaque density, regardless of solanezumab treatment group. Ongoing analyses are evaluating the impact of solanezumab treatment on change in amyloid plaque as measured by florbetapir, and the relationship between degree of baseline amyloid plaque density and subsequent cognitive decline.

Conclusion: The solanezumab trials provide a rich database for exploring the potential of amyloid PET imaging as an entry criteria and measure of target engagement in Alzheimer's disease clinical trials.

Keywords: *solanezumab, florbetapir*

Presented by: Mintun, Mark and Pontecorvo, Michael

Effect of Bapineuzumab on Brain Fibrillar Amyloid Burden in Mild to Moderate Alzheimer's Disease: Results from the PET Substudies of 2 Phase 3 Trials

Enchi Liu [1], Mark Schmidt [2], Richard Margolin [1], Julia Lull [2], Yuan Lu [1], Cristina Tudor [1], Keith Gregg [1], Derek Hill [3], Andrea Les[3], Brad Wyman [4], Eric Yuen [5], Michael Grundman [6], H Robert Brashear [1]

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Introduction: Bapineuzumab, an anti-amyloid-beta monoclonal antibody, was evaluated in separate phase 3 trials for APOE ε4 allele carriers (Study 302) and non-carriers (Study 301) with mild-moderate Alzheimer's disease (AD). A subset of enrolled subjects participated in PET substudies.

O**bjectives:** To examine the effect of bapineuzumab treatment on brain fibrillar amyloid deposition, as measured by ^{11}C-PiB PET.

Methods: Placebo or bapineuzumab was administered intravenously 6 times in 13-week intervals, with bapineuzumab 0.5 mg/kg in APOE ε4 carriers and 0.5 mg/kg or 1.0 mg/kg in non-carriers. ^{11}C-PiB PET scans were obtained at baseline and at 45 and 71 weeks after treatment initiation. Subjects were studied at 14 US PET centers using acquisition protocols and image QC criteria developed in ADNI. For each PET scan a standardized uptake value ratio (SUVr) was calculated for multiple ROIs defined in native PET space using the AAL atlas warped onto the subject's baseline 3D T1 MRI (intersected with a gray matter probability map), normalized to a cerebellar gray matter region, truncated inferiorly. A global cortical average (GCA) SUVr was calculated using 5 cortical ROIs known to accumulate substantial fibrillar amyloid in AD. Changes from baseline SUVrs were determined, and differences between treatment groups were compared using a mixed model for repeated measures (MMRM). Analyses included 115 APOE ε4 carriers and 39 non-carriers.

Results: In APOE ε4 carriers, a statistically significant treatment difference in fibrillar brain amyloid burden (GCA SUVr) at Week 71 was observed for bapineuzumab as compared to placebo (-0.101, p=0.004). In non-carriers, no difference was seen for the pooled dose levels (0.021, p=0.724). Pooling all bapineuzumab doses across studies revealed a difference between bapineuzumab and placebo treatment (-0.076, p=0.010).

Discussion: These studies confirmed the bapineuzumab-associated reduction of amyloid accumulation observed in phase 2. Analyses in mild vs moderate AD subpopulations will also be presented.

Keywords: *anti-amyloid therapy, bapineuzumab, clinical trial*

Presented by: Liu, Enchi

Session 8: Amyloid Imaging and Clinical Utility

CHAIRS:

Christopher Rowe, MD, ***Austin Health***

Agneta Nordberg, MD, ***Karolinska Institute***

Amyloid Imaging May Alter Diagnostic Thinking and Intended Management of Patients with Progressive Cognitive Decline

Andrew Siderowf [1], Michael Pontecorvo [1], Stephen Salloway [2], P. Murali Doraiswamy [3], Adam Fleisher [4], Carl Sadowsky [5], Anil Nair [6], Ming Lu [1], Anupa Arora [1], Daniel Skovronsky [1], Mark Mintun [1], Michael Grundman [7]

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[7] *Global R& D Partners*

Background: Florbetapir F18 is a PET imaging agent that estimates the burden of amyloid neuritic plaque pathology.

Objective: To determine whether amyloid imaging could influence the diagnosis and management of patients undergoing evaluation for cognitive decline.

Methods: 229 patients with progressive cognitive decline and an uncertain diagnosis were recruited to 19 clinical sites. The site physician provided a provisional diagnosis, an estimate of his/her diagnostic confidence, and a plan for diagnostic evaluation and management both before and immediately following receipt of the florbetapir F18 PET results.

Results: Visual interpretation of florbetapir F18 PET scans classified 49.3% (113/229) of subjects as amyloid positive and 50.7% (116/229) as amyloid negative. Sixty two percent (53/86) of subjects with a clinical diagnosis attributable to AD prior to the scan were amyloid positive and a similar percentage (57%; 12/21) with a non-AD diagnosis pre-scan was also amyloid positive. By contrast, only 39% (48/122) of subjects with a purely syndromic diagnosis (e.g. MCI/ dementia of unclear etiology) pre-scan were amyloid positive. After receiving florbetapir PET scan results, physicians changed their diagnosis in 54.6% (125/229) of cases. Diagnostic confidence increased by an average of 21.6%. 86.9% (199/229) of cases had at least one change in their management plan. Intended cholinesterase inhibitor or memantine treatment increased by 17.7% among amyloid positive cases and decreased by 23.3% among those with negative scans. In subjects who had not yet completed a work up at study entry, planned brain structural imaging (CTs/MRIs) decreased by 24.4% and planned neuropsychological testing decreased by 32.8%.

Conclusions: In this study, evaluation with florbetapir F18 PET altered physician diagnostic thinking, and intended testing and management plans in patients undergoing evaluation for cognitive decline. While limited in that the study could not follow actual treatment changes, the data indicates that amyloid imaging shows potential to meaningfully impact how physicians workup and treat their cognitively impaired patients.

Keywords: *impact on management; clinical diagnosis; clinical trial;*

Presented by: Siderowf, Andrew

Molecular Biomarkers in Clinical Practice: the Practical Utility of Amyloid and FDG PET in an Academic Dementia Center

Pascual Sánchez-Juan [1], Pia Ghosh [2], Jayne Hagen [2], Benno Gesierich [2], Maya Henry [2], Marilu Gorno-Tempini [2], Bruce L Miller [2], William J Jagust [3], Gil D Rabinovici [3]

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[2] Memory and Aging Center and Department of Neurology, University of California San Francisco
[3] Memory and Aging Center and Department of Neurology, University of California San Francisco; Helen Wills Neuroscience Institute, University of California Berkeley; Lawrence Berkeley National Laboratory.

Background/Aims: We evaluated the impact of amyloid and FDG PET on clinical decision making in a heterogeneous population of cognitively impaired patients.

Methods*:* We identified 138 patients (42.0%females; mean age 64.3±10.8; 45.7% diagnosed pre-scan with an Aβ syndrome) seen at UCSF who were studied with FDG and PIB PET and had at least one post-scan visit (median between visits=8.4 months). PIB and FDG scans were read blinded to clinical data and results were released to the clinician simultaneously. Changes to the primary diagnosis and treatment plan from pre – to post-scan visit were evaluated. To test factors that predicted change in diagnosis and treatment, we performed logistic regression that included PIB and FDG concordance with clinical diagnosis, age at PET and baseline diagnosis as predictors.

Results: PIB and FDG PET agreed in classifying 84.1% of patients. Concordance with pre-scan diagnosis was 87.9% for PIB and 77.9% for FDG. The primary diagnosis was changed after PET in 13/138 patients (9.4%): 12/13 changes were concordant with PIB and 8/13 with FDG results. In the univariate analysis, both discordant PIB ($p<0.0001$) and discordant FDG results ($p<0.01$) were associated with a change in diagnosis. However, logistic regression revealed that changes in diagnosis were independently associated with discordant PIB (OR=9.1, 95%CI 2.1-40.5; p=0.004) but not discordant FDG (p=0.12). 35% of patients had a change in AD symptomatic therapy post-PET (initiating or discontinuing acetycholinesterase inhibitors or memantine). Logistic regression revealed that changes in treatment were not associated with discordant PIB (p=0.14) or FDG results (p=0.85).

***Discussion*:** When obtained simultaneously, amyloid PET results were independently associated with changes in clinical diagnosis while FDG results were not. Neither scan impacted treatment.

Keywords: *PIB, FDG, clinical impact, treatment*

Presented by: Rabinovici, Gil D

HAI Program Abstracts

Poster Presentations

EFFECT OF BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF) VAL66MET POLYMORPHISM ON AMYLOID LOAD IN COGNITIVELY INTACT OLDER ADULT APOE E4 CARRIERS

Katarzyna Adamczuk [1], An-Sofie De Weer [1], Kewei Chen [2], Natalie Nelissen [1], Kristel Sleegers [3], Karolien Bettens [3], Christine Van Broeckhoven [3], Mathieu Vandenbulcke [4], Koen Van Laere [5], Eric M.Rik Reiman [6], Rik Vandenberghe [7]

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Background: Besides APOE, genetic determinants of amyloid load in cognitively intact individuals are relatively poorly understood. BDNF is a potent modulator of neural plasticity, a process that has been implicated in the pathogenesis of Alzheimer's disease (AD).

Research question: Does the BDNF val66met polymorphism influence amyloid deposition in cognitively normal older adults and how does this interact with APOE genotype?

Methods: The main cohort of 64 community-recruited healthy older adults (mean age=66, S.D.=5.1, range 53-74), scanned at the Alzheimer's Disease Centre KULeuven, were stratified according to a factorial design with APOE (e4 allele present vs absent) and BDNF (codon 66 met allele present vs absent) as factors. Subjects received an 18F-flutemetamol (investigational amyloid imaging agent) PET, volumetric MRI, and neuropsychological evaluation. Cerebral-to-cerebellar standardized uptake value ratios (SUVR) were calculated. SUVR images were compared using SPM, with APOE and BDNF as factors. The independent replication dataset was based on existing data from a cohort of 33 APOE e4 carriers who had been scanned using 11C-PIB at the Banner Alzheimer's Institute.

Results: The main effect of APOE was significant and was localized to posterior cingulate and precuneus (cluster-level corr. $P<0.05$). There was no main effect of BDNF. The interaction, however, between APOE and BDNF was significant: APOE e4 positive/BDNF met positive carriers had significantly higher SUVR than APOE e4 positive/BDNF met negative carriers and this effect was not seen in the APOE e4 non-carriers. This interaction effect was localized to orbitofrontal, posterior cingulate, and medial prefrontal cortex (cluster-level corr. $P<0.05$). The increase in SUVR in BDNF met carriers versus non-carriers was confirmed in the replication dataset in the orbitofrontal VOI (voxel-level corr. $P=0.028$).

Conclusions: BDNF polymorphism contributes to amyloid ligand retention in cognitively normal older adult APOE e4 carriers. Our findings establish a potential link between neural plasticity and AD pathogenesis.

Keywords: *BDNF, APOE, amyloid PET, Alzheimer, flutemetamol*

Presented by: Adamczuk, Katarzyna

Poster 1

USING THE CENTILOID SCALE TO QUANTIFY THE CHARACTERISTICS OF TRACERS, EFFECTS OF SMOOTHING, REFERENCE REGION AND ATROPHY ON CONFIDENCE INTERVALS

Suzanne Baker [1], Susan Landau [2], William Jagust [2]

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Purpose: The goal of this study was to use the Centiloid scale to determine how atrophy, smoothing and choice of reference region affect the confidence that two SUVR values reflect different amounts of amyloid uptake. Our approach used modeling for PIB, Florbetapir and fantasy tracers.

Methods: Using 326 Freesurfer-segmented MRIs of older adults from ADNI, we modeled amyloid scans by iteratively assigning uptake values to a composite cortical region (CCR), cerebellar white and hemispheric white (cerebellar gray(CereG)=non-composite gray=1). We smoothed the data by 5-8mm^3 and calculated post-smoothed SUVRs in CCR normalized by CereG or whole cerebellum. Multiple pre-smoothed values can result in a single smoothed value given white matter uptake and atrophy variation (figure 1a). These corresponding pre-smoothed values are normally distributed (figure 1b). An 80% Confidence interval is applied to smoothed values of 1.5 and 1.65, leaving 20% overlap between the two histograms. For centiloid=20, the Lack Of Confidence Interval (LOCI) would be 14-26. Another scan, with a centiloid value < 14 or > 26 is 80% likely to reflect an actual difference in binding.

Results: Table1 shows the effect of smoothing, white matter, reference region and atrophy on the LOCI for PIB and Florbetapir for low (20 centiloids), medium (50), and high (80) amounts of amyloid. Smoothing had minimal effect on LOCI. Increased white matter standard deviation (SD) resulted in moderate effects on LOCI depending on reference region. Atrophy variability within subject pool had huge effects on LOCI.

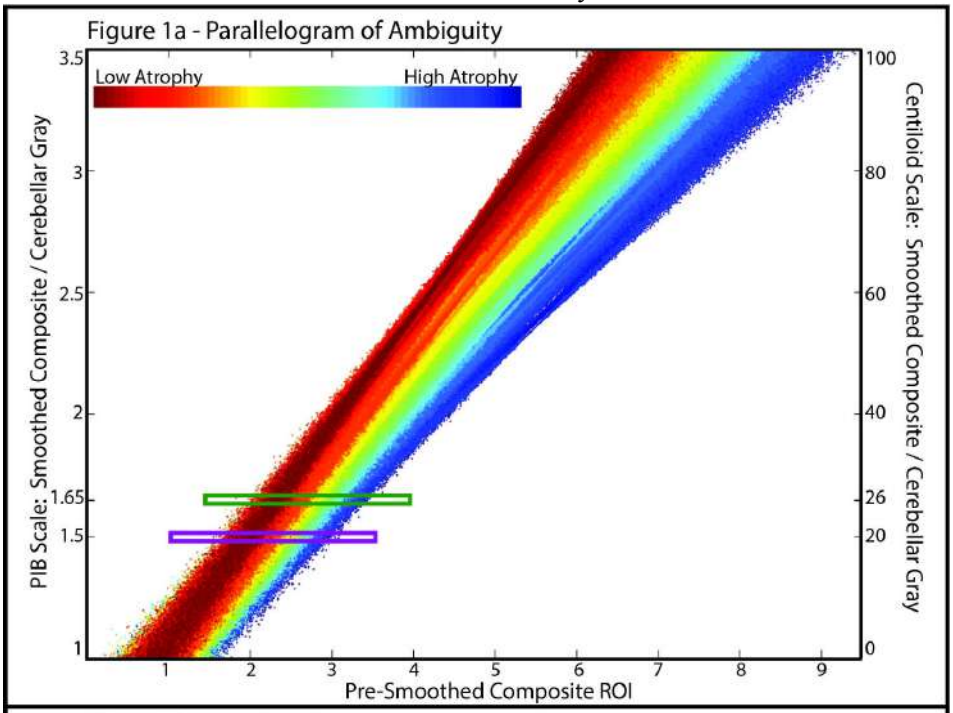

Figure 1a is an example of pre-smoothed composite vs. smoothed composite/cerebellar gray. The color of each dot corresponds to the degree of atrophy of the composite region from that MRI. The purple box corresponds to PIB=1.5 or Centiloid=20. The green box corresponds to PIB=1.65 or Centiloid=26. Figure 1b is the presmoothed distributions for Centiloid=20 and Centiloid=26 which show 20% overlap.

Table1 – PIB and Florbetapir – Lack of Confidence Interval

PIB Florbetapir	Normalized By Cerebellar Gray			Normalized By Whole Cerebellum		
	20	50	80	20	50	80
Smoothing 5mm³	15-26 12-28	42-59 40-61	70-91 68-93	15-26 14-27	41-60 40-62	67-95 66-96
Smoothing 8mm³	15-26 12-29	41-60 39-62	68-93 67-95	15-26 13-28	41-61 39-63	66-96 65-97
Smoothing Result	**1.10x** 1.08x	**1.13x** 1.11x	**1.14x** 1.13x	**1.12x** 1.11x	**1.08x** 1.08x	**1.06x** 1.06x
White SD 0.01	15-26 13-28	42-60 40-61	68-93 67-95	15-26 13-28	41-60 39-62	68-94 66-96
White SD 0.31	15-26 12-29	41-60 39-62	68-93 67-95	15-26 13-28	40-61 39-63	66-96 65-97
White SD 0.61	14-27 8-32	41-60 37-63	68-93 66-95	15-26 14-28	39-64 38-64	63-100 63-100
White SD Result	**1.26x** 1.65x	**1.07x** 1.23x	**0.99x** 1.01x	**1.00x** 0.94x	**1.32x** 1.15x	**1.46x** 1.25x
Atrophy 0 n=1	18-22 15-25	48-52 46-53	79-81 78-82	19-21 19-21	46-54 47-54	74-87 75-86
Atrophy 1 n=133	16-24 13-27	45-55 43-57	74-86 73-87	17-23 15-25	44-57 43-58	71-90 71-90
Atrophy 2 n=315	15-26 12-29	41-60 39-62	68-93 67-95	15-26 13-28	40-61 39-63	66-96 65-97
Atrophy Result	**2.49x** 1.69x	**5.64x** 3.30x	**13.61x** 7.97x	**4.63x** 6.39x	**2.60x** 3.48x	**2.23x** 2.86x

Table1 – Smoothing, White SD and Atrophy Results are the ratio of (LOCI range1)/(LOCI range2) within tracer and within reference region. Smoothing results compare LOCI range between 5mm³ and 8mm³. White SD results compare LOCI range between 0.01 and 0.61SD. Atrophy0 used 1 subject's MRI for the model with a mean amount of atrophy. Atrophy1 used MRIs within ±0.5SD of the mean atrophy. Atrophy2 used MRIs within 2SD of the mean atrophy. Atrophy results compare Atrophy0 and Atrophy2.

Table2 shows the results fromconcocting fantasy tracers by varying the range and starting value of post-smoothed amyloid before Centiloid conversion. The LOCI exponentially decreases with increasing dynamic range.

Table2 – Fantasy Tracer – Lack Of Confidence Interval

Fantasy	Normalized By Cerebellar Gray			Normalized By WholeCerebellum		
	20	50	80	20	50	80
Range 1-2	8-33	36-65	64-98	10-31	37-65	63-99
Range 1-3.5	15-26	41-60	68-93	15-26	40-61	66-96
Range 1-5	16-25	42-59	69-93	16-25	41-60	67-96
Range Result	**0.34x**	**0.56x**	**0.70x**	**0.45x**	**0.68x**	**0.82x**

Table2 – Range Result is a comparison of LOCI (Range1-2)/(Range1-5).

Conclusions: The Centiloid scale permits comparison of different tracers and reference regions. In this comparison, atrophy variability causes the greatest amount of uncertainty and increased tracer dynamic range minimizes uncertainty.

Keywords: *Methods, Centiloid, PIB, Florbetapir, Modeling*

Presented by: Baker, Suzanne

Poster 2

AMYLOID PET FOR ENROLLMENT INTO AD CLINICAL TRIALS: INITIAL EXPERIENCE AND POTENTIAL PITFALLS

Jerome Barakos [1], Derk Purcell [1], Gregory Klein [2], Joyce Suhy [2], Joonmi Oh [2], Ping-Chun Chiao [3], Jeff Sevigny [3]

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Objectives: A number of fluorinated amyloid tracers have been developed for use in the assessment of brain amyloid burden. As such, the use of amyloid PET scans is becoming a routine aspect of AD clinical trial enrichment, especially as earlier phases of the disease state are being studied. We report our initial experience in performing central readings for prodromal or mild Alzheimer's disease study enrollment.
Methods: Scans were interpreted by two trained neuroradiologists. Although the use of a binary reading paradigm has the potential of simplifying scan interpretation, a series of technical factors may lead to false interpretation. In this presentation we discuss various pitfalls which may lead to false positive and false negative interpretations. Strategies to mitigate the effects of these pitfalls are also outlined.
Results: Hypothetical pitfalls were grouped into several categories; including issues relating to window and leveling, partial voluming and co-registration. Window and leveling factors had the greatest potential for false positive interpretations. Partial voluming effects had the potential of generating false positive interpretations. Use of co-registered images were of greatest value in preventing false negative readings in cases with prominent cerebral sulci. In the future, quantitative image analysis with automated comparison to normative data sets and calculated z-scores may serve to supplement visual readings.
Conclusions: In summary, we report our initial experience with amyloid PET imaging as part of a phase Ib clinical trial enrichment strategy and outline various technical factors which should be optimized to ensure accurate amyloid PET interpretations.

Keywords: *Amyloid PET imaging, AD trials*

Presented by: Barakos, Jerome

Poster 3

DIFFERENTIAL RELATIONSHIPS OF AMYLOID BURDEN AND MEMORY RETRIEVAL FORMATS ACROSS THE ADULT LIFESPAN.

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Episodic memory is especially vulnerable to the effects of aging. Episodic memory performance has also been linked to beta amyloid (AB) pathology even in cognitively normal adults. Additionally, extensive research has shown that different types of memory retrieval (i.e., recall and recognition) are differentially affected by age. Specifically, recall memory tasks are more sensitive to age-related degradation of memory performance, whereas recognition tasks are less sensitive to memory performance because the benefits of contextual information provided at retrieval. We therefore examined the effect of mean cortical AB deposition on these two memory retrieval types in a large sample of healthy adults aged 30-89 (N=147, $Mean_{Age}$=63.37, $Mean_{MMSE}$=29.27).

Participants underwent PET imaging with F-18 Florbetapir which binds to fibrillar AB. Mean cortical AB SUVR was computed by extracting counts across 8 cortical regions of interest, normalized to cerebellar gray matter. Additionally, we computed standardized memory constructs for three tests of recall and recognition memory taken from the Hopkins Verbal Learning Task and from a Verbal Recognition Memory task.

We found differential age-related effects of mean cortical amyloid on recall and recognition performance. Specifically, younger adults (30-49) showed significant effects of amyloid on both recall and recognition performance, whereas this relationship was absent in adults 50-69. Adults, older than 80 showed significant association of amyloid selectively on recall performance.

These results suggest that the range of AB deposition in younger adults has important implication in explaining episodic memory differences. Furthermore, higher AB deposition as observed with advanced aging is associated with memory decrements. The vulnerability of episodic memory to the effects of aging might be partly due to age-specific AB deposition. Taken together these results support the idea of an early onset of the amyloid cascade with relationships to episodic memory.

Supported in part by the NIA, R-37-AG06265, IIRG-09-135-087. Avid Radiopharmaceuticals provided the radiotracer for this project.

Keywords: *adult lifespan, amyloid burden, memory retrieval formats,*

Presented by: Bischof, Gerard

Poster 4

A NOVEL RADIOTRACER FOR IN VITRO AND IN VIVO VISUALIZATION OF BACE1 DISTRIBUTION IN THE RODENT AND BABOON BRAIN

Michael Honer [1], Luca Gobbi [1], Alessandra Polara [1], Hiroto Kuwabara [2], Helmut Jacobsen [1], Thomas Hartung [1], Hansruedi Loetscher [1], Daria Esterhazy [3], Markus Stoffel [3], Robert Dannals [2], Dean Wong [2], Edilio Borroni [1]

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Background: The beta-site amyloid precursor protein cleaving enzyme (BACE1) is responsible for initiating generation of beta-amyloid, the major constituent of amyloid plaques in Alzheimer's disease (AD). Thus, BACE1 is a prime target for the therapeutic inhibition of beta-amyloid production in AD. In the absence of suitable radioligands for BACE1, our aim was to develop a tracer for *in vitro* and *in vivo* visualization of BACE1 brain distribution.

Methods: A potent BACE1 inhibitor was tritiated and its affinity and specificity for BACE1 was evaluated using rat brain membranes and sections from wild and BACE1 knockout animals. BACE1 protein distribution was visualized by *in vitro* autoradiography using brain sections from mouse, rat, monkey and human brain. *In vivo* uptake and distribution of the radioligand was studied by *ex vivo*autoradiographical analysis in rats and *in vivo* PET imaging of baboons after injection of the [^{11}C]-labeled radiotracer.

Results: Saturation analysis revealed high-affinity binding (KD = 4 nM) and a low binding site density in rat brain. Specificity of radioligand binding for BACE1 was confirmed by the absence of binding in brain sections of BACE1 knockout animals. A ubiquitous distribution of radioligand binding was found in rodent brain slices with higher binding in the CA1 and CA3 pyramidal cell layers and the granule cell layer of the hippocampus. Autoradiographical experiments in monkey and human hippocampus suggested relatively high BACE1 expression in the cell bodies of the dentate gyrus. The radiotracer revealed good penetration in the rat and baboon brain and an *in vivo* binding pattern comparable with that observed *in vitro*.

Conclusions: This study provides the first visualization of the distribution pattern of the BACE1 protein in the rodent and baboon brain. The consistent *in vivo* binding pattern of this radioligand warrant further development as a PET radiotracer for occupancy studies for BACE1 drug candidates.

Keywords: *Positron Emission Tomography (PET), Alzheimer's disease, Hippocampus*

Presented by: Borroni, Edilio

Poster 5

[11C]PIB, [18F]FDG AND MR IMAGING IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

Anna Brück [1], Jere Virta [1], Jaana Koivunen [1], Juha Koikkalainen [2], Noora Scheinin [1], Hans Helenius [3], Kjell Någren [4], Semi Helin[5], Riitta Parkkola [6], Matti Viitanen [7], Juha Rinne [1]

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[5] *Radiopharmaceutical Chemistry Laboratory, Turku PET Centre, University of Turku, Turku, Finland*
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Cortical glucose metabolism, brain amyloid ß accumulation and hippocampal atrophy imaging have all been suggested as potential biomarkers in predicting which patients with mild cognitive impairment (MCI) will convert to Alzheimer's disease (AD). We previously reported a follow-up study on [^{11}C]PIB uptake and hippocampal atrophy changes in patients with MCI. A subsample of these subjects also underwent [^{18}F]FDG PET imaging enabling the comparison of these three imaging methods in predicting the conversion to AD in the same MCI patient population.

29 patients with MCI (age mean±SD, 71.7±7.5 years, 18 males and 11 females, MMSE mean±SD 26.9±1.8) underwent [^{11}C]PIB PET and MR imaging for volumetric analysis of the hippocampi. Twenty-two of them also underwent [^{18}F]FDG PET. All subjects were invited back for clinical evaluation after two years.

During the follow-up 17 patients had converted to AD while 12 continued to meet the criteria of MCI. The two groups did not differ in age, gender or education level ($p>0.05$) but the converter group tended to have lower baseline MMSE and Word List learning than the nonconverter group ($p<0.05$). High [^{11}C]PIB retention in frontotemporal regions and anterior and posterior cingulate predicted conversion to AD ($p<0.05$). Also reduced [^{18}F]FDG uptake in the left lateral temporal cortex (LTC) predicted conversion ($p<0.05$) but quantitative hippocampal volumes did not ($p>0.1$). In receiver operating characteristic (ROC) analysis the measurements that best predicted the conversion were [^{11}C]PIB retention in the lateral frontal cortex and [^{18}F]FDG uptake in the left LTC. Both PET methods resulted in good sensitivity and specificity and neither was significantly superior to the other. Seven out of 8 subjects with both abnormal [^{11}C]PIB and [^{18}F]FDG uptake converted to AD during the follow-up time. The findings indicate that [^{11}C]PIB and [^{18}F]FDG are superior to hippocampal volumes in predicting conversion to AD in patients with MCI

Keywords: *[11C]PIB, [18F]FDG, MRI, MCI*

Presented by: Brück, Anna

Poster 6

CONSISTENCY OF REGIONAL AMYLOID-B DEPOSITION ASMEASURED BY PATHOLOGY AT AUTOPSY AND RELATED STRATEGIES FOR VISUAL READING OF [18F] FLUTEMETAMOL

Chris Buckley, Adrian Smith, Kerstin Heurling, Paul Sherwin

GE Healthcare

GE Healthcare's end of life study provided data where by the regional variability/consistency of pathology could be determined and this compared to regional PET assessments. The regional pathological concordance with the overall positive pathology is presented in the table below. 68 brains were evaluated in which 43 had one or more abnormal areas in which the neuritic plaque evaluation by Bielschowsky staining exceeded a threshold equivalent to moderate/frequent plaque density. The inferior parietal region had the greatest consistency of positivity when any of the other 8 regions is positive.

Region	Number SOT Positive (of 43)	% Positive Abnormal cases
Precuneus	32	74%
Anterior cingulate	33	77%
Mid frontal	35	81%
Primary visual cortex	35	81%
Superior temporal	35	81%
Posterior cingulate	36	84%
Mid temporal	37	86%
Inferior parietal	39	91%

The findings have implications for the refinement of visual read methodology for [^{18}F]flutemetamol. Visually assessing regions as abnormal or positive for amyloid-b is reliant on observing either the disappearance of the sulcal/gyral white matter pattern and/or observing elevated signal in the cortical grey matter ribbon. The main confounding factor in making a normal or abnormal classification is focal atrophy, generally leading to a misclassification of an area as negative and is variable for each region. The inferior parietal regions is shown to be a highly consistent region for abnormal pathology and it also reliable in PET visual assessment in that atrophy to this region is less confounding to assessment compared to the superior parietal region for example.

This presentation compares the susceptibility to confounding factors in visual reads to the pathology consistency. Recommendations are made on emphasis which may be given to particular regions in which PET images are equivocal in their visual interpretation.

Keywords: *Pathology, regional, visual read, consistency*

Presented by: Buckley, Chris

Poster 7

ASSOCIATION BETWEEN AMYLOIDOSIS AND NEURODEGENERATION MEASURED BY IMAGING BIOMARKERS AND CEREBROSPINAL FLUID

Laksanun Cheewakriengkrai, Jared Rowley, Sara Mohades, Marina Tedeschi Dauar, Monica Shin, Seqian Wang, Antoine Leuzy, Thomas Beaudry, Vladimir Fonov, Simon Fristed, Serge Gauthier, Pedro Rosa-Neto

McGill Centre for Studies in Aging, McGill University

Introduction: We explored the association between amyloidosis and neurodegeneration in CSF and imaging biomarkers obtained in the same individuals. Similar to what was previously described for [^{11}C]PIB, we expected an exponential association between CSF AB_{1-42} and global [^{18}F]florbetapir retention.

Method: We analyzed cross-sectional data from participants enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with PET [^{11}C]PIB or [^{18}F]florbetapir and CSF analyses for Beta-amyloid peptide (AB), total tau and p-tau. Data from 253 subjects were analyzed [normal control (CN; N=54), early mild cognitive impairment (EMCI; N=128), late mild cognitive impairment (LMCI; N=40) and AD patients (AD; N=31)] with corresponding CSF, amyloid and [^{18}F]FDG measurements were included in this study. Voxel-based SUVR maps for [^{18}F]FDG and [^{18}F]florbetapir were calculated using the cerebellar cortex and the pons as a reference region, respectively. Global SUV was estimated as the median SUVR value obtained using masks encompassing fronto-temporo-parietal regions. Linear and non-linear regression analysis was conducted between CSF (AB_{1-42}, t-tau, p-tau, t-tau/AB_{1-42}) and imaging biomarkers ([^{11}C]PIB, [^{18}F]florbetapir and [^{18}F]FDG).

Results: The associations between CSF AB_{1-42} and global [^{18}F]florbetapir or global [^{11}C]PIB were better described by an exponential decay model (Figure 1). In addition, voxel-based exponential regression between CSF AB_{1-42} and [^{18}F]florbetapir or [^{11}C]PIB SUV revealed significant associations only in cortical areas associated with regions known to have high concentrations of fibrillary amyloid in AD ($t>4.5$). No associations between CSF AB_{1-42} and the present amyloid imaging agents were observed in the white matter regions. A significant voxel-based exponential fitting was observed between CSF p-tau and [^{11}C]PIB PET at the right temporal lobe. Significant regression between [^{18}F]FDG voxels and CSF biomarkers did not survive to multiple comparisons.

Discussion/Conclusion: In contrast with a good equivalence between CSF and imaging biomarkers of amyloid load, CSF biomarkers of neurodegeneration and [^{18}F]FDG PET provide complementary information regarding AD pathophysiology.

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Keywords: *[11C] PIB, [18F] Florbetapir, AB1-42, total- tau, p-tau*

Presented by: Cheewakriengkrai, Laksanun

Poster 8

INCREASING AMYLOID BURDEN WITH AGE IN INDIVIDUALS WITH DOWN SYNDROME

Bradley Christian [1], Todd Barnhart [2], Peter Bulova [3], Darlynne Devenny [3], Regina Hardison [3], Sigan Hartley [1], Ansel Hillmer [1], Sterling Johnson [2], William Klunk [3], Chester Mathis [3], Dhanabalan Murali [1], Julie Price [3], Marsha Seltzer [1], Dustin Wooten [1], Ben Handen [3]

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[3] *University of Pittsburgh*

Introduction: Adults with Down syndrome (DS) are at an extremely high risk for developing Alzheimer's disease (AD). In the age range of 50-59 years, approximately 36% of adults with DS will be diagnosed with AD. The DS population offers a unique opportunity to study non-demented individuals who have a very high risk of developing amyloid deposition and dementia. The overall goal of this work is to examine amyloid deposition in adults with Down syndrome to study its effect on cognitive and behavioral functioning over time.

Methods: A total of 54 individuals with DS and age ≥ 30 years (mean = 38 yrs: 32 – 46 yrs) underwent testing, 52 subjects were non-demented and 2 were diagnosed with AD. Amyloid deposition was measured with [C-11]PiB PET scans using 50-70 min SUVR (ratio to cerebellum). PiB(+) subjects were defined as regionally positive when exceeding the SUVR threshold defined by spares k-means clustering in any one of six ROIs or as globally PiB(+) by exceeding the SUVR threshold in the global cortical region.

Results: Twenty subjects were PiB(+), with older age being highly related to PiB(+) status. With individuals of age ≥ 40 years (n=23), 74% were PiB(+) and no subjects were PiB(+) of age <36 yrs. The resulting odds ratio for PiB(+) status of 1.36 (1.17,1.59 95% CI) per year. Significant age dependent increases in PiB deposition were seen in all regions with the greatest increases seen in the anterior ventral striatum ($R^2 = 0.45$).

Conclusions: A significant relation between age and amyloid deposition was found in adults with DS of age 32 -46 years, with a large fraction of subjects >40 yrs being PiB(+). Follow-up studies (30 months) are ongoing to track the changes in amyloid binding and cognitive function to deepen our understanding of AD pathophysiology in DS.

Keywords: *Down syndrome, amyloid, pib*

Presented by: Christian, Bradley

Poster 9

EFFECT OF COGNITIVELY AND PHYSICALLY STIMULATING ACTIVITIES ON PIB-PET

Ann Cohen [1], Beth Snitz [2], Oscar Lopez [2], Howard Aizenstein [1], Robert Nebes [1], Lisa Weissfeld [3], Judith Saxton [2], Julie Price [4], Chester Mathis [4], William Klunk [1]

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Postmortem studies have shown that brain amyloid-beta (Ab) plaques are present in 25-50% of cognitively normal elderly control subjects and recent Pittsburgh Compound-B (PiB) PET studies have shown similar findings in living cognitively normal elderly. PiB retention in some controls can be as high as that observed in Alzheimer's disease (AD). An overarching question from these findings is why, in the face of substantial amyloid burden, some people develop AD and others remain normal. To that end, enriched lifestyle and exercise have been reported to confer resistance to development of dementia but the effect on Ab remains unclear. The present study explored the effects of participation in cognitively stimulating activities or exercise on PiB retention in a group of cognitively normal adults

Sixty-three cognitively normal elderly controls (mean age: 83.3±6.6 years; mean education: 14.8±2.7 years) underwent PiB-PET and a series of lifestyle questionnaires where they were asked to report on participation in both physically and cognitively stimulating activities. Subjects were then split into high and low participation groups and PiB SUVR (50-70 min) was then analyzed on both an ROI and voxel-wise basis using SPM8.

ROI and voxel-wise analysis revealed that participation in highly stimulating cognitive activities was associated with significantly lower PiB retention in several cortical regions ($p<0.01$), including frontal, parietal and precuneus. Additionally, walking was also associated with significantly lower PiB retention in cortical regions ($p<0.01$), including parietal and lateral temporal cortices.

These data suggest that participation in both cognitively and physically stimulating activities is associated with reduced Ab in the cortical brain regions. It remains unclear, however, if participation in stimulating activities during late-life is sufficient to have an effect on Ab or if lifelong participation may be necessary.

Keywords: *Pittsburgh Compound B, Physical Activity, Cognitively Normal Control,*

Presented by: Cohen, Ann

Poster 10

RELATIONSHIP BETWEEN MRI-BASED SUBTYPES OF AD AND AMYLOID LOAD

Ranjan Duara [1], David Loewenstein [2], Qian Shen [2], Warren Barker [1], Maria Greig [1], Daniel Varon [1], Melissa Murray [3], Dennis Dickson [3]

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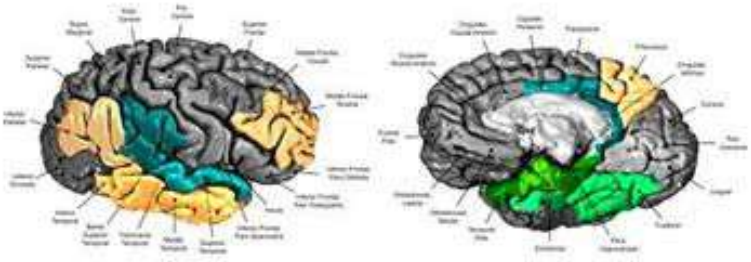
Background: Similar to recently described pathological subtypes of AD (Murray et al., 2011), MRI-based subtypes of AD and MCI in the ADNI cohort were identified, with distinguishable cognitive features, *APOE* e4 allele frequencies and rates of progression. The relationship of these subtypes to amyloid positive (Amy+) or negative (Amy -) status was assessed.

Methods: Elderly Normal (EN; n=91), amnestic MCI (n = 125) and AD (n=16), from the ADNI public database were classified as Amy+ or Amy-, on [F-18] AV-45 or [C-11] PiB PET scans and as MRI+ or MRI- on the basis of significant atrophy in any region. Factor analysis of regional brain volumes on MRI resulted in three atrophy patterns: Limbic, Neocortical 1 (*NeoC-1: precuneus, angular gyrus, middle/inferior temporal and middle frontal regions) and* NeoCortical 2 (NeoC-2: *transverse and superior temporal, insula, supramarginal gyrus and posterior cingulate).*

Results: Among ENs, 48.5% who were MRI+, and 31% who were MRI - were Amy+ (p =.09). AD and aMCI subjects were more frequently Amy+ than ENs ($p \leq .01$). Among MRI+ aMCI and AD subjects, 86% of those with NeoC-1, 64% with NeoC-2 and 71% with Limbic atrophy were Amy+, as compared to 64% of those who were MRI- (p=NS). Over a two year period, decline in memory scores was associated with Limbic atrophy at baseline (p<.001), regardless of Amy+ status; decline on Trails B scores was associated with NeoC-1 atrophy (p<.001), especially among Amy+ subjects (p<.02).

Conclusions: Amy+ status was associated with cognitive impairment; Amy+status tended to be associated with MRI+ status among ENs, but not among aMCI subjects. Among those with aMCI or AD, Amy+ status tended to be most frequent among those with NeoC-1 atrophy. Longitudinally, decline in memory measures was associated with having the Limbic MRI subtype, whereas decline in non-amnestic measures was associated with a combination Amy+ and NeoC-1 MRI subtype.

Figure 1. Patterns of regional brain atrophy



Limbic (LB) Pattern depicted in green includes the following regions: entorhinal cortex, parahypocampal gyrus, temporal pole, fusiform gyrus. Hippocampus and amigdala are part of this pattern of atrophy but are not seen in the figure.

Neocortical Type 1 (NC-1) Pattern depicted in yellow includes the following regions: inferior parietal, precuneus, middle and inferior temporal and rostral middle frontal.

Neocortical Type 2 (NC-2) Pattern depicted in blue includes the following regions: transverse temporal, superior temporal, insula, supramargiral gyrus and posterior/isthmus cingulate.

Cortical regions based on Desikan RS et al. Neuroimage 2006.

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Keywords: *ADNI, MRI, Amyloid*

Presented by: Duara, Ranjan

Poster 11

PRACTICE EFFECTS AND AMYLOID DEPOSITION: A METHOD FOR ENRICHING SAMPLES IN CLINICAL TRIALS

Kevin Duff, Norman Foster, John Hoffman
University of Utah

Background: Clinical trials in Alzheimer's disease are moving towards prevention studies in asymptomatic individuals with evidence of amyloid burden. However, we need methods to better identify individuals who are likely to be amyloid positive for these studies to be more feasible and cost effective.

Methods: The current study examined practice effects across one week on a visual memory test as a means to identify those with amyloid burden on neuroimaging with ^{18}F-flutemetamol PET imaging in 22 non-demented older adults.

Results: Whereas ^{18}F-flutemetamol uptake showed little association with baseline performance on a visual memory test (r=-0.04, p=0.86), it was significantly correlated with practice effects over one week on that same memory measure (r=-0.52, p=0.01), with greater amyloid burden being associated with lower practice effects. The odds ratio of having a positive amyloid scan was 16 times higher if the individual had low practice effects compared to high practice effects. The operating characteristics between practice effects and amyloid burden were relatively good (e.g., sensitivity = 0.71, specificity = 0.87, positive predictive power = 0.71, negative predictive power = 0.87).

Conclusions: One week practice effects on a visual memory test provide an affordable screening method to identify individuals who are amyloid positive and enrich samples for clinical trials designed to prevent Alzheimer's disease dementia.

Keywords: *amyloid, flutemetamol, practice effects, elderly, cognition, clinical trials*

Presented by: Duff, Kevin

Poster 12

CONSORTIUM TO DEVELOP AN ALPHA-SYNUCLEIN IMAGING AGENT

Andrew Medhurst [1], Kevin Nash [1], Andrew Gill [1], Scott Pollack [1], David Cronk [1], Brian Bacskai [2], Robert Mach [3], Jamie Eberling [4], Chester Mathis [5]

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[2] *Massachusetts General Hospital*
[3] *Washington University*
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[5] *University of Pittsburgh*

The Michael J. Fox Foundation (MJFF) is supporting a consortium with the goal of developing a PET radiotracer to image the distribution of alpha-synuclein in the brain. The accumulation of aggregated alpha-synuclein in the brain is the pathological hallmark of Parkinson's disease and dementia with Lewy bodies (DLB) and is a frequent target for therapeutic development. The ability to visualize alpha-synuclein in the brain could be useful both as a biomarker of the presence of disease and disease progression and as a tool for drug development.

Two approaches were pursued to identify compounds that bind to aggregated alpha-synuclein. The first approach utilized a competition binding assay using either the fluorescent ligand Thioflavin T or the radioligand [3H]-Chrysamine G. Following assay optimization, approximately 100,000 compounds selected from the BioFocus libraries were screened in both assay formats at a single concentration of 10 micromolar. From the Thioflavin T screen, approximately 2,000 compounds showing >45% inhibition of binding were selected for hit confirmation at 10 micromolar in duplicate, and 263 of these compounds proceeded to IC50 potency determination. Selectivity of these compounds was determined against aggregated beta-amyloid and tau using Thioflavin T and Thioflavin S assays respectively. The second approach utilized a Surface Plasmon Resonance (SPR) based Biacore assay developed to investigate the direct binding of compounds to monomeric alpha-synuclein, aggregated alpha-synuclein and aggregated beta-amyloid, immobilized to Biacore CM5 chips via amine coupling reactions. Following the screening of approximately 3,500 compounds against these three protein targets, 120 compounds were selected for KD determination.

Further characterization of interesting compounds identified from these approaches is ongoing, including binding studies in PD brains with Lewy body pathology.

Keywords: *alpha-synuclein, Lewy body, DLB, Parkinson's*

Presented by: Eberling, Jamie

Poster 13

VOXEL-BY-VOXEL CORRELATION BETWEEN AMYLOID LOAD AND MICROGLIAL ACTIVATION IN AD AND MCI SUBJECTS.

Paul Edison [1], Fan Zhen [1], David Brooks

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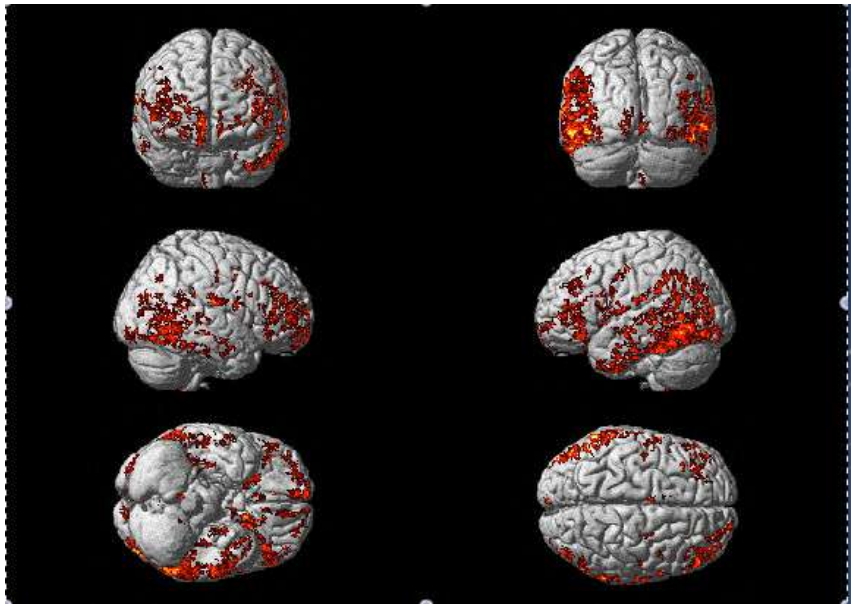
Background: Over 90% of probable Alzheimer's disease (AD) and 60% of amnestic MCI subjects have a significant brain amyloid load. Microglial activation is also present in these subjects. [11C]PIB PET is a marker of amyloid deposition, while [11C](R)PK11195 PET detects microglial activation.

Aim: The aims of this study were: 1) To investigate the correlation between amyloid load measured by [11C]PIB PET and microglial activation measured by [11C](R)PK11195 PET in AD and MCI subjects. 2) To evaluate at a voxel level the regional relationship between microglial activation and amyloid deposition in AD and MCI subjects.

Methods: A group of 10 AD, 11 MCI and 10 control subjects underwent T1 and T2 MRI, [11C]PIB and [11C](R)PK11195 PET scanning. Parametric images of [11C]PIB and [11C](R)PK11195 binding potential (BP) were interrogated using Region of Interest (ROI), Statistical Parametric Mapping (SPM) analysis, and voxel-voxel analysis using biological parametric mapping.

Results: 1) All AD cases revealed significant increases in [11C]PIB and [11C](R)PK11195 binding. Less pronounced increases in an AD-like pattern were found in MCI subjects. Microglial activation was seen in the absence of amyloid deposition in MCI subjects. 2) Individually, there was a positive correlation between amyloid load and microglial activation in 4 AD and 2 MCI subjects using ROI analysis. 3) Voxel-based correlation analysis revealed a positive correlation between [11C]PIB and [11C](R)PK11195 uptake in temporal lobe, frontal lobe and parietal lobe in AD, while MCI cases showed a significant correlation in the temporal lobe.



Conclusion: This study demonstrated for the first time that cortical microglial activation and amyloid deposition are correlated at voxel level in AD, supporting the amyloid cascade hypothesis. However, the presence of cortical microglial activation in MCI without amyloid deposition suggests that other neuropathological substrates can also trigger inflammation. Hence therapeutic intervention targeting microglia may act on different pathological substrates in dementia.

Keywords: *Amyloid, microglia, AD, MCI*

Presented by: Edison, Paul

Poster 14

3D EX VIVO AMYLOID IMAGING AND THE RELATIONSHIP WITH IN VIVO MRI-DERIVED MEASURES OF CORTICAL THICKNESS IN AN ALZHEIMER'S DISEASE MOUSE MODEL

Marilyn Grand'Maison [1], Simone Zehntner [2], Ming-Kai Ho [1], Francois Hebert [2], Andrew Wood [2], Felix Carbonell [2], Alex Zijdenbos [2], Barry Bedell [3]

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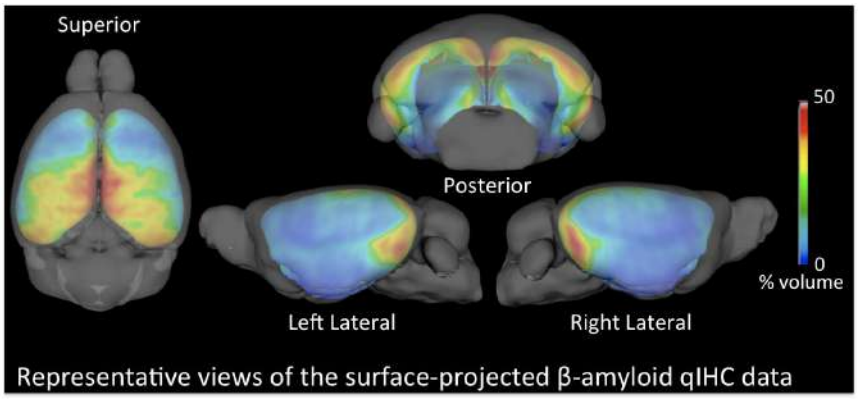
Background: The advent of human amyloid imaging has afforded the opportunity to study the association between beta-amyloid and brain morphometry in Alzheimer's disease (AD). However, the alterations in cortical structure at the pre-plaque stage have been largely unexplored. In this study, we sought to interrogate the relationship between early changes in cortical thickness and late-stage beta-amyloid deposition using a mouse model overexpressing mutant human amyloid precursor protein (APP). Ideally, this multi-parametric assessment could be performed via co-registration of non-invasive mouse brain MRI and amyloid PET images. However, while amyloid PET in mice has been reported, the relatively poor spatial resolution of animal PET scanners precludes accurate regional measures of β-amyloid burden in the mouse cerebral cortex. To this end, we employed a novel method to generate 3D *ex vivo* "amyloid images" and co-register these image volumes with *in vivo* structural MRI data.

Methods: Longitudinal, anatomical MRI scans were acquired from transgenic APP and age-matched wild-type mice at 1 and 3.5 months-of-age on a 7T animal MRI system. MR images were processed using a fully-automated pipeline to generate cortical thickness measures. Formalin-fixed, paraffin-embedded brains from 18 month-old mice were serially-sectioned from olfactory bulb through brainstem. The sections underwent immunohistochemistry (IHC) staining with 4G8 anti-amyloid monoclonal antibody and were counterstained with Acid Blue 129. The IHC sections were digitized using an automated, ultra-high-resolution slide scanner. The digitized tissue sections were then reconstructed into 3D "beta-amyloid image volumes", spatially normalized to the MRI data, and projected onto a standardized cortical surface (PERMITS™, Biospective Inc.). The group-average surface-projected amyloid maps are shown in the *Figure*.



Results/Conclusions: Aberrant changes in regional MRI cortical thickness measures in **young** mice showed a strong correlation with **late** beta-amyloid deposition. A distinct spatio-temporal pattern of early alterations in cerebral cortical structure was predictive of regional predisposition to beta-amyloid pathology.

Keywords: *MRI, cortical thickness, amyloid, APP mouse model, qIHC*

Presented by: Grand'Maison, Marilyn

Poster 15

COMPARISON OF [18F] FLUTEMETAMOL AMYLOID-BETA IMAGING WITH [11C] PIB ACROSS THE SPECTRUM OF ALZHEIMER'S DISEASE

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The aim is to identify the beta amyloid (Aβ) deposition by [18F]-Flutemetamol (FMM) PET across spectrum of Alzheimer's disease (AD), and clarify association in Aβ between [18F]-FMM and [11C]-PIB PET imaging.

Method: Twenty-two patients with AD, 40 with mild cognitive impairment (MCI) and 24 subjects with healthy control (HC) were studied. All patients underwent 30-min static [18F]-FMM PET, acquired 85 min after injection (196.1 ± 6.9 MBq), and 60-min dynamic [11C]-PIB PET. [18F]-FMM scans were assessed visually by 3 blinded readers as abnormal or normal cortical uptake, and the standardized uptake value ratios (SUVR) were defined quantitatively in regions of interest defined on co-registered MRI (cerebellar gray as a reference region). The PIB distribution volume ratios (DVR) were determined in same cortical regions.

Result: The visual assessments of [18F]-FMM PET had a typical increased uptake in 19 of 22 scans with AD and 2 of 24 scans with HC while a mild uptake in 2 scans with AD, corresponding to an overall sensitivity of 90.1% and a specificity of 91.6%. These findings were same to [11C]-PIB scans. The [18F]-FMM SUVR in whole cortical regions in AD was significantly greater than in HC (1.85 ± 0.25 vs 1.24 ± 0.09, $P<0.01$). MCI patients had a bimodal distribution of SUVR. The SUVR in 10 patients with [18F]-FMM positive MCI and 30 patients with negative MCI were 1.89 ± 0.27 and 1.21 ± 0.10, respectively. The [18F]-FMM SUVR values in all individual subjects were strongly correlated with [11C] PIB DVR values ($r=0.94$, $n=86$, $p<0.001$).

Conclusion: [18F] amyloid tracer Flutemetamol has imaging properties very similar to [11C] PIB. PET imaging with [18F] Flutemetamol is a reliable biomarker of Aβ deposition along continuum from normal cognitive status to dementia of AD.

Research Support: *This study was partly supported by GE Healthcare (UK).*

Keywords: *Amyloid PET, [18F]-Flutemetamol, [11C]-PIB, Alzheimer's disease*

Presented by: Hatashita, Shizuo

Poster 16

11C-PITTSBURGH COMPOUND B PET IMAGING AND POSTMORTEM NEUROPATHOLOGIC ANALYSIS OF AMYLOID BETA ACCUMULATION

Hiroyuki Hatsuta [1], Masaki Takao [1], Kenji Ishii [2], Kiichi Ishiwata [2], Yuko Saito [3], Kazutomi Kanemaru [4], Tomio Arai [5], Tetsuya Suhara [6], Hitoshi Shimada [6], Hitoshi Shinotoh [7], Shigeo Murayama [1]

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[7] *Neurology Chiba Clinic, Chiba, Japan*

Neuropathologic basis of ^{11}C-Pittsburgh compound B (PIB) uptake on PET-images has not been well analyzed in human. To clarify correlation of PIB images and amyloid beta protein (A*B*) accumulation, we studied PIB-PET images and neuropathologic changes on six subjects (3 males, 3 females) with neurodegenerative disorders. The mean interval between PET imaging and autopsy was 26.8 months. The mean age at death was 84.0 years old. Quantitative measures of PIB uptake (SUVR, a ratio of activity in target grey matter to that in a cerebellar reference region) were analyzed at 2l areas (11 cortical regions and 10 subcortical grey matter areas). In each area, we obtained A*B* burden (% area) using immunohistochemical staining with anti-A*B* 11-28 antibody. Two out of three PIB positive cases (mean cortical SUVR [mcSUVR]= 2.97 and 2.60) were consistent with Alzheimer's disease (AD) because of numerous neuritic plaques. In the AD cases, there was a strong correlation of SUVR and % area (case 1; r=0.65 [*p*=0.03], case 2; r=0.80 [*p*= 0.003]) in the 11 cortical regions. But, there was no correlation between regional SUVR and % area or neuritic plaques in 10 subcortical areas. The other PIB positive case (mcSUVR 1.57), amyotrophic lateral sclerosis with dementia, showed focal PIB uptake. There was no significant correlation between regional SUVR and % area as well as neuritic plaques. In three cases with PIB negative (mcSUVR < 1.4), there was no correlation between regional SUVR and % area as well as neuritic plaques. Based on these results, significant PIB positivity in the cerebral cortex suggests the presence of enough A*B*deposition including numerous neuritic plaques that is important hallmark of AD. Although a careful interpretation must be considered when PIB positivity is observed in the basal ganglia, high mean cortical SUVR is a reliable marker of clinical diagnosis of AD.

Keywords: *Alzheimer's disease, senile plaques, amyloid beta protein, 11C- Pittsburgh compound B (PIB), positron emission tomography (PET)*

Presented by: Hatsuta, Hiroyuki

Poster 17

META-ANALYSIS OF AMYLOID-COGNITION RELATIONS IN COGNITIVELY NORMAL OLDER ADULTS

Trey Hedden [1], Hwamee Oh [2], Alayna Younger [1], Tanu Patel [2]

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Objective: We conducted a meta-analysis of relationships between amyloid burden and cognition in cognitively normal older adult humans.

Methods: Methods of assessing amyloid burden included were cerebrospinal fluid or plasma assays, histopathology, and positron emission tomography ligands. Cognitive domains examined were episodic memory, executive function, working memory, processing speed, visuospatial function, semantic memory, and global cognition. Sixty-five studies representing 7140 subjects met selection criteria, with 3495 subjects from 34 studies representing independent cohorts. Weighted effect sizes were obtained for each study. Primary analyses were conducted limiting to independent cohort studies using only the most common assessment method (Pittsburgh Compound B). Secondary analyses included all assessment methods.

Results: Episodic memory (r = .12) had a significant relationship to amyloid burden. Executive function and global function did not have significant relationships to amyloid in the primary analysis of Pittsburgh Compound B (r = .05 and r = .08, respectively), but did when including all assessment methods (r = .08 and r = .09, respectively). The domains of working memory, processing speed, visuospatial function, and semantic memory did not have significant relationships to amyloid. Differences in the method of amyloid assessment, study design (longitudinal versus cross-sectional), or inclusion of control variables (age, etc.) had little influence.

Conclusions*:* Based on this meta-analytic survey of the literature, increased amyloid burden has small but non-trivial associations with specific domains of cognitive performance in individuals who are currently cognitively normal. These associations may be useful for identifying preclinical Alzheimer's disease or developing clinical outcome measures.

Keywords: *memory, executive function, cognition, meta-analysis*

Presented by: Hedden, Trey

Poster 18

DYNAMIC AND STATIC AMYLOID PET IMAGING: INVESTIGATION OF PARAMETRIC IMAGES OF [18F]FLUTEMETAMOL

Kerstin Heurling [1], Chris Buckley [2], Gill Farrar [2], Koen Van Laere [3], Mark Lubberink [4], Rik Vandenberghe [3]

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Objective: Parametric images of [^{18}F]flutemetamol binding potential (BP_{ND}), showing a quantitative measure of amyloid load, may be of additional clinical value in follow-up of cognitively impaired patients. The aim of the present work was to investigate the performance of various parametric analysis methods and SUVR by comparison with arterial input-based compartment modeling.

Methods: Dynamic 90 min [^{18}F]flutemetamol scans were performed in six subjects, three clinically diagnosed with Alzheimer's disease and three elderly controls. Parametric binding potential (BP_{ND}) images were generated using multilinear reference tissue methods (MRTMo, MRTM, MTRM2) (Ichise et al. 2003) and receptor parametric mapping (RPM, RPM2) (Lammertsma et al. 1996 and Wu and Carson, 2002) and the semiquantitative measurement SUVR (over 70-90 min p.i) using cerebellar gray matter as reference region. The resulting BP_{ND} values were compared with regional analysis, using arterial input two tissue compartment modeling (2TC).

Results: RPM, RPM2 and MRTM2 showed high average correlation with arterial input compartment analysis. SUVR showed a good correlation with arterial input compartment analysis, as well as with parametric BP_{ND} methods. Representative plots in Figure 1.

Conclusions: Of the parametric methods studied MRTM2, RPM and RPM2 BP_{ND} correlated best with regional compartment analysis with arterial input. SUVR also showed a high correlation regional compartment analysis with arterial input. This study shows that parametric imaging can be used to estimate the specific binding of [^{18}F]flutemetamol and also indicates that SUVR based on 20 min static scanning produces similar results.

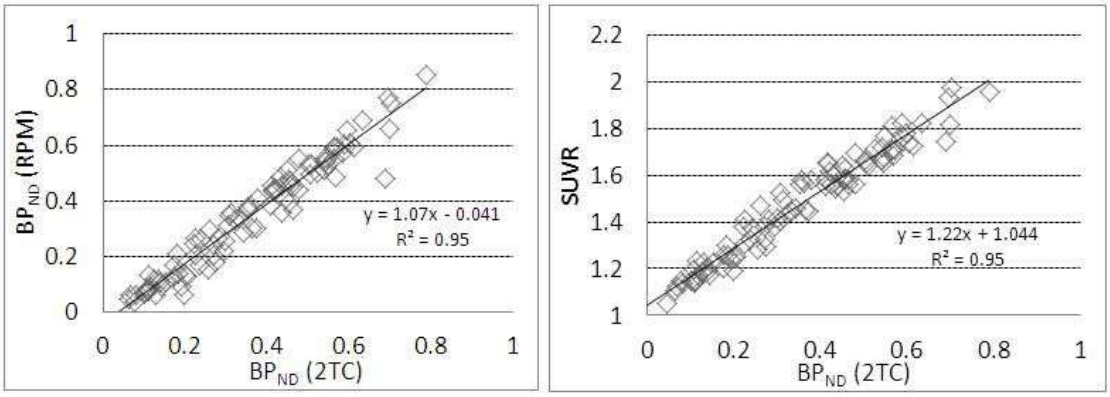

Figure 1. Correlation plots of binding potential estimated using the two tissue compartment model using arterial input vs (left) receptor parametric mapping and (right) vs the SUVR, using cerebellar gray matter as reference region. Each marker represents a region of interest in a subject.

References:

Ichise, M., Liow, J.S., Lu, J.Q., Takano, T., Model, K., Toyama, H., Suhara, T., Suzuki, T., Innis, R.B., Carson, T.E., 2003. Linearized reference tissue parametric imaging methods: application to [C-11]DASB positron emission tomography studies of the serotonin transporter in human brain. J. Cereb. Blood Flow Metab. 23,1096–1112. Lammertsma, A.A., Hume, S.P., 1996. Simplified reference tissue model for PET receptor studies. NeuroImage 4, 153–158. Wu, Y., Carson, R.E., 2002. Noise reduction in the simplified reference tissue model for neuroreceptor functional imaging. J. Cereb. Blood Flow Metab. 22, 1440–1452.

Keywords: *positron emission tomography, flutemetamol, modeling*

Presented by: Heurling, Kerstin

Poster 19

MULTISITE LONGITUDINAL 11C-PIB PET STUDIES IN BAPINEUZUMAB INTERVENTIONAL TRIALS: ISSUES RELEVANT TO ACQUISITION AND ANALYSIS

Derek Hill [1], Andrea Les [1], Robert Koeppe [2], Vahan Sharoyan [3], Joyce Suhy [3], Mark Schmidt [4], Richard Margolin [5], Keith Gregg[5], Michael Grundman [6], Eric Yuen [5], H Robert Brashear [5], Enchi Liu [5]

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[2] *University of Michigan, Department of Radiology*
[3] *Synarc, Inc.*
[4] *Janssen Research and Development*
[5] *Janssen Alzheimer Immunotherapy*
[6] *Global R&D Parners, LLC.*

Introduction: Variability in multisite longitudinal ^{11}C-PiB PET data may arise from biological or technical sources and may confound treatment effects.

Objectives: To examine the effect of quality control measures on baseline and longitudinal change in brain amyloid burden measured with ^{11}C-PiB PET in subjects enrolled into bapineuzumab Phase 3 trials.

Methods: Bapineuzumab, an anti-amyloid-beta monoclonal antibody in development for the treatment of mild to moderate Alzheimer disease (AD), was evaluated in separate phase 3 trials for APOE E4 carriers and non-carriers. A subset of subjects participated in PET substudies. ^{11}C-PiB PET scans were obtained at baseline and after 45 and 71 weeks of treatment at 14 US PET centers using ADNI acquisition protocols and image QC criteria applied visually by an expert prior to analysis. For quantitation, a cortical average SUVr was calculated from 5 ROIs known to accumulate substantial fibrillar amyloid. ROIs were defined in native PET space using the AAL atlas warped onto the subject's baseline 3D T1 MRI scan (intersected with a grey matter probability map), normalized to a cerebellar grey matter region truncated inferiorly.

Results: Baseline and treatment scans were available for 123 carriers and 61 non-carriers. Approximately 10% of scans failed initial expert QC; some were recovered by re-reconstruction. Review of these scans revealed frequent movement artefact and/or transmission/emission scan misalignment. Analysis QC identified scans for which MRI distortion impacted the quality of the analysis. Three subjects failed analysis because atrophy prevented adequate atlas warping.

Discussion. Ongoing QC soon after acquisition was essential for corrective action by sites. Analysis QC identified additional technical failures. Despite QC, variability in longitudinal measurements remained high. An independent reference metric, e.g. a white matter stability index, may assist in identifying data that has high longitudinal variability.

Keywords: *multicenter, quality control, technical variability*

Presented by: Hill, Derek

Poster 20

EPISTASIS AND AMYLOID BURDEN IN THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

Timothy Hohman, Mary Ellen Koran, Tricia Thornton-Wells

Vanderbilt University Medical Center

Recent Genome Wide Association Studies (GWAS) have identified genetic variants associated with increased risk of Alzheimer's disease (AD). Based on a meta-analysis of current literature, alzgene.org lists the top 10 gene associations: APOE, BIN1, CLU, ABCA7, CR1, PICALM, MS4A6A, CD33, MS4A4E, and CD2AP. We examined epistatic genetic effects among the non-APOE risk genes on amyloid deposition and cognitive change using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We used data from ADNI-1 as a discovery dataset to identify gene-gene interactions. Amyloid was quantified using data acquired by Positron Emission Tomography (PET) scans making use of 11C-Pittsburgh Compound-B (PIB). For replication, an independent dataset from ADNI-Grand-Opportunity (GO) and ADNI-2 was used with amyloid data quantified using 18F-AV-45. Finally, we tested for associations between replicated genetic interactions and cognition using a composite score of executive function.

One gene-gene interaction, CD33xBIN1, replicated when correcting for multiple comparisons (**Figure 1**). Carrying the minor allele in both BIN1 and CD33 was related to higher levels of amyloid deposition. In addition, ABCA7xCR1 replicated without correction with the minor allele of CR1 modifying the relationship between the ABCA7 minor allele and amyloid deposition (**Figure 2**).This ABCA7xCR1 interaction also showed an association with executive function. The presence of both minor alleles was related to better executive function performance over time, especially compared to those carrying the CR1 minor allele alone. The beneficial effect of carrying both minor alleles was especially apparent in the most clinically impaired individuals within this sample (**Figure 3**).These findings suggest the AD pathological cascade may be modified by gene-gene interactions in the immune response, complement cascade, and amyloid pathways. Future work focusing on the mechanisms of such relationships may provide novel targets for clinical intervention.

Figure 1

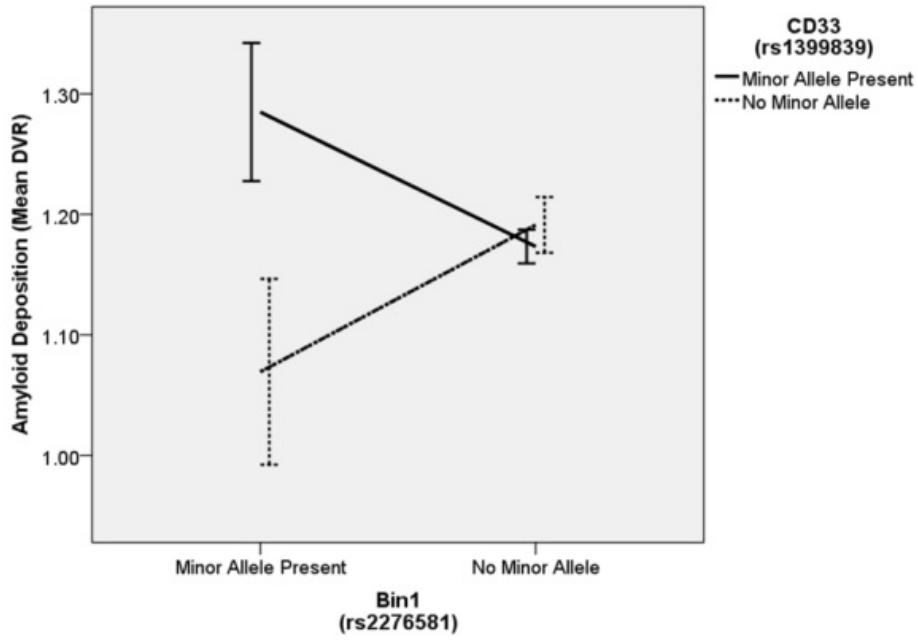


Figure 2

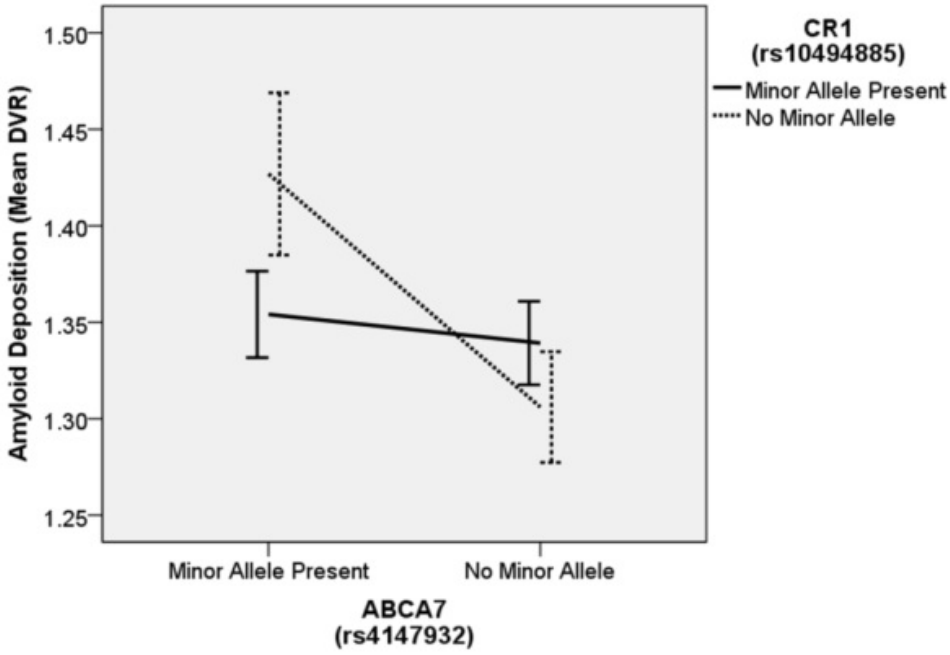
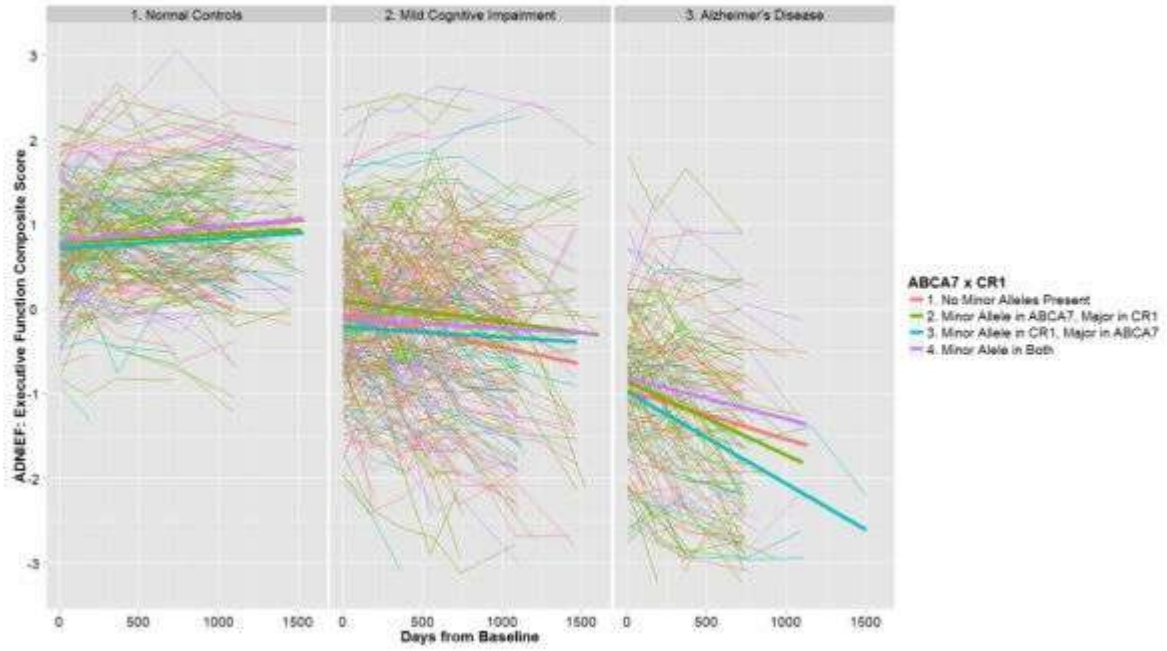


Figure 3



Keywords: *Epistasis, Genetics, PET, ADNI, Cognition*

Presented by: Hohman, Timothy

Poster 21

FAILURE TO MODULATE BRAIN ACTIVITY FROM BASELINE IS RELATED TO AMYLOID IN HEALTHY OLDER ADULTS

Willem Huijbers [1], Trey Hedden [2], Aaron Schultz [2], Andrew Ward [1], Sarah Wigman [1], Elizabeth Mormino [2], Keith Johnson [3], Reisa Sperling [4]

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[4] *Harvard Medical School, Brigham and Women's Hospital, Massachusetts General Hospital, Martinos Center for Biomedical Imaging.*

Objective*:* The impact of amyloid accumulation on brain activity in clinically normal older individuals remains a topic of active debate. Functional MRI studies have reported both increased and decreased activity associated with high amyloid burden within the default-network, using a variety of cognitive paradigms. Although linked to episodic memory, the default-network is known for its robust deactivations during various task conditions. Therefore, we investigated the consequence of amyloid burden on task-induced deactivations across encoding and retrieval conditions.

Methods*:* Fifty-four cognitively normal older individuals from the Harvard Aging Brain study completed PiB-PET amyloid imaging, fMRI and neuropsychological testing. Adults were classified as PiB- (n=31) or PiB+ (n=23) using a cut-off of 1.15 based on a mean cortical average. To isolate brain activity, adults conducted a memory task inside the fMRI scanner using novel and previously studied face/name pairs. To identify task-induced deactivations (and activations), we modeled all task events (encoding and retrieval-) versus fixations. We then computed voxel-wise differences between PiB+ vs. PiB-.

Results*:* Both PiB+ and PiB- groups demonstrated robust task-induced activations ($p<0.005$, FDR corrected) in visual cortex and fronto-parietal regions, including dorsal parietal cortex (DPC), as well as robust task-induced deactivations in the default-network, including posteromedial cortex (PMC). PIB- subjects showed greater activation in the DPC compared to PIB+ subjects. In contrast, PIB+ subjects showed relatively greater activity in the PMC, hippocampal formation and caudate than PIB- subjects ($p<0.005$, uncorrected). This PiB+>PiB- effect in the PMC was driven by a failure to deactivate in PiB+ individuals.

Conclusion: These results are consistent with previous fMRI studies that have associated high amyloid burden with greater activity in the hippocampal formation and studies that linked high amyloid burden with a failure to deactivate the default-network. Together these results suggest that amyloid accumulation contributes to an age-related failure to modulate task-related brain activity.

Keywords: *fMRI, deactivations, posteromedial cortex, pre-clinical, PiB*

Presented by: Huijbers, Willem

Poster 22

IMAGING OF AMYLOID DEPOSITS IN PATIENTS WITH CEREBRAL AMYLOID ANGIOPATHY RELATED INFLAMMATION

Takeshi Ikeuchi [1], Yasuhisa Akaiwa [1], Atsushi Honma [2], Takayoshi Tokutake [1], Masatoyo Nishizawa [1], Jun Toyohara [3], Kiichi Ishiwata [3], Kenji Ishii [3]

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Cerebral amyloid angiopathy (CAA) is characterized by amyloid-ß deposition in the walls of small arteries of the brain. Inflammatory response to Aß-laden vessels occurs spontaneously in some patients with CAA, and this condition is designated as CAA related inflammation. We here present three patients who developed CAA related inflammation with unique [^{11}C]PIB positron emission tomography (PET) findings. Brief clinical descriptions of these patients are as follows: *Patient 1*, 71 years old male, MMSE 22, *APOE* 4*4; *Patient 2*, 71 year old male, MMSE 19, *APOE* 2*4; *Patient 3*, 76 year old patient, MMSE 0, *APOE*3*3. T2*-weighted or susceptibility-weighted image (SWI) MRI revealed multiple microbleeds and fluid-attenuated inversion recovery (FLAIR) images showed asymmetrical high intensity lesions with swelling in the white matter in three patients. [^{11}C]PIB-PET revealed an increased uptake to various extents predominantly in the occipital cortex in *Patient 1*, the frontal and parietal cortex in *Patient 2*, and the frontal cortex in *Patient 3*. Notably, the PIB uptake was relatively low in the cerebral lesions where the white matter abnormalities were visualized by FLAIR MRI imaging. *In vivo* imaging of activation of microglia with [^{11}C](R)PK11195-PET in *Patient 2* revealed an increased uptake in the left cerebral lesions which corresponded to the area where PIB uptake was relatively spared. The present findings obtained by PET suggest the notion that inflammatory reaction may induce the phagocytosis of Aß by microglial activation. This mechanism is postulated to mediate the reduction of Aß burden in Alzheimer patients who received Aß vaccination therapy. This may suggest that inflammation occurring in CAA may enhance the clearance of parenchymal Aß deposits to some extent. Our findings highlight the importance of examining more patients with CAA-related inflammation by amyloid PET to better understand the pathophysiology of CAA-related inflammation.

Keywords: *cerebral amyloid angiopathy white matter lesions microglial activation immunological response Alzheimer disease*

Presented by: Ikeuchi, Takeshi

Poster 23

BRAIN IMAGING USING A NOVEL MOBILE BRAIN PET-CT

Jinsong Ouyang [1], Keith Johnson [2], Matthew Keeler [3], Ali Bonab [1], Paul Domigan [3], Quanzheng Li [1], Yoann Petibon [1], Geroges El Fakhri [1]

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[2] *Radiology Department, Harvard Medical School, Massachusetts General Hospital*
[3] *PhotoDiagnostic Systems Inc.*

The newly developed mobile NeuroPET-CT scanner is a full-ring brain PET-CT imaging system with a FOV of 25-cm in diameter and 21-cm in length. It uses 155316 2.3×2.3×10mm dual-layer LYSO crystals and 12096 SiPMTs. The PET scanner was designed to achieve both high sensitivity and good spatial resolution. The CT has 3264 detector channels with 8 axial channels at spacing of about 1.25mm. The X-ray source, capable of 140 keV at 7.0 mA, can rotate at 60 rpm for 1440 views/sec. The NeuroPET-CT was installed at Massachusetts General Hospital (MGH) in late 2011. The performance of this new system has been investigated using procedures based on the NEMA PET standard. The transverse resolution is 2.5 mm near the center and becomes 3.3 mm at a distance of r=5 cm from the center. The axial resolution is 3.0 mm at the center and 3.3 mm at r=5 cm. The overall system sensitivity for true events, which is calibrated to the activity within the FOV, is 42 cps/kBq in the center of FOV using an energy threshold of 420 keV. The maximum NEC rate of about 38 kcps was achieved for an activity concentration of 3.7 Bq/ml. Additionally, a Hoffman brain phantom was used to assess the image quality. Fifteen human subjects have been scanned using the NeuroPET-CT at MGH. For each subject, a CT, 15-minute FDG (5 mCi injection dose), and a 20-minute PIB (15 mCi injection dose) scans were performed.

Keywords: *amyloid, PET, instrumentation*

Presented by: Johnson, Keith

Poster 24

FIVE-YEAR FOLLOW-UP OF 11C-PIB UPTAKE IN PATIENTS WITH ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

Nina Kemppainen [1], Noora Scheinin [1], Jaana Koivunen [1], Jarkko Johansson [1], Kjell Någren [1], Johanna Rokka [1], Mira Karrasch [2], Riitta Parkkola [3], Juha Rinne [1]

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[2] *Department of Psychology and Logopedics, Abo Akademi University, Turku, Finland*
[3] *Department of Clinical Radiology, Turku University Central Hospital, Turku, Finland*

Background: Knowing the course of brain amyloid accumulation in Alzheimer's disease (AD) is essential in clinical PET diagnostics, but also in evaluating the predictive value of amyloid PET imaging in mild cognitive impairment (MCI) as well as in anti-amyloid drug development. Most of the previous longitudinal PET studies in MCI and AD with [11C]PIB have been restricted to a short follow-up period, results showing variable PIB uptake changes and inconsistent association between baseline PIB uptake and MCI-AD conversion.

Methods: Six AD patients, 10 MCI patients and eight healthy control subjects underwent a [11C]PIB PET scan at baseline and at two- and five-year follow-up time points. Clinical status in MCI patients was controlled every six months. Between-groups differences and within-group changes in [11C]PIB uptake were analyzed.

Findings: AD and MCI groups had significantly higher brain [11C]PIB uptake at every follow-up point as compared to controls. MCI group showed significant increase in [11C]PIB uptake over time, with similar increase from baseline to two years (4,7%/y) and from two to five years (5,0%/y). Eight (80%) MCI patients converted to AD, two of whom showed negative PIB scan at baseline. No significant group-level increase in [11C]PIB uptake was seen in AD.

Interpretation: Our results showed a significant increase in [11C]PIB uptake over time in MCI but not in AD. This is in line with the current hypothesis of the amyloid cascade in AD. However, our data revealed significant increase in amyloid load even at the time of AD diagnosis. Moreover, a positive PIB scan at baseline in MCI strongly predicted future conversion to AD but a negative PIB in MCI did not exclude the conversion to PIB positive scan and AD. These results suggest that a pronounced brain amyloid accumulation may take place even at the time of conversion from MCI to AD.

Keywords: *Alzheimer, MCI, PET, PIB, follow-up*

Presented by: Kemppainen, Nina

Poster 25

CONTRIBUTIONS OF IMAGING BETA-AMYLOID AND WHITE MATTER HYPERINTENSITIES TOWARD ISOLATING NORMAL COGNITIVE AGING

Beth Snitz [1], Robert Nebes [2], Howard Aizenstein [2], Anne Cohen [2], Edythe Halligan [2], Lisa Weissfeld [3], Julie Price [4], Chester Mathis [4], WIlliam Klunk [2]

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[2] *Dept. of Psychiatry, University of Pittsburgh*
[3] *Dept. of Biostatistics, University of Pittsburgh*
[4] *Dept. of Radiology, University of Pittsburgh*

Introduction: Substantial between-individual differences exist in the magnitude of normal age-associated cognitive decline. Potential contributors to intersubject variability include white matter hyperintensities (WMH) and increased beta-amyloid deposition. This study examined whether older individuals with minimal evidence of WMH and/or PiB-PET retention still show significant cognitive decrements compared to the young.

Methods: Participants included n=71 older individuals (mean age=74.2, SD 5.4 years) conservatively screened for normal range performance on an ADRC neuropsychological test battery. WMHs were quantified via consensus ratings from three expert raters using a validated 0-9 WMH rating scale and median rating split defining two groups, WMH(+) and WMH(-). PiB(+) was defined by regional PiB positivity in any one of six specified regions. Participants completed cognitive tasks of information processing speed, working memory and inhibitory function, with domains selected for their centrality to prevailing theories of cognitive aging. A young control group (n=37; mean: 22.6±3.3 years) from a previous study completed the same cognitive tasks.

Results: There were no significant differences in cognitive performance between PiB(+) (n=18) and PiB(-) (n=53) elderly (p-values > 0.05). The WMH(+) (n=26) and WMH(-) (n=40) groups also did not differ on cognitive tasks. The older participants who werebothPiB(-) and WMH(-) (n=30) performed significantly worse than the young on cognitive tasks from all three domains. Effect sizes (Cohen's *d*) indicated small mean task differences in the expected directions for pathology (+) vs. (-) groups, which were mostly outsized by higher magnitude *d's* reflecting age effects.

Conclusions: Carefully screened, normal elderly individuals whose brain scans show minimal evidence of beta-amyloid deposition or WMH still demonstrate a major decrement in performance, compared to a group of younger persons, on measures of processing resources, working memory and inhibitory efficiency.

Keywords: *PiB-PET, normal aging, white matter, cognitive aging*

Presented by: Klunk, WIlliam

Poster 26

LONGITUDINAL STUDIES OF FLORBETAPIR IN ADNI-2

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Introduction: Amyloid imaging using positron tomography has proven useful in the study of Alzheimer's type dementias. As amyloid deposition often begins years before onset of symptoms, the time course of amyloid accumulation in the brain still needs to be better characterized.

Methods: Longitudinal PET studies using [^{18}F]-florbetapir are part of the Alzheimers Disease Neuroimaging Initiative (ADNI-2). Fifty-four subjects (15 controls, 23 early MCI, and 16 subjects continuing from the ADNI-1 who entered the study with a diagnosis of MCI) received two PET scans at an interval of 24±1 month. Subjects were injected with 7-11 mCi of [^{18}F]-florbetapir and scanned from 50-70 minutes post-injection (four 5-min scans). The frames of each scan were co-registered and averaged. Both scans were registered to the subject's baseline FDG scan. Four different reference regions were used for normalization of the averaged florbetapir images: cerebellar gray matter, pons, white matter, and a combined region including the previous three.

Results: No significant differences were observed in the SUVr change between diagnostic groups for any of the normalization methods, though the EMCI group showed the largest average change. However, in the relatively small sample of ADNI-2 subjects rescanned so far, approximately the same percentage of subjects in each group was amyloid positive (NC 7 of 15; EMCI 10 of 23; MCI 8 of 16). Thus, analyses were run comparing the 25 amyloid positive to the 29 amyloid negative subjects. The table gives the mean and standard deviation of the change for both negative and positive groups for each of the normalization methods.

% Change in SUVr	Cerebellar Gray	Pons	White Matter	Combined
Amyloid Negative: Mean±SD	–0.5±5.7%	-1.7±5.9%	-0.4±7.2%	-0.4±4.5%
Amyloid Positive: Mean±SD	0.1±9.7%	2.9±7.7%	3.6±3.8%	2.3±3.7%

Conclusions: Only small changes were detected in the 2-year follow-up florbetapir scans. A combined reference region showed considerably better longitudinal reproducibility.

Keywords: *SUVr, longitudinal change, reference region*

Presented by: Koeppe, Robert A.

Poster 27

MULTI-SLICE 3T T1RHO-WHEIGHTED MRI AS AN EARLY BIOMARKER OF ALZHEIMER'S PATHOLOGY: A VOXEL-BASED ANALYSIS IN MCI, AT RISK, AND CONTROL SUBJECTS

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[5] *Vanderbilt University Institute of Imaging Science*
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We evaluated T1rho MRI as a non-invasive method for detection of early Alzheimer Disease (AD) pathology. This sequence probes macromolecular environments and chemical exchange rates and is sensitive to amyloid plaques in mice at high field strengths (4T) (Borthakur, A., et.al.: 2006). T1rho is expected to decrease with increased plaque load, as it did in the mouse model, and is expected to increase with increased extracellular space. T1rho in human studies at 1.5T showed increased values in subjects with AD, most likely due to detection of atrophy in addition to plaque in individuals (Haris,M., et.al.: 2010). We aimed to detect early stage T1rho differences that trended in the same direction as the immuno-histochemically validated mouse model data. We investigated quantitative T1rho with on a multi-slice, voxel-wise basis at 3T between subjects *at risk* for AD, early in disease course versus normal controls (NC). The at risk subjects include persons with mild cognitive impairment (MCI) or a family history (FH) of AD. **Because we are investigating patients early in the disease trajectory, we hypothesize that T1rho will trend with plaque load as follows MCI<FH<NC, where subjects at highest risk for plaque load have the lowest T1rho values.**T1rho, T1, and T2 images were acquired on 32 subjects (11 NC, 12 FH, 9 MCI). We acquired T1rho images at multiple spin lock frequencies and times. Voxel-wise T1rho, T1, and T2 quantitative maps for each subject were generated and were used to plot individual dispersion curves for each FreeSurfer delineated ROI. In many AD-related regions of interest, like the parietal cortex, middle temporal gyrus, cingulate gyrus, and temporal-occipital region, we observed the expected trend (MCI<FH<NC). These preliminary findings provide additional support for the hypothesized relationship between T1rho and amyloid plaque deposition in the human brain.

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Keywords: *T1rho, MRI, human, Alzheimer, biomarker*

Presented by: Koran, Mary Ellen

Poster 28

NEURONAL ENDOPHENOTYPES OF FAMILIAL RISK FOR LATE-ONSET ALZHEIMER'S DISEASE

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E Lampert, K Roy Choudhury, CA Hostage, JR Petrella, PM Doraiswamy for ADNI*

Introduction: A positive family history (FH) is a risk factor for late-onset Alzheimer's disease (AD) but its effects on pathological and neuronal loss biomarkers has not been fully studied.

Methods: We analyzed data from cognitively normal (CN), mild cognitive impairment (MCI), and AD subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (n=262) [ages 55-89] to examine the effects of a family history of AD on pathological (cerebrospinal fluid (CSF) abeta, tau, and tau/abeta ratio) on neuronal loss (hippocampal volumes) markers.

Results: We found no significant differences in age, baseline cognition, MRI-measured hippocampal volumes ($p=0.55$, 0.83, 0.43) or intracranial volumes ($p=0.28$, 0.22, 0.51) between FH+ and FH- in CN, MCI or AD. Among MCI, CSF Abeta-42 was lower ($p=.005$), t-tau was higher ($p=0.02$) and t-tau/Abeta-42 ratio was higher ($p=0.002$) in FH+ than FH- subjects. The effect of FH remained after covarying for ApoE4 ($p<0.05$). Among CN, 47% of FH+ exhibited "pathologic signature of AD" (CSF t-tau/Abeta-42 ratio >0.39) versus 21% of FH- controls ($p=0.03$). The specificity of CSF biomarkers for distinguishing AD from CN by FH status was ($p=0.03$). The FH effect on Abeta and tau disappeared with the onset of clinical AD.

Conclusions: A positive family history is associated with an abnormal cerebral beta-amyloid and tau protein phenotype prior to the onset of clinical AD and with earlier onset of preclinical pathologic AD. These data also point to a missing pathologic heritability not explained by ApoE4.

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Keywords: *Alzheimers, Neuronal endophenotypes*

Presented by: Lampert, Erika

Poster 29

REDUCED AMYLOID DEPOSITION AND GREATER HYPOMETABOLISM IN APOE4-POSITIVE AD PATIENTS

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Objective: We aimed to assess the relationship between amyloid deposition, glucose metabolism and ApoE4 status in a clinically heterogeneous population of AD subjects.
Method: The study included 48 probable AD patients with high-likelihood AD pathophysiology (NIA-AA) (age 63.7 (8.9), 56% male): 22 ApoE4+ (14 heterozygous, 8 homozygous) and 26 ApoE4-. Groups consisted of language-variant AD, visual-variant AD, and AD patients with amnestic and dysexecutive deficits (3/4/15 in ApoE4+, 8/9/9 in ApoE4-negative group, p=0.07). ApoE4 groups were matched for age, gender, education and MMSE. A group of 50 healthy controls was included for comparison. Voxel-wise comparisons of FDG and PIB were performed between groups. Analyses were adjusted for age, gender and education, with additional correction for MMSE in the between-patient group comparisons. Differences between controls and patients were corrected for multiple comparisons, whereas between-patient group differences are shown uncorrected.

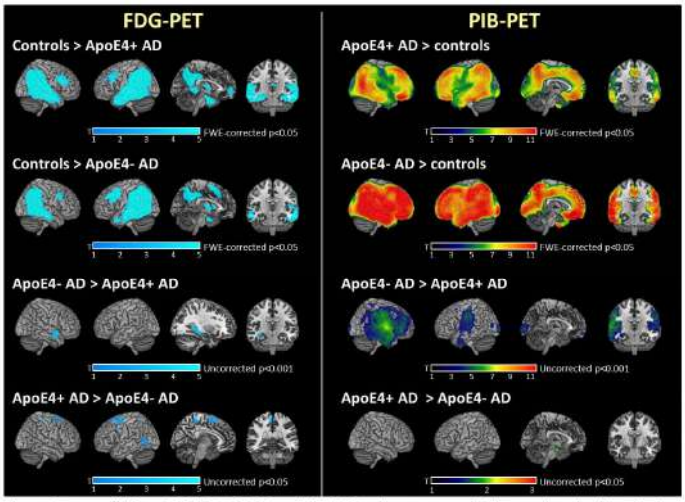

Figure: Patterns of FDG and PIB in ApoE4+ AD and ApoE- AD patients compared with controls and with each other. Control comparisons are corrected for multiple comparisons (FWE p<0.05), whereas between-patient group differences are shown at uncorrected thresholds (p<0.001 for ApoE4- > ApoE4+; p<0.05 for ApoE4+ > ApoE4-).

Results: Whilst PIB patterns were diffuse in both ApoE4 groups, ApoE4- patients showed higher PIB uptake than ApoE4+ patients across the cortex (Figure). Higher PIB uptake in ApoE4- was particularly significant in right lateral frontotemporal regions. In contrast, similar patterns of hypometabolism relative to controls were found in both ApoE4 groups, mainly involving lateral temporoparietal cortex, precuneus, posterior cingulate cortex, and middle frontal gyrus. Comparing patient groups, ApoE4+ subjects showed greater hypometabolism in bilateral medial temporal and right lateral temporal regions, and ApoE4- patients showed greater hypometabolism in cortical areas including supplementary motor cortex and superior frontal gyrus. Results were unchanged after applying partial volume correction.
Conclusion: ApoE4-carriers showed a similar degree of hypometabolism in the presence of lower amyloid burden than matched ApoE4-noncarriers, suggesting greater metabolic vulnerability in ApoE4-carriers that is not explained by Abeta burden. Small reductions in metabolism in medial temporal regions in ApoE4-carriers correspond to the reported link between ApoE4 and an amnestic clinical phenotype in AD.

Keywords: *Alzheimer's disease, apolipoprotein E, PIB, FDG*

Presented by: Lehmann, Manja

Poster 30

INCREASED MEAN DIFFUSIVITY IS ASSOCIATED WITH HYPOMETABOLISM BUT NOT AMYLOIDOSIS IN MCI AND AD: A DTI / [18F]AV45 / [18F]FDG PET STUDY.

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Introduction: Increased mean diffusivity (MD) in Alzheimer's disease (AD) is thought to provide an index of white matter (WM) degeneration, and can be measured using diffusion tensor imaging (DTI). While considered a potential imaging biomarker, the link between WM alterations and AD pathophysiology remain largely unexplained. Using DTI, [^{18}F]AV45, and [^{18}F]FDG—Positron Emission Tomography (PET) radiopharmaceuticals allowing for in-vivo quantification of fibrillary beta-amyloid and cerebral glucose metabolism, respectively—we sought to examine the association between increased MD, amyloid load, and cerebral metabolism.

Methods: We analyzed a subsample of 8 cognitively normal (CN), 35 MCI and 4 AD participants from ADNI for whom DTI, [^{18}F]AV45 and [^{18}F]FDG data were available. PET uptake ratios (UR) were calculated by dividing [^{18}F]AV45 and [^{18}F]FDG, telencephalic uptake by the median counts of cerebellar GM and pons respectively. Total amyloid load and metabolism were then calculated using median uptake in frontal, temporal, and parietal GM. FSL-FDT-DTIFIT was used to create mean diffusivity maps (MD). These maps were nonlinearly registered to MNI-152 space. Voxel-based regression between MD maps and amyloid load and metabolism were calculated using R-Minc.

Results: No significant between group differences were found in terms of age, sex, or body weight. When subgroups were collapsed, global amyloid uptake was found not to associate with MD. In contrast, global FDG uptake—all subgroups collapsed—was associated with increased MD in the anterior cingulate (right, t=-4.15; left, t=-3.78), insula white matter (left, t=-4.00), anterior superior longitudinal fasciculus (right, t=-4.27), and posterior superior longitudinal fasciculus (right, t=-3.96).

Conclusion: Our results suggest that amyloidosis and WM neurodegeneration—as indexed by increased MD—are not associated, a finding that contrasts with predictions based on the amyloid cascade hypothesis model. In addition, we found that hypometabolism and WM neurodegeneration co-localize to regions known to be affected in AD.

Keywords: *DTI, amyloidosis, hypometabolism, MCI, AD*

Presented by: Leuzy, Antoine

Poster 31

IMAGING BIOMARKER CORRELATION WITH AUTOPSY AT THE MAYO CLINIC

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Mayo Clinic Rochester

Background: Recent publications by the NIA-AA workgroup include guidelines for integrating biomarkers into diagnostic algorithms for dementia. Since the impact of these recommendations has not been fully evaluated with autopsy data, we evaluated the utility of PiB and FDG PET in a group of subjects with brain autopsy.

Methods: Brain autopsies from 26 subjects in the Mayo Clinic Study of Aging and Mayo Clinic Alzheimer's Disease Research Center were analyzed. Autopsy diagnoses were compared PiB and FDG imaging results (scans were performed 0.19 to 3.93 years before death).

Results: Autopsy diagnoses included AD (N=12), vascular disease (VaD) (N=4), PSP (N=3), LBD (N=3), normal (N=3), and metastatic cancer (MC) (N=1). PiB categorized all subjects correctly except for the MC subject (PiB of 1.6) and 1 normal subject (PiB of 1.9). Of the 12 AD subjects, 2 had a consensus diagnosis of LBD prior to death and one of these also had mixed DLBD pathology; FDG and PiB data helped categorized both of these subjects in concordance with autopsy findings. PSP, VaD and the remaining normal subjects all had normal PiB scans. Of the 3 PSP subjects, 1 had a consensus diagnosis of AD prior to death and 2 of MCI; PIB was negative in all 3 (1.19-1.23). Of the VaD subjects, 2 had a consensus diagnosis of MCI; both were negative on PiB (1.17-1.25).

Conclusions: PiB and FDG biomarkers were concordant with autopsy diagnoses in 7 subjects (2 AD, 3 PSP, and 2 VaD) who had LBD, AD, or MCI consensus diagnoses antemortem. Therefore, in 27% (7/26) of subjects, PiB and FDG biomarkers improved disease characterization. These data support the integration of FDG and PiB PET in dementia diagnostic guidelines.

Keywords: *FDG, PiB, autopsy, biomarkers, dementia*

Presented by: Lowe, Val

Poster 32

RELATIONSHIP OF CSF ABETA42 AND CMRGLU TO APOE EPSILON 4 CARRIER STATUS AND AMYLOID BURDEN IN ADNI SUBJECTS WITH A DIAGNOSIS OF AD: FOCUS ON APOE E4 NEGATIVE/AMYLOID-NEGATIVE SUBJECTS

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Introduction: Amyloid PET is used in AD therapeutic trials for sample enrichment and to measure treatment effect. Evidence suggests signal differences between apolipoprotein E4 carriers (APOE4+) and non-carriers (APOE4-) that may impact these applications. In observational studies, APOE4+ individuals demonstrate higher baseline SUVRs and greater increases than non-carriers. Also, APOE4- individuals may more commonly have a non-AD etiology than APOE4+ individuals.

Besides APOE4 status, trial participants can be categorized as amyloid-positive (amy+) or negative (amy-) using tracer-specific cutoffs. Recent reports indicate a relatively high percentage of amy- individuals in AD trials; APOE4-/amy- individuals may have a particularly high misdiagnosis rate and/or unusual clinical or biomarker trajectories.

Two biological characteristics have been proposed as supporting a clinical diagnosis of AD: reduced CSF ABeta42 concentration and regional cerebral glucose (rCMRglu) hypometabolism.

Objectives: To investigate the impact of APOE4 status and amyloid burden on the frequency of these characteristics.

Methods: We explored the relationships between APOE4 status, amyloid burden, CSF ABeta42 concentration and rCMRglu in ADNI-1 and ADNI-2 subjects with a clinical diagnosis of dementia-stage AD, focusing on the APOE4-/amy- group. We hypothesized that both CSF ABeta42 concentration and CMRglu inconsistent with AD diagnosis would be higher in APOE4- and amy- groups, and that the APOE4-/amy- group would have the highest inconsistency level.

Results: Among 88 ADNI AD subjects, 30 (34%) were APOE4-. While amyloid positivity was 95% among APOE4+, it was only 53% among APOE4-. Of 13 APOE4- subjects with CSF ABeta42 measurements, 7/8 amy+ had reduced concentrations, but no amy- did. Of 12 APOE4-/amy- subjects with CMRglu measurements, none had an AD-characteristic pattern.

Conclusion: APOE4- and amy- individuals with AD (and especially the APOE4-/amy- group) have a high frequency of AD-inconsistent biomarker characteristics. CSF ABeta42 and CMRglu may add value to clinical diagnosis in subject selection for treatment trials.

Keywords: *APOE4, ABeta42, CMRglu, ADNI, AD*

Presented by: Margolin, Richard

Poster 33

THE IMPACT OF SCANNER VARIABILITY UPON AMYLOID BURDEN MEASUREMENTS USING 18F TRACERS

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Background: The availability of fluorinated amyloid tracers has greatly expanded the number of sites providing amyloid plaque measurement as a biomarker in clinical trials and diagnosis. Quantitation involves use of a reference region lacking fibrillar amyloid, e.g. cerebellum (Standardized Uptake Value Ratio; SUVR). However, SUVRs can be affected by several confounds including scanner characteristics. Significant scanner-related differences have previously been demonstrated with 11C-PiB and attributed in part to limited count rates, but whether the same issues exist in fluorinated tracers with higher activity is unclear.

Objective: To assess inter-scanner effects on fluorinated amyloid PET data in ADNI-GO/2.

Methods: We evaluated 18F-florbetapir scans from 520 ADNI subjects acquired on six scanner types: Siemens PET/CT (154 scans, 13 sites), GE Discovery (149,[16]), Siemens HR+ (107,[12]), Philips Allegro (27,[3]), Philips Gemini TOF (42,[4]), and Siemens HRRT (18,[3] and 23,[1]). Cortical average region of interest (ROI) SUVRs were measured using cerebellar gray matter (cGM), whole cerebellum, pons, and subcortical white matter (SWM) as comparative reference regions. SWM was also evaluated as an ROI due to its relative stability across subjects regardless of cortical SUVR. Using an amyloid positivity threshold of 1.28, positive (247) and negative (273) scans were evaluated together and separately.

Results: Significant SUVR differences of up to >16% (.39 SUVR) were found between certain scanner models. Average SWM SUVR referenced to cGM ranked: Gemini TOF, HRRT1 > Discovery, HR+, Siemens PET/CT >Allegro, HRRT2. ROI differences between scanner types were reduced when using references other than cGM .

Conclusions: Fluorinated amyloid tracer SUVRs can be significantly affected by scanner characteristics. Values must be evaluated in the context of the scanner used, particularly in multicenter studies and in case of scanner changes in longitudinal studies. Comparisons of alternate reference regions and use of adjustment factors may help to address these differences.

Keywords: *amyloid, florbetapir, scanners*

Presented by: Matthews, Dawn

Poster 34

APOE E4 AND AMYLOID BURDEN INDEPENDENTLY INCREASE CEREBRAL BLOOD FLOW IN COGNITIVELY NORMAL OLDER ADULTS

Donald McLaren [1], Aaron Schultz [1], Jasmeer Chhatwal [1], Elizabeth Mormino [1], Karleyton Evans [2], Keith Johnson [1], Reisa Sperling[3]

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[2] *MGH*
[3] *BWH/HMS*

Background: Substantial work in preclinical Alzheimer's disease (AD) has been focused on understanding the relationships between amyloid, cognition, atrophy and neural activity; however, there have been limited investigations of cerebral blood flow (CBF) to date. Recently, CBF, as measured with pulsed arterial spinning labeling (pASL), has been shown to be a reliable marker of blood flow in cognitively normal older adults (CN) and may have potential as an early AD biomarker.

Objective: Assess the effect of amyloid burden and APOE ε4 carrier status on CBF using pASL.

Methods: 142 CN participants in the Harvard Aging Brain Study underwent a pASL scan. pASL images were motion corrected, smoothed and entered into the UPenn ASL Toolbox to compute CBF maps. The CBF maps were then normalized to MNI space and additionally smoothed. Mean cortical (mc) DVR PiB values (N=129) and/or APOE genotypes (N=107) were obtained from a subset of these subjects. CBF was contrasted according to APOE genotype (ε3/ε3 vs ε3/ε4) and modeled with mcPiB, APOE genotype, and age as predictors. Whole brain maps were thresholded at $p<0.005$.

Results: The APOE ε4 carrier status was associated with increased CBF in posterior cingulate and lateral parietal regions ($p<0.005$, uncorrected; Figure 1) and mcPiB was associated with increased CBF in prefrontal regions ($p<0.005$, uncorrected; Figure 2), however, we did not observe any interaction of APOE and mcPiB in in these regions.

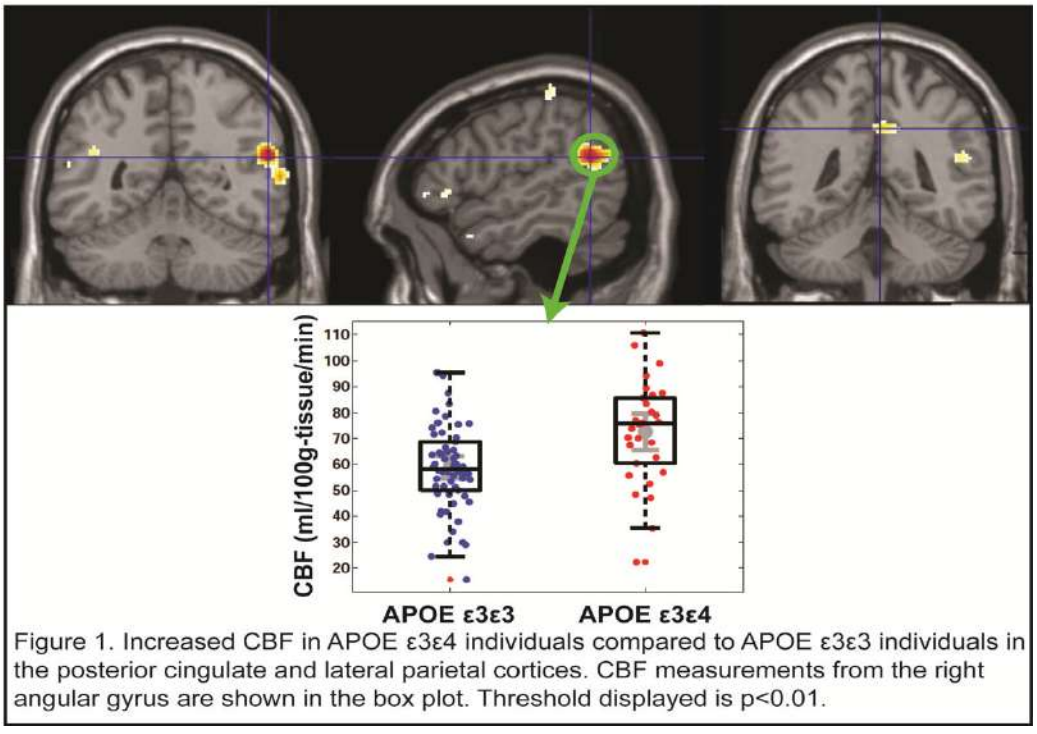

Figure 1. Increased CBF in APOE ε3ε4 individuals compared to APOE ε3ε3 individuals in the posterior cingulate and lateral parietal cortices. CBF measurements from the right angular gyrus are shown in the box plot. Threshold displayed is $p<0.01$.

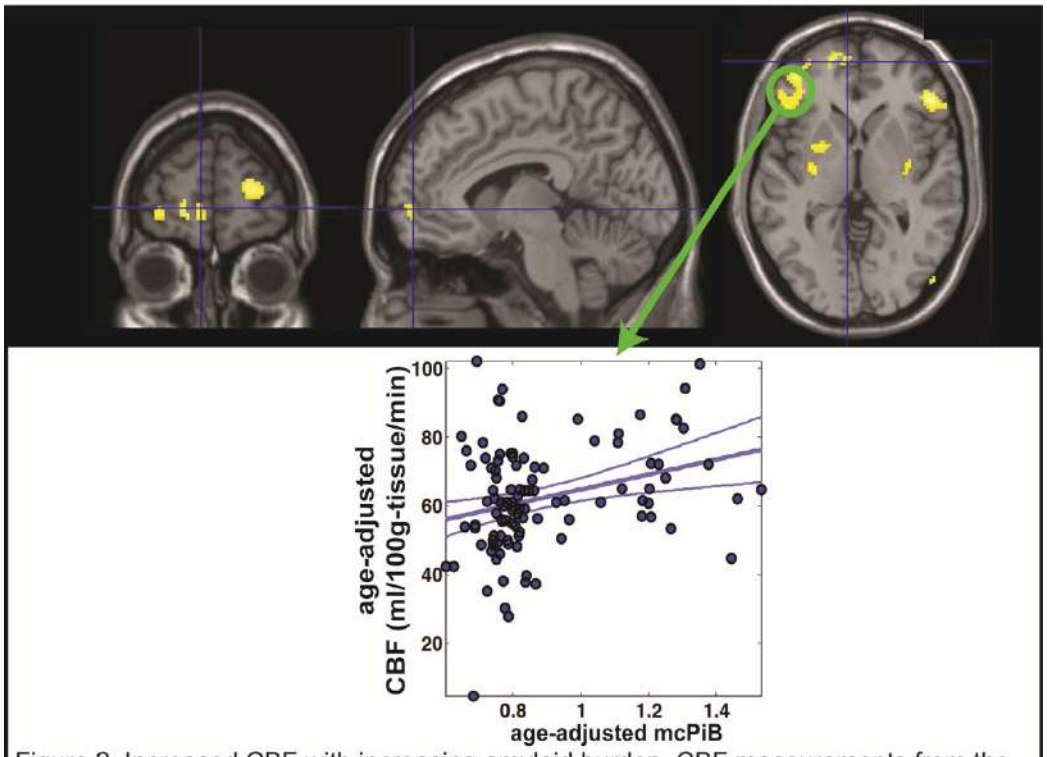

Figure 2. Increased CBF with increasing amyloid burden. CBF measurements from the left prefrontal cortex are shown in the box plot. Threshold displayed is p<0.01.

Conclusions: APOE genotype and amyloid burden independently increase CBF. The independence of APOE and amyloid effects warrants further study to understand their effects before considering pASL as an AD imaging biomarker. Future research will focus on increasing the sample size and on the longitudinal changes in CBF associated with APOE and amyloid burden.

Keywords: *Cerebral Blood Flow, APOE, Amyloid, preclinical AD, ASL*

Presented by: McLaren, Donald

Poster 35

ASSOCIATION BETWEEN HEAD TRAUMA, AMYLOID, AND NEURODEGENERATION IN A POPULATION-BASED STUDY OF COGNITIVELY NORMAL AND MILD COGNITIVE IMPAIRMENT PARTICIPANTS

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Background: Head trauma has been associated with an increased risk of dementia and Alzheimer's disease (AD). Animal and post-mortem studies suggest that head trauma increases amyloid production and plaque deposition, but *in vivo* assessments are limited. We examined whether head trauma was associated with greater amyloid deposition and/or neurodegeneration among individuals who were cognitively normal (CN) or had Mild Cognitive Impairment (MCI).

Methods: A population-based sub-sample of 589 individuals (448 CN and 141 MCI), aged 72-95, from the Mayo Clinic Study of Aging underwent PIB-PET, FDG-PET, and MR imaging. A history of head trauma was defined as a self-reported brain injury with at least momentary loss of consciousness or memory. We used Wilcoxon rank sum tests and chi-square tests to assess differences between subjects with and without a self-reported head trauma by cognitive status.

Results: Among the 448 CN individuals, 74 (16.5%) had a self-reported head trauma. There were no differences in PiB-PET, FDG-PET, or MR measures between CN subjects with and without head trauma. Of the 141 MCI cases, 25 (17.7%) self-reported a head trauma. Compared to those MCI without a head trauma, those with a head trauma had higher median PiB level (SUVR 2.2 vs. 1.6, $p = 0.003$). There was also a trend for lower hippocampal volumes (-0.95 vs. -0.72, $p = 0.10$), adjusted for head size. When stratified by APOE E4 genotype, the relationships were stronger among non-E4 carriers. However, we only had 9 MCI cases with a head trauma and an E4 allele.

Conclusion: Results suggest that a history of self-reported head trauma is associated with higher levels of amyloid deposition in individuals with MCI, but not among CN individuals. These data raise interesting questions about the linkages between head trauma, amyloid, and cognitive impairment, although recall and other biases must be considered.

Keywords: *head trauma; amyloid; neuroimaging; neurodegeneration*

Presented by: Mielke, Michelle

Poster 36

NEUROPSYCHOLOGICAL TESTING IDENTIFIES PATIENTS WITH PATHOLOGIC LEVELS OF BETA-AMYLOID IN THE LIVING BRAIN AS DEMONSTRATED BY FLORBETAPIR F18 POSITRON EMISSION TOMOGRAPHY

Heidi Bender [1], Effie Mitsis [2], Mary Sano [2], Jane Martin [1], Jennifer Woehr [1], Anna Miley-Akerstedt [1], Stephanie Towns [1], Lale Kostakoglu [3], Martin Goldstein [1], Josef Machac [3], Sam Gandy [2]

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[3] *Mount Sinai Medical Center*

Objective: To determine the clinical utility of neuropsychological testing in identifying patients with pathologic levels of beta-amyloid in the living brain. The newly FDA-approved florbetapir F18 PET ligand with high affinity and specificity to beta-amyloid permits in vivo quantitative assessment of this objective biomarker of AD.

Methods: A case series was conducted including 11 participants, aged 60 - 89 years, with histories of cognitive dysfunction. A neuropsychological test battery evaluating attention, executive functioning, language, motor speed, learning and memory was administered. A clinical diagnosis (i.e., amnestic MCI, AD, FTLD, vascular-related dementia or clinically normal) was made by neuropsychologists who were blind to PET findings. All participants underwent florbetapir PET scans for clinical evaluation which were visually scored by nuclear medicine as positive or negative for pathologic levels of beta-amyloid aggregation.

Results: Five participants were diagnosed with amnestic MCI, 4 with FTLD, 2 with clinically normal presentations, and none with AD or vascular-related dementia. Positive florbetapir F18 PET scans were found in 4 of those with MCI; 0 of those with FTLD and 0 of those deemed normal.

Conclusions: Findings suggest that neuropsychological testing has robust clinical utility in identifying patients with amnestic MCI who exhibit biomarkers of AD on florbetapir F18 PET imaging. These data underscore the benefit of neurometrics in the early identification process, thereby facilitating accurate diagnosis and informing treatment planning.

Keywords: *Florbetapir 18F, Neuropsychological Testing, Clinical Utility*

Presented by: Mitsis, Effie

Poster 37

FLORBETAPIR SCANNING EXCLUDES ALZHEIMER'S DISEASE IN A RETIRED NFL PLAYER WITH DELAYED COGNITIVE IMPAIRMENT

Effie Mitsis [1], Silvana Riggio [1], Emily D'Antonio [2], Martin Goldstein [2], Steven DeKosky [3], Thomas Naidich [4], Bradley Delman [4], Josef Machac [4], Gregory Elder [1], Mary Sano [1], Sam Gandy [1], Wayne Gordon [2]

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Single severe traumatic brain injury (TBI) is believed to increase risk for typical Alzheimer's disease (AD), while chronic repetitive TBI in boxers is believed to increase the risk for a tangle-only disease, or tauopathy, known as dementia pugilistica (DP). DP-like pathology has been observed in retired NFL players and in military veterans exposed to blast injury where the term chronic traumatic encephalopathy (CTE) is applied. The clinical distinction of AD from other causes of what we term "delayed post-traumatic cognitive impairment (DPTCI)" is challenging, but accurate diagnosis is required to avoid including subjects without cerebral amyloidosis in trials of Aβ-reducing agents. A retired NFL player was evaluated for progressive cognitive impairment. During his 10-year professional career in the 1960s-1970s, the patient reported experiencing multiple concussions. By twelve hours post-game, he was at times unable to name which team he had just played against. Neuropsychological testing revealed impaired information processing speed, impaired verbal comprehension, and impaired immediate and delayed recall but intellectual function and learning ability were preserved. An NFL Neurological Care Program team -- consisting of a neurologist, a neurologist-psychiatrist, a neuropsychologist, and two neuroradiologists -- evaluated the patient. All evaluators agreed on the diagnosis of possible DPTCI, but they were unable to reach unanimity on the inclusion of possible AD. Two independent neuropsychologists from the ADRC reviewed the test results and supported the inclusion of possible AD, although the primary examining team (with the exception of one of the neurologists) opposed the inclusion of possible AD. Florbetapir scanning excluded cerebral amyloidosis -- thereby excluding AD -- and the patient was given a diagnosis of DPTCI without amyloidosis with possible CTE. This case illustrates the potential for brain amyloid imaging to prevent the inappropriate inclusion of non-AD patients (including those with a history of TBI) in trials of Aβ-reducing agents.

Keywords: *Florbetapir, dementia pugilistica, NFL, TBI, Delayed Post-traumatic Cognitive Impairment*

Presented by: Mitsis, Effie

Poster 38

FLORBETAPIR F18 POSITRON EMISSION TOMOGRAPHY - IDENTIFICATION OF BETA-AMYLOID IN THE LIVING BRAIN: A CONSECUTIVE CLINICAL CASE SERIES

Effie Mitsis [1], Heidi Bender [2], Lale Kostakoglu [3], Josef Machac [3], Jane Martin [2], Jennifer Woehr [3], Martin Goldstein [2], Mary Sano[1], Sam Gandy [1]

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Introduction: Identification and quantification of beta-amyloid in brain using Amyvid™ (Florbetapir F 18) PET imaging was recently approved by the FDA as a clinical tool to estimate neuritic plaque density in patients being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline. Imaging with [^{18}F]Amyvid may increase the accuracy of the clinical diagnosis of AD and differentiate among individuals with AD vs. those without who have non-AD types of neurodegeneration.

Methods: A consecutive case series of 17 patients (age 60-89; 8M/9F) were evaluated clinically for cognitive problems and referred for [^{18}F]Amyvid PET imaging. Evaluation included neurological examination and neuropsychological assessment. Trained nuclear medicine physicians rated the scans as positive or negative for amyloid. Clinical diagnosis was made prior to scanning.

Results: Clinical diagnoses were: Four patients with frontotemporal dementia (FTD), two with behavioral variant and two with primary progressive aphasia (PPA). Amyvid scans were negative in patients with FTD+PPA but mixed between two patients with FTD, behavioral variant (one positive and the other negative). One patient was diagnosed with Parkinson's disease (PD) and AD (positive scan) and the other with PD+depression (negative scan). Four patients with MCI, amnestic and 3 with AD had positive scans. [^{18}F]Amyvid was negative in one patient with cognitive complaints and diagnosed with depression in the absence of neurodegenerative diagnosis. Two patients with normal cognition had negative scans. Another with multiple concussions, with memory and information processing impairment but preserved intellectual function and diagnosed with delayed post-traumatic cognitive impairment (DPTCI), had a negative scan.

Conclusions: In patients with AD or MCI, amnestic, [^{18}F]Amyvid imaging was positive and consistent with clinical diagnosis prior to scanning. In contrast, patients with PD, DPTCI, depression and normal cognition were negative indicating the value of [^{18}F]Amyvid in clinical discrimination.

Keywords: *[18F]Amyvid PET, Alzheimer's disease, Mild Cognitive Impairment, clinical*

Presented by: Mitsis, Effie

Poster 39

AGE-RELATED REDUCTIONS IN GRAY MATTER THICKNESS INTERACT WITH BIOMARKER STATUS TO INFLUENCE COGNITION IN AGING

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Massachusetts General Hospital

Objective*:* We investigated whether reduced gray matter thickness in clinically normal (CN) older individuals classified as biomarker negative for beta-amyloid, white matter hyperintensities (WMH) and APOE4 carrier status, is associated with cognition and/or interacts with biomarker status to influence cognition.

Methods*:* We studied 166 CN subjects from the Harvard Aging Brain study. All subjects completed PIB-PET, MRI, and neuropsychological testing. APOE genotyping was available on 98 subjects. Episodic memory and executive function factors scores were created using a confirmatory factor analysis. Subjects were classified as PIB+ or PIB- (cut off=1.15), as well as WMH+ or WMH- (cut off=4945mm^3). Subjects who were PIB-, WMH- and APOE4- were considered "biomarker-." Gray matter thickness maps were contrasted between biomarker- older subjects and a group of young subjects (N=75, age=22±4y). The average thickness value from this contrast mask was extracted and related to the cognitive factor scores in biomarker- and biomarker+ subjects.

Results*:* Compared to young, biomarker- old subjects showed widespread thickness reductions in frontal, primary motor, lateral inferior parietal, lateral temporal and posteromedial cortices. Thickness values from this contrast mask were correlated with age in both old and young groups (old: r=-0.27; young: r=-0.30). Within old subjects, thickness was associated with memory (r=0.15) and executive function (r=0.17). Importantly, biomarker status modified the relationship between thickness and cognition, such that a positive relationship between thickness and cognition was present only in biomarker+ subjects for both memory (biomarker+: r=0.44; biomarker-: r=-0.07) and executive function (biomarker+: r=0.45; biomarker-: r=-0.03).

Conclusion*:* Prominent age-related changes in gray matter thickness are present in the absence of positive biomarkers. Although age-related changes to gray matter may begin prior to evidence of neuropathological processes, these reductions may interact with pathological changes to determine an individual's vulnerability to cognitive decline in old age.

Keywords: *aging, beta-amyloid, white matter hyperintensities, APOE, gray matter thickness*

Presented by: Mormino, Elizabeth

Poster 40

THE COMPARATIVE EFFECT OF APOLIPOPROTEIN E4 GENOTYPE, AGE, AND COGNITIVE STATUS ON CORTICAL DISTRIBUTION OF BETA-AMYLOID NEURITIC PLAQUES

Kelly Ryan Murphy [1], Susan Landau [2], Haris Sair [3], Yekaterina Shpanskaya [1], Christopher Hostage [1], Kingshuk Roy Choudhury [1], Jeffrey Petrella [1], Terence Wong [1], P. Murali Doraiswamy [1]

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Objective: To determine the relative effect sizes of apolipoprotein E4 versus Alzheimer's disease on regional cortical neuritic plaque density across the elderly cognitive spectrum.

Methods: We studied florbetapir F18-PET uptake in 4 cortical regions (frontal, cingulate, parietal, temporal) in 602 subjects (194 normal controls (C), 212 early mild cognitive impairment (EMCI), 132 late MCI (LMCI), 64 Alzheimer's disease (AD) patients) enrolled in a national biomarker study. A multivariate model tested the relative contributions of diagnostic stage versus ApoE4 allele on amyloid status after adjusting for age and gender.

Results: The effect of diagnosis on amyloid levels was significant (AD > LMCI > EMCI >C) with the difference in effect size between AD and controls (Cohen's D 0.51, $p<0.0001$) being roughly twice as large as that between LMCI and controls (Cohen's 0.34, $p<0.0001$) and almost thrice as large as that between EMCI and controls. The effect of ApoE4 was approximately twice as large as the effect of AD stage (Cohen's D 0.96, $p<0.0001$). All four brain regions differed significantly from each other (C>F>P>T, $p<0.001$).

Interpretation: Across the cognitive spectrum of Aging to EMCI to LMCI to AD there is a proportional increase in beta-amyloid plaque density across four cortical regions. The ApoE4 allele has a much larger effect on beta-amyloid deposition across the spectrum of aging to AD than either age or a clinically determined diagnosis, suggesting ApoE4-driven effects on amyloid deposition precede cognitive and functional changes that contribute to diagnosis. These data support the use of biomarker driven disease staging and warrant studies of additional genetic determinants of beta-amyloid.

**Data used in preparation of this abstract were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). 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.*

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Keywords: *ApoE4, amyloid, florbetapir-PET, cognitive spectrum, cortical regions*

Presented by: Murphy, Kelly Ryan

Poster 41

RELATIONSHIPS BETWEEN AGE, BETA-AMYLOID, AND GLUCOSE METABOLISM

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Objectives: Although hypometabolism is commonly seen in aging and Alzheimer's disease (AD), the relationship between glucose metabolism and Aβ deposition in cognitively normal older adults remains unclear. In this study, we examined changes in glucose metabolism due to aging and Aβ deposition across healthy young people (Y), cognitively normal older adults (ON), and AD patients.

Methods: 110 subjects (9 Y, 81 ON, and 20 AD) underwent [^{11}C]PIB-PET, [^{18}F]FDG-PET and structural MRI scans. FreeSurfer-based parcellation was applied to MRI, FDG, and PIB data. ON subjects were categorized as PIB- or PIB+ based on averaged PIB DVR values across multiple cortical regions. We compared young and PIB-ON groups and PIB- and PIB+ON groups to assess aging- and Aβ-related changes in glucose metabolism in cortical and subcortical regions, respectively. In addition, among 40 cortical regions, we selected the top and bottom 10 regions reflecting highest and lowest glucose use in the Y group. These regions were used to examine the effects of aging and Aβ on relationships between glucose use and Aβ deposition.

Results: Aging-related hypometabolism was found in frontal, parietal, temporal, and anterior cingulate cortices while glucose metabolism in posterior cingulate, precuneus and subcortical regions was preserved. Aβ-related hypermetabolism was found in the right precuneus with no significant changes in metabolism in other regions related to Aβ. The pattern of glucose metabolism across cortical regions was the same in PIB+ and PIB- ON as in Y subjects. Brain regions that showed the highest metabolism were associated with higher Aβ deposition in PIB+ON (Figure).

Conclusion: Aβ-related changes in glucose metabolism in cognitively normal elderly seem to occur as hypermetabolism in brain regions that do not undergo aging-related hypometabolism. Furthermore, brain regions that start with higher baseline glucose metabolism early in life may relate to higher Aβ production and deposition during aging.

Keywords: *Aging, beta-amyloid, glucose metabolism, PET*

Presented by: Oh, Hwamee

Poster 42

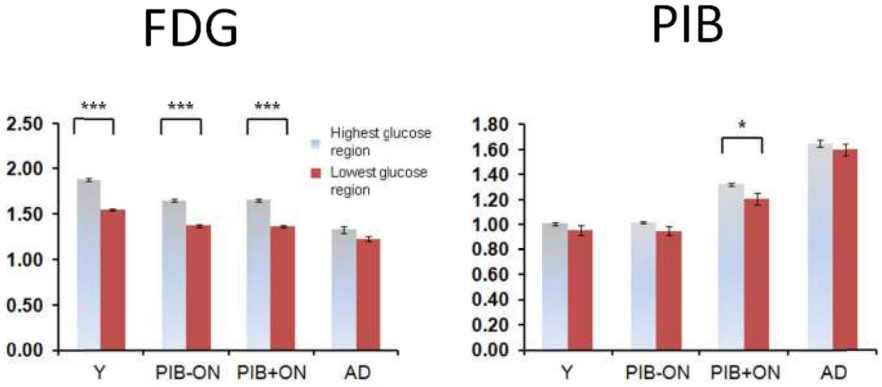

Figure. Regional variation in glucose metabolism (FDG) and Aβ deposition (PIB) across Y, PIB- ON, PIB+ ON, and AD in cortical regions with different baseline glucose use. Silver and red bars represent 10 cortical regions showing highest and lowest glucose metabolism determined in young adults, respectively.

[18F]THK-5105 AND [18F]THK-5117 AS POSSIBLE PET PROBES FOR IN VIVO DETECTION OF TAU PATHOLOGY IN ALZHEIMER'S DISEASE

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[2] *Division of Radiopharmaceutical Chemistry, CYRIC, Tohoku University*
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Objectives: Noninvasive imaging of tau protein deposits in the brain will provide useful information regarding tau pathophysiology in Alzheimer's disease (AD). However, no positron emission tomography (PET) probes are currently available for in vivo detection of tau pathology in AD. We have reported [^{18}F]THK-523 as a candidate of tau-imaging radiotracer. Following compound optimization, we developed novel ^{18}F-labeled arylquinoline derivatives, [^{18}F]THK-5105 and [^{18}F]THK-5117. In this study, binding, pharmacokinetic and safety properties of these compounds were assessed as potential PET tau-imaging probes.

Methods: ^{18}F-labeled compounds were prepared from the corresponding tosylated precursors. Binding affinity of compounds to synthetic tau aggregates and tau-rich AD brain homogenates was determined by saturation and competition binding assays. Binding selectivity of compounds to tau pathology was evaluated by autoradiographic analyses of AD brain sections. Pharmacokinetics of THK compounds was assessed in biodistribution studies in normal mice. A 14-day toxicity study with intravenous administration of THK compounds was performed using SD rats and ICR mice.

Results: In vitro binding assays demonstrated higher binding affinity of THK-5105 and THK-5117 to tau protein aggregates and AD brain homogenates (Kd < 10 nM) than THK-523. In autoradiographic images of postmortem AD brain sections, the distributions of [^{18}F]THK-5105 and [^{18}F]THK-5117 coincided with Gallyas-Braak staining and tau immunostaining, but not with the distribution of [^{11}C]PiB and Aβ immunostaining. After intravenous administration, these compounds demonstrated abundant initial brain uptake (> 6 %ID/g) and short brain clearance half-life in normal mice. Furthermore, a single intravenous administration of these compounds at 1 mg/kg caused no systemic toxicity in rats or mice.

Conclusions: [^{18}F]THK-5105 and [^{18}F]THK-5117 are considered as promising candidates for PET tau-imaging radiotracers. Future clinical studies will clarify the usefulness of these radiotracers for the early detection of tau pathology in AD patients.

Keywords: *Alzheimer's disease, Tau, Positron emission tomography, Neurofibrillary tangles*

Presented by: Okamura, Nobuyuki

Poster 43

IS VERBAL EPISODIC MEMORY IN ELDERLY WITH AMYLOID DEPOSITS PRESERVED THROUGH ALTERED NEURONAL FUNCTION?

Rik Ossenkoppele [1], Cindee Madison [2], Hwamee Oh [2], Miranka Wirth [2], Bart van Berckel [3], William Jagust [2]

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Introduction: The mechanisms that enable intellectual preservation in elderly with cerebral amyloid pathology are not yet fully understood. In the present study we explored the inter-relationships between amyloid deposition, glucose metabolism and cognitive performance in 81 cognitively normal elderly (mean age: 75±5, MMSE: 29±1).

Methods: Subjects were divided into low-amyloid (n=53), intermediate-amyloid (n=13) and high-amyloid (n=15) groups as defined by their [11C]PIB status. To assess glucose metabolism, pons normalized standardized uptake value ratios of [18F]FDG images were extracted for the posterior cingulate and bilateral angular and inferior temporal gyri (MetaROI regions). Previously validated factor scores for verbal and visual episodic memory, semantic memory, working memory and executive functioning were used to evaluate cognitive performance.

Results: Linear regression analysis, adjusted for age, education and APOE, showed an association between precuneus [11C]PIB retention and composite MetaROI [18F]FDG uptake at trend level that became significant after additional adjustment for cortical gray matter volume. Precuneus [11C]PIB was negatively correlated with visual episodic memory, but this finding did not survive adjustment for age, education and APOE genotype. Across all subjects, composite and regional [18F]FDG uptake were not associated with cognitive performance. Within the intermediate-amyloid group, however, verbal episodic memory correlated positively with composite and left and right angular gyrus [18F]FDG uptake.

Discussion: There are at least two mechanisms that may account for increased glucose metabolism in elderly with elevated [11C]PIB retention. First, it may reflect compensatory activation of the brain to counteract neurotoxic effects of amyloid-beta. Second, there is evidence that synaptic activity increases the deposition of amyloid pathology. The positive association between verbal episodic memory performance and metabolic activity in subjects with elevated amyloid levels seems in favor of the "compensation hypothesis". Altogether, these findings suggest that asymptomatic elderly with cerebral amyloidosis are, at least temporarily, able to preserve cognitive function through altered neuronal function.

Keywords: *PIB, FDG, PET, cognition, aging*

Presented by: Ossenkoppele, Rik

Poster 44

AMYLOID ACCUMULATION AND NEURODEGENERATION IN A RAT MODEL OF ALZHEIMER'S DISEASE

Maxime Parent [1], Sonia Do Carmo [2], Antonio Aliaga [3], Jean-Paul Soucy [3], Serge Gauthier [1], Claudio Cuello [2], Pedro Rosa-Neto [1]

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Neurodegeneration following amyloidosis may take several years to evolve. Animal imaging models of brain amyloidosis are needed to understand the role of amyloid progression and amyloid-induced neurodegeneration in Alzheimer's Disease (AD). The McGill-R-Thy1-APP rat is a transgenic rat carrier of Swedish and Indiana mutations, and has shown accumulation of amyloid plaques as well as behavioral deficits. We aim to study the impact of brain amyloidosis on synaptic function and neurodegeneration of McGill-R-Thy1-APP rat. We predicted decline of [^{18}F]FDG uptake co-existing with [^{11}C]PiB retention in aged transgenic rats, analogous to human AD.

A total of ten 18 months-old rats (5 TG, 5 controls) were scanned using Positron Emission Tomography (PET) with [^{11}C]PiB and [^{18}F]FDG. Outcome measures were BP_{ND} for [^{11}C]PiB and SUVr for [^{18}F]FDG.

TG rats had lower [^{18}F]FDG SUVr across the entire frontal cortex and olfactory bulb, with an average reduction of 12.3% [t(8) = 5.06, p = 0.001)] (fig. 1a). Increased [^{11}C]PiB BP_{ND} was observed in the thalamus, hippocampus and anterior cingulate (ACC), with average binding higher by 10.5% [t(8) = 4.25, p = 0.003)] (fig. 1b). Additionally, the presence of amyloid in the ACC strongly predicts [^{18}F]FDG reduction in the ACC itself as well as throughout the ventral cortical areas, with a peak R^2 of 0.91 ($p < 0.001$) (fig. 2a). [^{18}F]FDG connectivity between ACC and striatum is reduced by 55.8% in TG animals (fig. 2b).

In conclusion, the McGill-R-Thy1-APP rat appears to have both amyloidosis and neurodegeneration at the levels of synaptic function and large-scale networks, similar to what can be found in human pathology.

Figure 1

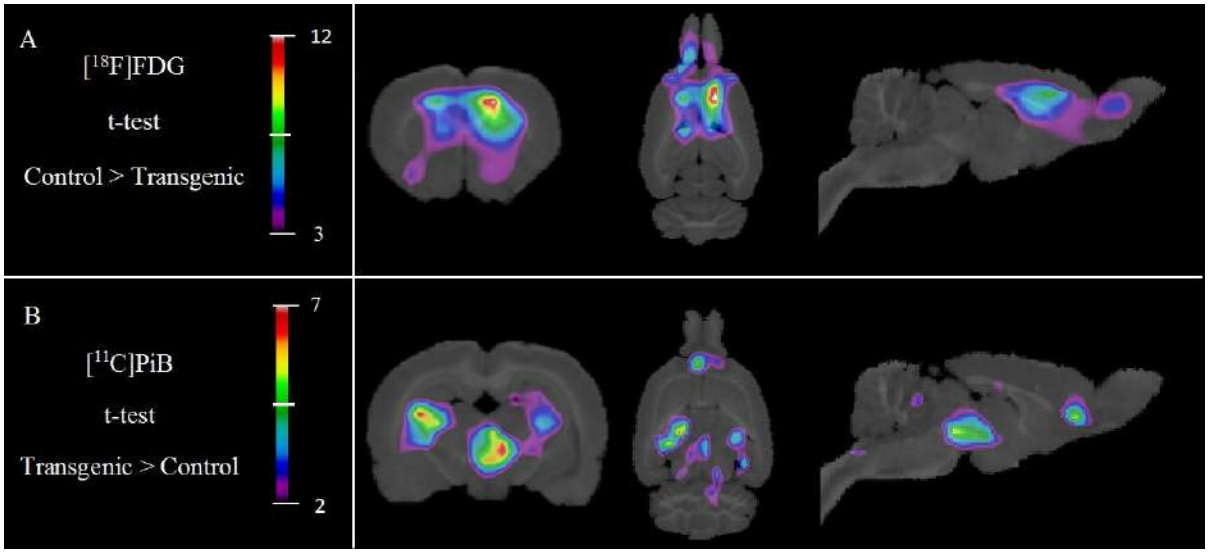
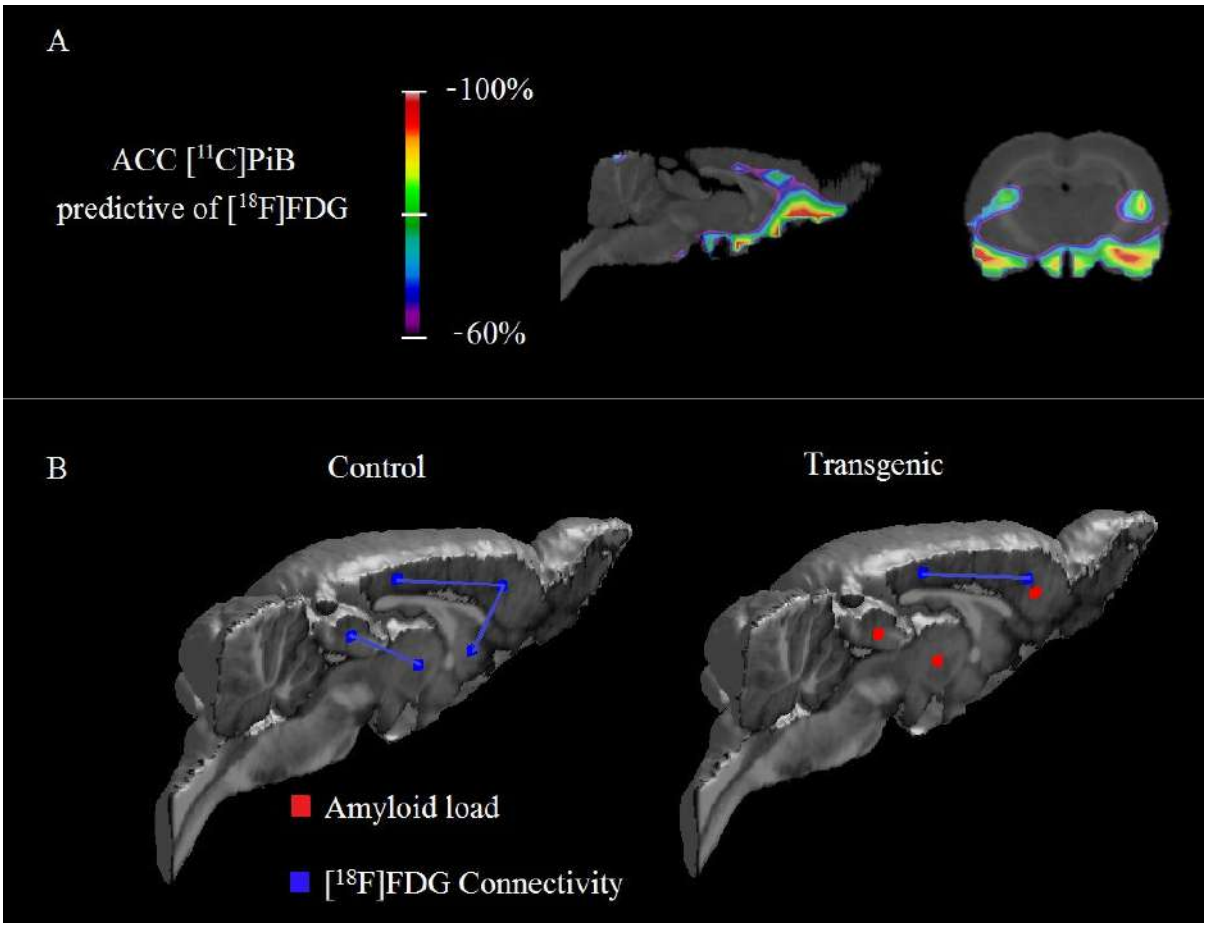


Figure 2



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Keywords: *Rat model, PET, neurodegeneration, connectivity,*

Presented by: Parent, Maxime

Poster 45

AGE, EDUCATION AND AMYLOID DEPOSITION: CONFIRMATION OF COGNITIVE RESERVE

Denise Park [1], Gerard Bischof [1], Kristen Kennedy [1], Karen Rodrigue [1], Michael Devous, Sr. [2]

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The concept of cognitive reserve suggests that there is a pool of neural resources that protects against age-related cognitive decline. In support of this notion, recent studies have suggested that a high level of education confers some protection from cognitive decline and Alzheimer's disease, and may blunt the impact of amyloid deposition on behavior (Rentz et al., 2010). To test this hypothesis, we added a second sample of adults to the Dallas Lifespan Brain study who were less educated than the initial sample. We focused on adults in our healthy aging sample aged 50-79 from whom we collected PET data using F-18 Florbetapir (Amyvid). We compared total SUVR in adults with 14 years of education or less (n = 84) to SUVR levels in those who had a Master's degree or greater (n = 41) . (We excluded subjects from the contrast who had a Bachelor's degree (n=46). We found that there was a main effect of education, with higher educated adults showing significantly higher amyloid levels ($p < .05$), confirming the hypothesis that highly-educated adults can better withstand the impact of amyloid deposition on their cognition, and maintain sufficiently high levels of cognitive health to qualify for a healthy aging study. Moreover, we report an Age x Education interaction ($p = .04$) that occurred because there was a steeper increase in amyloid in more highly-educated adults across age ($r = .44$, $p < .01$) compared to lower-educated adults ($r = .21$, $p < .05$). This finding suggests that adults with lower education who accrue amyloid tend to "age out" of a healthy aging study at earlier ages. Our results provide strong evidence that education is protective of cognition as amyloid deposition increases.

Keywords: *cognitive reserve, amyloid deposition, healthy aging, normal aging, education*

Presented by: Park, Denise

Poster 46

SERUM LIPIDS AND CEREBRAL AMYLOID IN PERSONS WITH HIGH VASCULAR RISK

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[2] *University of California, Berkeley*
[3] *University of Southern California*

Background: Cholesterol is involved in the generation, transport, and deposition of beta amyloid (Aβ). There is limited evidence that lipid profiles that elevate cardiac risk are associated with lower CSF Aβ and memory dysfunction. We investigated whether or not there is an association between serum lipids and Aβ deposition.

Methods: Participants were 66 persons from the Aging Brain study, a cohort enriched for vascular risk; 31 had Clinical Dementia Rating Scale (CDR) scores of 0 (normal), 32 scored 0.5, and 3 scored 1 (demented). Mean age was 78. Fasting HDL, LDL cholesterol, and triglycerides were assayed. Cerebral Aβ was measured using PIB PET quantified with a global brain DVR (90 min, cerebellar reference) PIB index; 31 cases were PIB positive.

Results: Mean total cholesterol was 174 and the mean HDL/LDL ratio was .65; 72% of cases were on cholesterol lowering drugs. In a multiple regression covarying age, sex, and E4 status both HDL and LDL cholesterol were associated with PIB index. Lower HDL ($p = .023$) and higher LDL ($p = .043$) were independently associated with higher PIB. E4 independently elevated PIB ($p = .03$). Covarying CDR did not alter the results, nor did co-varying anti-cholesterol drug treatment. Neither triglycerides nor total cholesterol were associated with PIB.

Comment: In this small, "vascular" sample HDL and LDL cholesterol levels show the same pattern of association with Aβ levels as they do with cardiac risk. However, the cohort's mean lipid profile falls within "desirable" levels with regard to cardiac health. We previously reported increased Aβ is not associated with infarcts/WML and therefore hypothesize that cholesterol fractions alter Aβ production or clearance. The regulation of cholesterol and the processing of APP are lifelong processes; animal work suggests that the timing of cholesterol manipulations may be critical in terms of its consequences for Aβ deposition.

Keywords: *cholesterol, vascular risk factors, preclinical Alzheimer's disease*

Presented by: Reed, Bruce

Poster 47

COGNITION, AMYLOID BURDEN AND GLUCOSE METABOLISM IN NORMAL AGING

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Background: We have previously reported that cognitively normal (CN) older individuals with higher levels of amyloid-beta deposition demonstrate worse memory performance on challenging tests of episodic memory. (Rentz 2010)

Objective: To test whether highly sensitive cognitive measures in CN subjects relate independently to both ^{18}F-flourodeoxyglucose (FDG) metabolism and Pittsburgh Compound B (PiB) retention.

Methods: CN subjects (N=129), ages 65 to 87 (mean age=73.7 ± 5.9; MMSE=29.1±0.9; CDR=0) underwent cognitive testing that covered the realms of attention, executive function, memory, language and visuospatial processing, Education was utilized as a proxy for cognitive reserve. Factor scores for episodic memory (EM) and executive function (EF) were created from a confirmatory factor analysis (Hedden 2012). PiB retention and FDG metabolism were measured in a cortical aggregate of supramarginal and angular gyri and precuneus.

Results: Regression models controlling for age, education and brain atrophy revealed that EM was inversely related to PiB (Beta=-0.654, p=0.043) and directly related to FDG (Beta=2.167, p=0.032). EF was significantly related to FDG (Beta=1.993, p=0.026) but not to PiB. PiB and FDG were uncorrelated (r=-0.04); however, the main effect of FDG predicting education was significant, adjusting for age, memory score, and PiB status (positive/negative)(R^2=0.238, p< 0^-5). Interestingly, the FDG-education association was significantly modified by PiB status (p=0.001), with a positive relationship between FDG and education in PiB- subjects (Beta = 0.007, p=0.013) but a negative relationship in PiB+ subjects (Beta = -0.008, p=0.01), i.e., amyloid-positive subjects with higher reserve demonstrated lower glucose metabolism for a given level of cognitive performance.

Conclusions: These findings suggest that in clinically normal older adults: 1) amyloid-beta deposition and FDG metabolism independently predict EM performance, 2), FDG metabolism but not amyloid-beta deposition contributes to EF performance, and 3) at higher levels of cognitive reserve, normal cognition may be maintained despite increased amyloid-beta deposition and lower FDG metabolism.

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Keywords: *normal aging, PIB deposition, preclinical AD, FDG metabolism, cognitive reserve*

Presented by: Rentz, Dorene

Poster 48

CORTICAL 11C-PIB UPTAKE IS ASSOCIATED WITH AGE, APOE GENOTYPE AND GENDER IN "HEALTHY AGING"

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Aims: We investigated which specific attributes contribute to a seemingly healthy elderly populations' brain beta-amyloid accumulation.

Methods: A cross-sectional ^{11}C-PIB PET study in 64 cognitively healthy subjects of different ages (54-89 years) was conducted. They underwent PET, MRI, neuropsychological testing and apoE genotyping. The explored factors' effects on ^{11}C-PIB uptake and the factors' possible interactions were assessed with a statistical general linear model and with Statistical Parametric Mapping (SPM).

Results: The effects of age (p=0.000), apoE epsilon 4 carrier status (p=0.003) and sex (p=0.001) on composite cortical ^{11}C-PIB uptake were all significant. The effect of educational level was non-significant. No significant interactions between the studied factors were found. Cortical ^{11}C-PIB uptake increased by 1.1%, on average, with every year of age. ApoE epsilon 4 positive subjects had higher ^{11}C-PIB uptake than apoE epsilon 4 negative subjects (unadjusted means 1.49±0.34 *vs.* 1.29±0.26) and males had higher uptake than females (1.49±0.39 *vs.* 1.29±0.22). The results of the voxel-based analysis were similar. A *post hoc* SPM analysis revealed that lower total CERAD was associated with higher ^{11}C-PIB uptake in the frontal cortex. In contrast, no association between CERAD score and composite cortical ^{11}C-PIB uptake was found.

Conclusions: Age and apoE epsilon 4 genotype are known independent risk factors for cortical beta-amyloid accumulation –this was reflected in ^{11}C-PIB uptake in the present study. In our cognitively healthy subject population, men exhibited higher cortical^{11}C-PIB uptake than women. This was not explained by a possible cognitive reserve effect brought by education. This difference in^{11}C-PIB uptake between healthy elderly men and women has not been demonstrated to date, and the finding's explanations and implications deserve further investigation. The possible association between neuropsychological test scores and regional ^{11}C-PIB uptake in the cognitively healthy also warrants attention.

Keywords: *11C-PIB, healthy aging, risk factor, apoE, gender*

Presented by: Rinne, Juha O

Poster 49

MICROPET IMAGING OF TIME COURSES OF ASTROCYTOSIS AND AMYLOID DEPOSITION IN ALZHEIMER TG2576 APPSWE TRANSGENIC MICE

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There is increasing evidence for a tight linkage between neuroinflammation and neurodegeneration in Alzheimer's disease (AD). We recently reported increased astrocytosis in MCI patients as an early phenomenon in AD in a multi-tracer PET study (Carter *et al*., 2012). PET studies in familial AD (FAD) indicate that pathological changes start decades before cognitive symptoms. Transgenic mice harboring the same mutations as FAD patients can be considered as models of asymptomatic AD, allowing access to the earliest pathological changes. We hypothesize that astrocytosis is an early event of AD, temporally preceding amyloid-beta deposition. To test this hypothesis, we applied multi-tracer *in vivo* microPET imaging in an APPswe transgenic mouse model of AD (Tg2576).

MicroPET imaging was conducted using a Mediso nanoScan® PET/MRI system. Tg2576 mice were divided into three age groups (6, 10-15 and 20-23 months) with n=4 animals per group. Wild-type (wt) mice (8-month-old) served as control (n=2). The average mice weight was 27.6±5.6 g. Mice were anesthesized (isofluorane) and administered tail venous injections of ^{11}C-AZD2184 (10.0±2.1 MBq), ^{11}C-PIB (9.9±0.2 MBq) or ^{11}C-deuterium-L-deprenyl (^{11}C-DED) (9.7±1.7 MBq) tracers. Tracer uptake was obtained by Region-of-Interest (ROI) analysis using PMOD software and a 3D digital mouse brain atlas, by 20-40 min integration of time-activity curves for each ROI. Higher ^{11}C-PIB, ^{11}C-AZD2184 and ^{11}C-DED were observed in Tg2576 mice brains compared to wt. The ^{11}C-DED binding in Tg2576 mice was elevated as early as 6-month, suggesting astrocytosis being an early event. In addition, *in vitro* binding assays, autoradiography using ^{3}H-PIB/AZD2184, ^{3}H-L-deprenyl, and immunostaining were performed for amyloid-beta and activated astrocytes.

Translational *in vivo* molecular imaging studies in AD transgenic mice with varying degrees of brain pathology and correlative postmortem studies may offer insight into the interactive mechanisms between amyloid-beta and inflammatory processes during disease progression and aid in testing future disease-modifying drugs for AD.

References

Carter et al. (2012), "Evidence for astrocytosis in prodromal Alzheimer disease provided by 11C-deuterium-L-deprenyl: a multitracer PET paradigm combining 11C-Pittsburgh compound B and 18F-FDG", Journal of Nuclear Medicine 53, 37-46

Keywords: *astrocytosis, microPET, mice, APPswe, neuroinflammation*

Presented by: Rodriguez-Vieitez, Elena

Poster 50

PET IMAGING OF ASTROCYTOSIS AS AN EARLY BIOMARKER IN AD: BLOOD FLOW ANALYSIS IN A MULTI-TRACER PET STUDY

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Neuroinflammation is potentially an early phenomenon leading to AD neurodegeneration. We recently reported (Carter *et al.*, 2012) that the PET tracer ^{11}C-deuterium-L-deprenyl (^{11}C-DED), which binds to monoamine oxidase B (MAO-B) located in reactive astrocytes, showed increased binding in mild cognitive impairment (MCI) patients with high fibrillar amyloid in their brains, compared to AD and MCI patients with low amyloid. Since CBF is impaired in AD, it is important to investigate how ^{11}C-DED binding might be dependent on CBF.

Objectives: To investigate the relationship between astrocytosis, fibrillar amyloid deposition, glucose metabolism and CBF, specifically: (1) the contribution of CBF to ^{11}C-DED binding; (2) investigating ^{11}C-DED as a dual pathological (inflammation) and physiological (blood flow) biomarker.

Methods: ^{11}C-DED, ^{11}C-PIB and ^{18}F-FDG PET (211±66, 228±70, 229±49 MBq doses) were performed in 11 MCI (62.4±6.2 yr) and 7 AD patients (64.4±6.0 yr). A modified reference Patlak model was applied to ^{11}C-DED. Mean target-to-cerebellum regional values were obtained for ^{11}C-PIB and ^{18}F-FDG.

Results: An optimum 1-4 min early time frame of ^{11}C-DED and ^{11}C-PIB showed the highest correlation with late ^{18}F-FDG uptake (30-45 min) and thus constituted a reliable measure of CBF. After controlling for CBF (as measured by either early ^{11}C-DED or ^{11}C-PIB), astrocytosis remained elevated in MCI-PIB-positive compared to AD or MCI-PIB-negative groups.

Conclusions: The dual pathological/physiological biomarker use of ^{11}C-DED offers potential clinical use since it could provide information on both CBF changes and astrocytosis, and may be useful as an early diagnostic biomarker in AD.

References

Carter et al. (2012), "Evidence for astrocytosis in prodromal Alzheimer disease provided by 11C-deuterium-L-deprenyl: a multitracer PET paradigm combining 11C-Pittsburgh compound B and 18F-FDG", Journal of Nuclear Medicine 53, 37-46

Keywords: *neuroinflammation, astrocytosis, biomarker, CBF*

Presented by: Rodriguez-Vieitez, Elena

Poster 51

VISUAL AND SEMIQUANTITATIVE VALIDATION OF EARLY AND LATE IMAGING APPROACHES USING 18F-NAV4694

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Background: The recently developed F-18 labelled amyloid radiotracer, ^{18}F-NAV4694 (formerly AZD4694) displays very similar characteristics to ^{11}C-PiB, with fast brain kinetics, high binding to cortical amyloid and low white matter retention. The purpose of this study was to compare and validate early and late ^{18}F-NAV4694 imaging protocols using both visual and semiquantitative approaches.

Methods: Forty-five participants (25 healthy elderly controls, 10 subjects with mild cognitive impairment, and 10 dementia patients) underwent 70 min dynamic PET imaging with ^{18}F-NAV4694. Specific binding (SB) and tissue ratio (SUVR) time activity curves were generated using the cerebellar cortex as reference region. Images of early (20-30 min) and late (40-60 min) were visually rated by three blinded readers. In order to compare the ability of early and late imaging approaches to distinguish healthy from Alzheimer's disease (AD) patients, their respective effect sizes were compared.

Results: In the visual readouts, late imaging provided higher inter-rater reliability (Fleiss' kappa 0.90 vs. 0.87, respectively) and much greater reader confidence (0.93 vs. 0.63, respectively) than early imaging. Similarly, larger effect sizes were obtained from late imaging SB (d=2.6 vs. d=2.1, respectively) and SUVR (d=3.2 vs. d=2.0, respectively) than the same values from early imaging.

Conclusions: Tissue ratios provide better discrimination between healthy controls and AD patients than measures of specific binding. Late scanning (40-60 min) with ^{18}F-NAV4694 also provides higher reader confidence in the visual readouts than early scanning.

Keywords: *Amyloid imaging, Alzheimer's disease, positron emission tomography*

Presented by: Rowe, Christopher C

Poster 52

ABETA(42) INDUCED MRI CHANGES IN AGED RABBIT BRAIN RESEMBLES AD BRAIN

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Alzheimer's disease is the most common form of dementia and is structurally characterized by brain atrophy and loss of brain volume. Aβ is one of the widely accepted causative factor of AD and is known to initiate the early cascade in AD. Aβ deposition is positively correlated with brain atrophy in AD. In the present study, structural brain imaging techniques such as Magnetic Resonance Imaging (MRI) were used to measure neuroanatomical alterations in Alzheimer's disease brain. MRI is a non-invasive method to study brain structure. The objective of the present study was to elucidate the role of Aβ on brain structure in the aged rabbit brain. Among 20 aged rabbits, one batch (n=10) rabbits was injected chronically with Aβ(1-42) and another batch (n=10) with saline. The MRI was conducted before Aβ(1-42)/ saline injection and after 45 days of Aβ(1-42)/ saline injection. All the aged rabbits underwent MRI analysis and were euthanized after 45 days. The MRI results showed a significant reduction in thickness of frontal lobe, hippocampus, midbrain, temporal lobe and increases in the lateral ventricle volume. We also conducted an MRI study on AD (n=10) and normal (n=10) cases and analyzed for the thicknesses of frontal lobe, hippocampus, midbrain, temporal lobe and lateral ventricle lobe. We found significant reductions in thickness of the frontal lobe and the hippocampus. However, no significant reduction in the thickness of midbrain, temporal lobe or increase in the lateral ventricle volume was observed compared to normal. Correlations in brain atrophy changes between rabbit brain and human AD brain were found for frontal lobe and hippocampal regions. In contrast, other regions such as midbrain, temporal lobe, and lateral ventricles were not correlated with rabbit brain atrophy changes in the corresponding regions. The relevance of these changes in AD is discussed

Keywords: *Abeta(42), MRI changes, Atrophy, Aged rabbit brain, AD brain*

Presented by: Sambasiva Rao, Krothapalli Raja Surya

Poster 53

BRAIN FIBRILLAR AMYLOID BURDEN IN MILD TO MODERATE AD SUBJECTS ENROLLED IN PET SUBSTUDIES OF BAPINEUZUMAB PHASE 3 TRIALS: POTENTIAL FACTORS AFFECTING BASELINE SIGNAL AND LONGITUDINAL CHANGE

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Introduction: Amyloid burden assessed by PET is a recognized biomarker supporting the diagnosis of mild-moderate AD, and is being used in interventional trials. Understanding the contribution of biological factors such as APOE E4 allele carrier status and methodological factors to amyloid PET signal is essential for optimal use of PET imaging in clinical trials.

Objectives: To characterize amyloid burden using ^{11}C-PiB PET at baseline longitudinally in the placebo arm of phase 3 bapineuzumab trials and examine the effect of different factors.

Methods: Bapineuzumab, an anti-amyloid-beta monoclonal antibody, was evaluated in separate phase 3 trials for APOE E4 allele carriers and non-carriers with mild-moderate AD. A subset of subjects participated in PET substudies. ^{11}C-PiB PET was performed at baseline and at 45 and 71 weeks of treatment at 14 US PET centers using ADNI protocols and QC criteria. For each scan a cortical average SUVr was determined from 5 regions known to accumulate substantial fibrillar amyloid. Regions of interest were defined in native PET space using the AAL atlas warped onto the subject's baseline 3DT1 MRI (intersected with a grey matter probability map), normalized to a cerebellar grey matter region truncated inferiorly.

Data were analyzed for 123 APOE E4 carriers and 61 non-carriers with a baseline scan and 46 APOE E4 carriers and 26 non-carriers who received placebo and had ≥ 1 post-baseline scan.

Results: Demographics and clinical characteristics were similar between APOE E4 carriers and non-carriers. Baseline amyloid burden was higher in carriers than non-carriers, and a higher frequency of very low SUVr was observed in non-carriers. Analysis of APOE E4 allele dose effect and potentially confounding clinical and/or methodological factors will be presented.

Conclusion: APOE E4 carrier status affects baseline and longitudinal PiB signal and must be considered in conducting interventional trials using amyloid PET.

Keywords: *Apolipoprotein, E4 allele, longitudinal change in brain amyloid,*

Presented by: Schmidt, Mark

Poster 54

CHANGES IN BRAIN GLUCOSE METABOLISM PREDICT COGNITIVE DECLINE AND AMYLOID BURDEN AT FOUR YEAR FOLLOW-UP

David Scott [1], Gregory Klein [1], Vahan Sharoyan [1], Joonmi Oh [1], Susan Landau [2], Jeff Sevigny [3], Ping-Chun Chiao [3], Joyce Suhy [1]

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PET imaging allows the *in vivo* examination of neurobiological processes thought to impact the onset and progression of Alzheimer's Disease. In the brain, hypometabolism and beta-amyloid deposition are each thought to be associated with cognitive decline and conversion to AD, though amyloid burden may precede both cognitive decline and metabolic changes. We sought to examine whether change in glucose metabolism over one year (measured by FDG-PET) was predictive of amyloid deposition (measured by florbetapir) at four year follow-up. We identified 82 subjects (33 normal, 49 with mild cognitive impairment) who underwent PET scanning with both FDG and florbetapir as part of the Alzheimer's Disease Neuroimaging Intiative (ADNI). After a baseline FDG-PET scan, all subjects underwent another FDG-PET scan at one year follow-up; florbetapir scanning occurred at least four years after baseline. Composite scores for spatially normalized images of FDG-PET and florbetapir binding were computed by comparing uptake within a template-space MRI mask of cortical regions-of-interest against uptake within the cerebellum. Across all subjects, the change in FDG-PET composite score from baseline to one year follow-up was significantly negatively correlated with florbetapir binding at four year follow-up ($r = -0.37$, $t = -3.6$, two-tailed $p = 0.0006$). The one year change in FDG-PET composite score was also significantly predictive of whether a subject's diagnosis would convert from normal to MCI, or from MCI to AD, at four year follow-up ($t = 2.1$, two-tailed $p < 0.05$). Changes in metabolism are thus associated with the progression of AD symptomatology and pathology, and may serve as a useful predictor of cognitive decline and amyloid deposition.

Keywords: *imaging, PET, florbetapir, metabolism, cognition*

Presented by: Scott, David

Poster 55

HIPPOCAMPAL SUBFIELD VOLUME LOSS IN COGNITIVELY NORMAL PARTICIPANTS CORRELATES WITH AMYLOID BINDING

Yvette Sheline [1], Daniel Marcus [1], Bruce Fischl [2], Koen Van Leemput [2], Tammie Benzinger [1], John Morris [1]

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Background: With the recent development and validation of hippocampus subfield segmentation it is possible to reliably analyze changes across populations and to correlate these differences with other biomarkers. Increased cortical amyloid binding is among the earliest changes in preclinical AD, preceding overall hippocampal atrophy. In this investigation we sought to determine hippocampal subfield volume loss correlation with mean amyloid cortical binding potential (MCBP).

Method: Cognitively normal participants with the clinical dementia rating (CDR) scale = 0 (n = 74; 52 females (70%)) were assessed at the Washington University ADRC. MRI was perfomed on a 3T Siemens Trio; Hippocampal subfield segmentation used the Freesurfer pipeline (Martinos http://surfer.nmr.mgh.harvard.edu/) yielding 7 hippocampus segments: CA1, CA2-3, CA4-DG, subiculum, presubiculum, fimbria and hippocampal fissure. Amyloid –β PET imaging was conducted following injection of approximately 12 mCi of [^{11}C] PIB and 60 min dynamic PET scan in 3D mode (septa retracted). Mean cortical binding potential (MCBP) was determined as previously described.

Results: Participants were divided into PIB+ (MCBP $\geq$ 0.18) vs PIB- MCBP < 0.18). PIB+ participants had significantly smaller volumes in: presubiculum (10.5%, p = 0.008), subiculum (10.2%, p = 0.005) and CA4/dentate gyrus (6.7%, p = 0.04). Pearson correlation between MCBP and hippocampal subvolumes were: CA1 r = -.25 (p = .03); CA2-3 r = -0.27 (p = 0.02); CA4 (DG) r = -0.30 (p = 0.009); presubiculum r = -0.28 (p = 0.01); subiculum r = -0.36 (p = 0.002).

Conclusions: In this healthy cognitively normal population there were volume decreases in presubiculum, subiculum and dentate gyrus (CA4). However, there were correlations with amyloid binding across most hippocampal subregions, suggesting that observed volumetric changes are correlated with overall brain amyloid burden. In further analyses correlation with neuropsychological test scores will determine if there is an effect on cognitive performance.

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Keywords: *amyloid, hippocampus, segmentation, preclinical dementia*

Presented by: Sheline, Yvette

Poster 56

EFFECTIVENESS OF AN ELECTRONIC TRAINING PROGRAM TO TEACH INTERPRETATION OF [18F]FLUTEMETAMOL PET AMYLOID IMAGES

Paul Sherwin, Jan Wolber, Fred Longenecker, Paula Clark, Adrian Smith, Francois Nicolas, Gillian Farrar, Brian Heath, Sharon Weick, Christopher Buckley

GE Healthcare

As an alternative to in-person training, we developed and evaluated the effectiveness of an electronic training program (ETP) to teach interpretation of [^{18}F]flutemetamol PET images for brain amyloid density. From 9 prior [^{18}F]flutemetamol studies, 276 [^{18}F]flutemetamol image sets were selected (either all or a random sample, depending on study), and 29 (~10%) were randomly selected and duplicated (to assess intra-reader reproducibility), for a total of 305 sets. Five nuclear medicine technologists inexperienced in amyloid imaging trained with the ETP in image orientation and each independently checked (and corrected as needed) the orientation of 1/5 of the images. Five physician readers (3 nuclear medicine physicians, 2 radiologists) inexperienced in amyloid imaging independently trained with the ETP, then interpreted all 305 image sets blinded to patient information (forced choice between *normal* or *abnormal* for brain amyloid). Where confirmation of brain amyloid status was available (n = 135), image interpretations were classified as true/false positives/negatives. The study met the two predefined success criteria (i.e., the null hypotheses were rejected): 1) that the lower bounds of the 95% confidence intervals (CI) for sensitivity and specificity would both exceed 70% for each of at least 3 of the 5 readers; 2) that the lower bound of the 95% CI for kappa would exceed 0.6. The majority read values for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for brain amyloid were 94%, 92%, 87%, and 96% respectively. Inter-reader agreement was 81% (kappa 0.83). Intra-reader reproducibility was 93% to 100%. PET images with available CT/MRI images (to assist in identifying atrophy) were re-randomized and evaluated separately; anatomic images were helpful in some cases but overall results were not significantly different. In conclusion, the ETP was highly effective in training inexperienced readers to read [^{18}F]flutemetamol PET amyloid images with high accuracy and reproducibility.

Keywords: *Flutemetamol, PET, amyloid, sensitivity, specificity*

Presented by: Sherwin, Paul

Poster 57

REGIONAL DISTRIBUTION OF AMYLOID-BETA AND RELATED MOLECULES IN NON-DEMENTED INDIVIDUALS

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Objective: To reveal the underlying mechanisms responsible for the regional vulnerability to amyloid-beta (Abeta) accumulation prior to the development of Alzheimer's disease, we studied distribution of Abeta, apolipoprotein E (apoE), synaptic markers and other molecules involved in Abeta metabolism in multiple brain areas of non-demented individuals.

Methods: Twelve brain regions including neocortical, limbic and subcortical areas were dissected from brains of non-demented individuals (n = 27, age = 89.7 ± 9.4 years) and extracted according to increasing insolubility by a sequential three-step method (TBS, Triton-X and guanidine). The levels of Abeta40, Abeta42, apoE, APP-CTFbeta, presenilin-1, neprilysin, insulysin, LRP1, LDLR, synaptophysin, PSD95, GFAP and lactate were determined by ELISAs or enzymatic assays.

Results: The regional distribution of apoE showed moderate-to-strong inverse correlation with Abeta levels, especially in Triton-X and guanidine fractions ($r = -0.8811$; $p = 0.0002$; Spearman test). On the other hand, the regional distributions of synaptic markers, particularly PSD95, showed moderate-to-strong positive correlation with Abeta levels, especially in TBS fraction ($r = -0.8951$; $p < 0.0001$). The regional correlations between Abeta and LRP1, GFAP or lactate were mild-to-moderate. Moderate-to-strong positive regional correlations were observed between apoE and GFAP or lactate and between PSD95 and LRP1. No significant positive regional correlations were detected between Abeta and APP-CTFbeta or presenilin-1, both involved in Abeta production. There were no significant negative regional correlations between Abeta and two major Abeta degrading enzymes, neprilysin and insulysin. These regional correlations remained consistent throughout individuals with different degree of Abeta accumulation or cognitive status.

Conclusion: The regional vulnerability to Abeta accumulation prior to the development of Alzheimer's disease may be due to net balance between two competing processes: (1) synapses involved in promoting the initial Abeta accumulation and (2) astrocyte-derived apoE involved in preventing Abeta accumulation. These findings would help interpretation of amyloid imaging results.

Keywords: *Amyloid-beta, brain regional vulnerability, synapses, apolipoprotein E*

Presented by: Shinohara, Mitsuru

Poster 58

EDUCATION MODIFIES HIPPOCAMPAL ATROPHY AND AMYLOID PLAQUE DENSITY IN ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is believed to result from a combination of genetic and lifestyle risks. There is great interest in examining the links between cognitive reserve (CR) and severity of brain pathology. We examined the effects of education, a potential marker of CR, on measures of neuronal loss and neuropathology.

Methods: We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large national biomarker study of AD, to analyze the effects of education on MRI-measured hippocampal volumes and 18F-florbetapir-PET scan measured global and regional neuritic beta-amyloid density (standard uptake value ratios, SUVRs). At baseline, hippocampal volume data was available for 145 AD subjects (mean age 75, mean MMSE score of 23.5, 66% APOE e4 carriers) and PET data available for 63 AD subjects (average age of 76, 65% APOE e4 carriers). Education was categorized into ≤12, 13 – 16, and 17+ years. Linear models, chi-squared, and correlation analyses were conducted.

Results: The effect of education on hippocampal volume was significant ($p<0.05$) even after adjusting for other factors. Post-hoc analyses revealed that differences in total, right, and left hippocampal volumes were significant between low and high education groups. Cortical amyloid SUVR analysis also revealed a significant effect of education groups on global ($p<0.05$) and regional ($p<0.05$) SUVR levels after adjusting for age, gender and ApoE4. All cortical regions examined showed a significant effect of education.

Conclusion: Our initial analyses of ADNI and ADNI 2 data from Alzheimer's patients suggests that education may have a significant cross-sectional effect on hippocampal volume and amyloid PET density. These findings may provide a biological basis for the effects of education on cognition. We are currently expanding our analyses to include MCI and NC subjects to test whether these data would support the cognitive reserve hypothesis.

Keywords: *Alzheimer's Disease, Hippocampus, Amyloid*

Presented by: Shpanskaya, Katie

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ALZHEIMER DISEASE GENES AND BRAIN AMYLOID BURDEN IN AGING

Madhav Thambisetty, Yang An, Toshiko Tanaka, Michael Nalls, Yun Zhou, Andrew Singleton, Dean Wong, Luigi Ferrucci, Susan Resnick
1

Recent Genome-Wide Association Studies have identified 11 novel risk genes for late-onset Alzheimer's disease (AD). We recently reported that the common AD risk variant rs3818361 single nucleotide polymorphism in CR1 was associated with lower levels of brain amyloid in non-demented older individuals[1]. We also observed a CR1 x APOE interaction that influenced brain amyloid burden in these individuals. In the current study, we investigated the association between other recently discovered AD risk genes and global brain amyloid burden in non-demented participants in the Baltimore Longitudinal Study of Aging (BLSA). We asked whether AD risk variants in the CLU, PICALM, BIN1, ABCA7, MS4A6A, MS4A4E, CD2AP, EPHA1, CD33 and EXOC3L2 genes influenced brain amyloid burden. A second aim of the study was to examine whether these genes interacted with APOE genotype to influence brain amyloid levels.

This analysis was carried out in 48 non-demented Caucasian participants within the neuroimaging substudy of the BLSA (mean age; 79 years) who underwent ^{11}C PiB-PET imaging to quantify brain amyloid burden. We did not observe any significant differences in mean cortical distribution volume ratio (cDVR) of amyloid between risk allele carriers and non-carriers of any of the novel AD risk genes examined. There was also no evidence of interactions between these genes and APOE genotype influencing brain amyloid levels. These results suggest that the novel AD risk genes may enhance disease risk independent of strong effects on brain amyloid burden during normal aging. An important limitation that must be considered in the interpretation of our findings is the relatively small sample size which may be under-powered to detect subtle effects of these genes on brain amyloid levels.

References

Thambisetty M et al. The effect of complement CR1 on brain amyloid burden during aging and its modification by APOE genotype. BIOLOGICAL PSYCHIATRY (2012) (in press)

Keywords: *Alzheimer disease, gene, risk, GWAS, brain amyloid burden*

Presented by: Thambisetty, Madhav

Poster 60

AMYLOID DEPOSITION IS ASSOCIATED WITH INCREASED MEDIAL TEMPORAL LOBE ACTIVATION DURING MEMORY ENCODING IN THE COGNITIVELY NORMAL ELDERLY

Dana Tudorascu, Kathryn Edelman, Robert Nebes, Beth Snitz, Annie Cohen, Julie Price, Chet Mathis, Lisa Weissfeld, William Klunk, Howard Aizenstein

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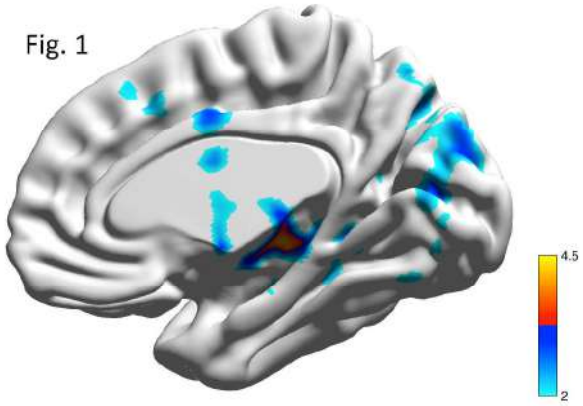

Introduction: Previous studies have shown that amyloid deposition is present in 20-30% of cognitively unimpaired elderly. However, the effect of amyloid on the medial temporal lobe (MTL) memory circuits in these individuals unclear: is the MTL circuit unaffected by 'early' amyloid deposition or do compensatory mechanisms allow the MTL memory circuit to compensate for the amyloid deposition? In this study we address this using fMRI on a paired-associate memory task in cognitively unimpaired elderly, who also underwent PiB PET imaging.

Methods: Data were from 36 subjects (mean Age=77.08, SD=4.93), 20 PiB(-) (15f, 5m) and 16 PiB(+) (11f, 5m). Subjects were also classified based on Word Recall performance (WR) into high and low memory performance: low (WR<=21, 12PiB(-), 9PiB(+)) and high (WR>21, 8PiB(-), 7PiB(+)). Robust Regression using Weighted-Least-Squares SPM toolbox was used to perform first level analysis for our fMRI memory task data. Two-way ANOVA with PiB (+/-), Word Recall (Low/High) and interactions was performed followed by two sample t-tests for PiB(+) versus PiB- within the Low/High WR.

Results: Using the two-way ANOVA an interaction effect between PiB status and WR was observed in the medial temporal lobe ($p<.005$, uncorrected, Fig.1).

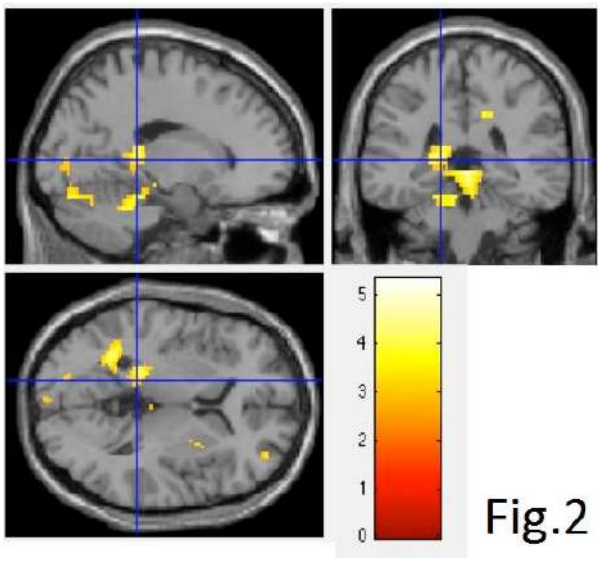

Fig.2

Using two-sample t-test, greater medial temporal activation was found in PiB(+) versus PiB(-) individuals ($p<.005$, uncorrected). Also, in the High WR group, PiB(+) had higher activation as compared to PiB(-) in the para-hippocampus area ($p< .05$, small volume correction, Fig.2).

Conclusion: In this study cognitively unimpaired elderly with high amyloid burden showed evidence of greater activation in the medial temporal lobe during a paired-associate memory task. Moreover the result was most significant in individuals with the best performance, suggesting a compensatory mechanism.

References

Diedrichsen, J., & Shadmehr, R. (2005). Detecting and adjusting for artifacts in fMRI time series data. Neuroimage, 27(3), 624-634.

Keywords: *amyloid,cognitive unimpared, memory task*

Presented by: Tudorascu, Dana

Poster 61

RELATIONSHIP OF CEREBRAL AMYLOID LOAD TO EPISODIC MEMORY PERFORMANCE IN COGNITIVELY INTACT OLDER INDIVIDUALS: EFFECT OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) VAL66MET POLYMORPHISM

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Background: The relationship between amyloid load and cognitive performance in cognitively intact older adults is still a matter of debate. The BDNF val66met and ApoE ε4 polymorphisms both negatively affect episodic memory and hippocampal function in healthy older subjects.

Research question: Does the BDNF val66met affect the relationship between subclinical amyloid deposition and episodic memory scores in cognitively intact older individuals, and how does this interact with ApoE polymorphism?

Methods: 18F-flutemetamol PET (investigational amyloid imaging agent), structural MR and neuropsychological testing were obtained in 64 community-recruited, demographically matched, healthy older controls (mean age= 66, S.D.=5.1, range 53-74) stratified according to a factorial design with BDNF (met allele present vs absent) and ApoE (ε4 allele present vs. absent) as factors. Episodic memory was measured by the 15-word list of the Auditory Verbal Learning test (AVLT) (2 outcome variables: sum of the 5 encoding trials (total = 75) (TL) and percentage delayed recall (delayed recall divided by the score obtained on the last encoding trial) (DR)). The relationship between 18F-flutemetamol SUVRcomp and episodic memory measures (AVLT DR or TL) was assessed by a linear regression analysis, over the entire group as well as within each genetic group separately.

Results: SUVRcomp correlated negatively with AVLT DR (P=0.03, r=-0.26) and TL (P=0.04, r=-0.26). Analyzed for each genetic group separately, the negative correlation between SUVRcomp and AVLT DR or TL was observed only in the group of BDNF met positive/ApoE ε4 positive carriers (DR P=0.006, r=-0.65, TL P=0.03, r=-0.54) and not in any of the other subgroups (P>0.2).

Conclusion: The relationship between amyloid ligand retention and cognitive scores depends on the genetic constitution of the subject sample. In BDNF met/ApoE ε4 carriers a significant relationship is found in contrast with the other genetic subgroups. Genetic variations between cohorts may partly account for discrepancies between studies in how amyloid ligand retention relates to cognitive function.

Keywords: *Flutemetamol, episodic memory, cognitively intact*

Presented by: Vandenberghe, Rik

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EFFECT OF INTELLECTUAL LIFESTYLE AND AD BIOMARKERS ON RATE OF COGNITIVE DECLINE: MAYO CLINIC STUDY OF AGING

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Mayo Clinic

Objective: To investigate the effect of intellectual lifestyle and biomarkers of AD pathophysiology on rate of cognitive decline in a non-demented elderly population. The biomarkers evaluated were brain Aβ-amyloid load via PIB-PET, neuronal dysfunction via FDG-PET and neurodegeneration via Structural-MRI.

Methods: We studied 369 non-demented (317 cognitively normal, 52 MCI) participants in the population based Mayo Clinic Study of Aging who had a baseline 3T MRI, PET scans, baseline cognitive assessment, had lifestyle measures and at least one additional clinical follow-up. We consolidated education and job-score into early intellectual lifestyle and mid and late life cognitive questionnaires into mid/late leisure lifestyle measures. We computed global PiB-PET and FDG-PET uptakes and hippocampal-volume (adjusted for TIV). We used a global cognitive Z-score as a measure of cognition. We used linear mixed-effects models to investigate the associations between demographic, lifestyle measures, AD biomarkers and the global cognitive Z-score trajectories.

Results: Baseline cognitive performance was lower in males($p=0.002$), with lower early intellectual lifestyle($p<0.001$), lower baseline FDG uptake($p<0.001$) and smaller baseline hippocampal volume($p<0.001$). The interaction between the two lifestyle measures was significant($p=0.0007$) suggesting that the association between higher mid/late leisure lifestyle and higher baseline cognitive performance is strongest in the absence of high early intellectual lifestyle.

Only baseline age($p=0.0008$) and baseline hippocampal volumes($p=0.0013$) were significantly associated with change in cognitive performance from baseline.

Interpretation: Intellectual lifestyle measures explained variability in the baseline cognitive performance but were not associated with rate of cognitive decline. While baseline FDG uptake, hippocampal volume, and sex were associated with baseline cognitive performance only higher age and smaller hippocampal volume were associated with faster rate of cognitive decline. Interestingly, higher mid/late leisure lifestyle improved baseline cognitive performance only in those with low early intellectual lifestyle. Amyloid was not associated with baseline cognition or cognitive decline after accounting for other variables.

Keywords: *Cognitive Reserve, Biomarkers, Rate of Cognitive Decline*

Presented by: Vemuri, Prashanthi

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COMPARISON OF SIMPLIFIED PARAMETRIC METHODS FOR VISUAL INTERPRETATION OF [11C]PIB-PET IMAGES

Marissa D. Zwan [1], Rik Ossenkoppele [1], Alexandra J.M. Beumers [1], Reina W. Kloet [2], Sofie M. Adriaanse [1], Ronald Boellaard [2], Albert D. Windhorst [2], Pieter Raijmakers [2], Human Adams [2], Adriaan A. Lammertsma [2], Philip Scheltens [3], Wiesje M. van der Flier [4], Bart N.M. van Berckel [2]

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Introduction: The aim of this study was to evaluate and compare the agreement of visual interpretation of parametric [^{11}C]Pittsburgh compound-B ([^{11}C]PIB) PET images derived from 4 analytical methods in a mixed memory clinic population.

Methods: Dynamic [^{11}C]Pittsburgh compound-B PET scans of 90 minutes duration were obtained for 30 Alzheimer's Disease (AD) patients, 30 patients with non-AD dementia, 30 patients with mild cognitive impairment (MCI) and 30 healthy subjects. Images were derived from 4 analytical methods; Parametric images of non-displaceable binding potential (BP_{ND}) of both 60 minutes (1) and 90 minutes (2), summed 60-90 min activity concentration images (3) and standardised uptake value ratio (SUVr) images (4). For BP_{ND} images and SUVr images, cerebellum grey matter was used as reference region. All images were classified as positive or negative by 3 independent readers. Besides, level of confidence in visual interpretation was assessed. Inter-reader agreement and intra-reader agreement were determined. In addition, an optimal 90 minutes [^{11}C]PIB BP_{ND} cut-off value for interpretation was determined using ROC analysis.

Results: Both 90 minutes BP_{ND} images (Fleiss κ for three readers=0.88) and 60 minutes BP_{ND} images (Fleiss κ for three readers=0.89) showed excellent inter-reader agreement, while agreement was less for summed images (Fleiss κ for three readers=0.57) and SUVr images (Fleiss κ for three readers=0.68). Intra-reader agreement between methods varied substantially between readers (Fleiss κ for 4 methods varied from 0.54 to 0.92). ROC curves comparing consensus visual interpretation and global 90 minutes PIB BP_{ND} revealed that the optimal global [^{11}C]PIB BP_{ND} cut-off value was 0.19, with a sensitivity of 98% and a specificity of 97%.

Conclusion: For widely used SUVr images, visual interpretation of [^{11}C]PIB PET images is less clear-cut than often assumed. Interpretation of [^{11}C]PIB BP_{ND} images shows the highest agreement and therefore would be the method of choice for visual interpretation of [^{11}C]PIB PET scans

Keywords: *Visual assessment, [11C]PIB, PET, Dementia, Alzheimer's Disease*

Presented by: Zwan, Marissa D.

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