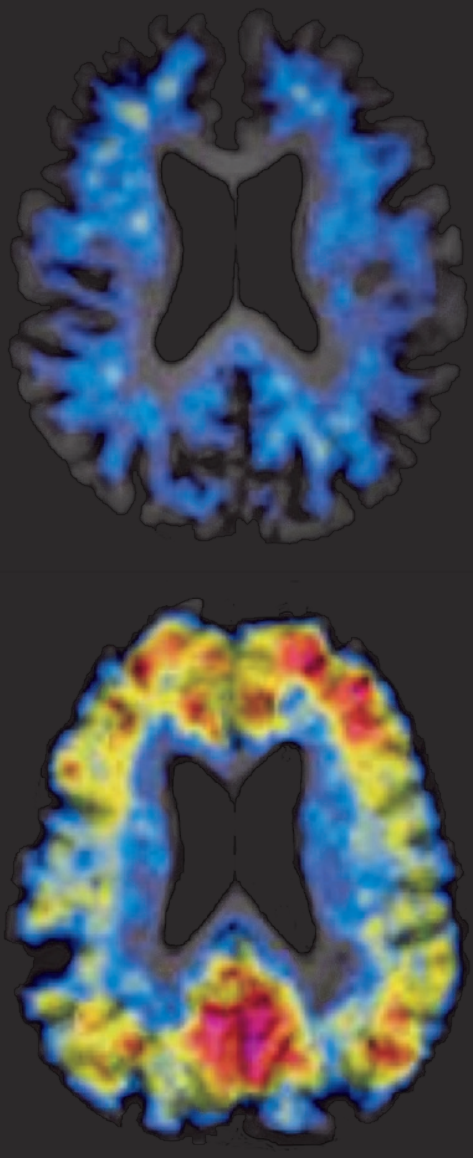

Human Amyloid Imaging

Miami 2012

January 12-13
Miami Beach Resort

Schedule and Abstract Book

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Poster Presentations

Program

Thursday, January 12		
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7:30-8:00	Registration and Breakfast *(Poster installation begins at 7 am)*	
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8:15-9:45	**Session 1: Genetically At-Risk Populations**	**Chairs: William E. Klunk, MD, PhD, *University of Pittsburgh, Pittsburgh, PA, USA* and Juha Rinne, MD, PhD, *University of Turku, Turku, Finland***
8:15-8:30	[11C] PIB, FDG and MR Findings of Preclinical Alzheimer's Disease in the DIAN Cohort	Tammie L.S. Benzinger, MD, PhD, *Washington University School of Medicine, St. Louis, MO, USA*
8:30-8:45	Amyloid-Beta Burden and Neuropsychological Test Performance in Cognitively Normal First-Degree Relatives at Varying Genetic Risk for Alzheimer's Disease	Christopher H. Van Dyck, MD, *Yale University School of Medicine, New Haven, CT, USA*
8:45-9:00	Florbetapir Imaging in the World's Largest Autosomal Dominant Early-Onset Alzheimer's Disease Kindred: Pilot Data from the Alzheimer's Prevention Initiative Biomarker Project	Adam S. Fleisher, MD, *Banner Alzheimer's Institute, Phoenix, AZ, USA*
9:00-9:15	Arctic APP Mutation Carriers Show Low PIB PET Retention in the Presence of Pathological CSF Biomarkers and Reduced FDG Uptake	Agneta Nordberg, MD, PhD, *Karolinska Institutet, Stockholm, Sweden*
9:15-9:45	**Session 1 Discussion**	Chairs and Presenters
9:45-10:00	Break	
10:00–11:30	**Session 2: Neuropathology Correlations**	**Chairs: Vahram Haroutunian, PhD, *Mount Sinai School of Medicine, New York, NY, USA* and Claudia Kawas, MD, *University of California, Irvine, CA, USA***
10:00-10:15	Neuropathological Evaluation of [C-11]PIB PET Imaging Detection Threshold	Milos Ikonomovic, MD, *University of Pittsburgh, Pittsburgh, PA, USA*
10:15-10:30	Correspondence of Florbetapir-PET and Beta-Amyloid Pathology: Analysis of 59 Subjects Who Came to Autopsy	Daniel Skovronsky, MD, PhD, *Avid Radiopharmaceuticals, Philadelphia, PA, USA*
10:30-10:45	PIB+ Scans in Dementia Patients are Associated with High Post-Mortem Amyloid Burden	Gil D. Rabinovici, MD, *University of California, San Francisco, CA, USA*
10:45-11:00	[18F]-Flutemetamol PET Amyloid Imaging and Cortical Biopsy Histopathology in Normal Pressure Hydrocephalus: Pooled Analysis of Four Studies	Juha Rinne, MD, PhD, *University of Turku, Turku, Finland*
11:00-11:30	**Session 2 Discussion**	Chairs and Presenters
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1:45-2:15	**Keynote Lecture: Studies in the Oldest Old: The 90+ Study**	**Claudia Kawas, MD, *University of California, Irvine, CA, USA***
2:15-2:30	**Discussion**	
2:30-4:00	**Session 3: Normal Aging**	**Chairs: Victor L. Villemagne, MD, *Austin Hospital, Melbourne, VIC, Australia* and Reisa A. Sperling, MD, *Brigham and Women's Hospital, Boston, MA, USA***
2:30-2:45	Predictors of Amyloid Accumulation in a Population-Based Study of Cognitively Normal Elderly Controls	Michelle M. Mielke, PhD, *Mayo Clinic, Rochester, MN, USA*
2:45-3:00	Fibrillar Amyloid-Beta Burden in Cognitively Normal Middle-Aged Adults Enrolled in the Wisconsin Registry for Alzheimer's Prevention	Ozioma C. Okonkwo, PhD, *University of Wisconsin, Madison, WI, USA*
3:00-3:15	Beta-Amyloid Deposition and White Matter Hyperintensities Both Contribute to Age-Related Decline in Cognition in Healthy Adults	Gerard N. Bischof, MS, *University of Texas at Dallas, Dallas, TX, USA*
3:15-3:30	Maternal Dementia Age of Onset in Relation to Amyloid Burden in Non-Demented Offspring	Jacqueline E. Maye, BS, *Massachusetts General Hospital, Boston, MA, USA*
3:30-4:00	**Session 3 Discussion**	Chairs and Presenters
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4:15–5:15	**Session 4: Amyloid Imaging in the Clinic (Panel Discussion)**	**Moderator: William J. Jagust, MD, *University of California, Berkeley, CA, USA***
		Christopher C. Rowe, MD, *University of Melbourne, Melbourne, VIC, Australia*
		Jason H. Karlawish, MD, *University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
		Ranjan Durara, MD, *Mount Sinai Medical Center, Miami Beach, FL, USA*
	Session 4 Discussion	Chairs and Presenters
5:30-7:30	**Poster Session and Networking Reception**	

Friday, January 13		
Time	**Title**	**Name**
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8:15-8:30	The Use of an Adaptive Template for Spatial Normalization of [18F]Flutemetamol Amyloid Imaging Data	Lennart Thurfjell, PhD, *GE Healthcare, Uppsala, Sweden*
8:30-8:45	Classification of Amyloid-Positivity in Controls: Comparison of Approaches	Ann D. Cohen, PhD, *University of Pittsburgh, Pittsburgh, PA, USA*
8:45-9:00	Evaluation of a Binary Read Methodology for Florbetapir-PET Images	Mark A. Mintun, MD, *Avid Radiopharmaceuticals, Philadelphia, PA, USA*
9:00-9:30	**Session 6: Invited Didactic Lecture:** Basic Principles and Controversies in PET Amyloid Imaging	**Robert A. Koeppe, PhD, *University of Michigan, Ann Arbor, MI, USA***
9:30-10:15	**Sessions 5 and 6 Discussion**	Chairs and Presenters
10:15-10:30	Break	
10:30-12:15	**Session 7: Longitudinal Studies**	**Chairs: Keith A. Johnson, MD, *Massachusetts General Hospital, Boston, MA, USA* and Susan Resnick, PhD, *National Institute on Aging, Bethesda, MD, USA***
10:30-10:45	A Two-Year Longitudinal Assessment of A-Beta Deposition in Late MCI with 18F-Florbetaben	Christopher C. Rowe, MD, *University of Melbourne, Melbourne, VIC, Australia*
10:45-11:00	Use of Florbetapir-PET to Assess Progression of Amyloid Burden over Time	Michael J. Pontecorvo, PhD, *Avid Radiopharmaceuticals, Philadelphia, PA, USA*
11:00-11:15	Tracking Fibrillar Amyloid Accumulation and Estimating Prevention Trial Sample Sizes in Cognitively Normal APOE E4 Homozygotes, Heterozygotes and Non-Carriers	Jessica Langbaum, PhD, *Banner Alzheimer Institute, Phoenix, AZ, USA*
11:15-11:30	Conversion to Preclinical Alzheimer's Disease in Cognitively Normal Adults: The Characteristics from Longitudinal [11C] PIB PET Study	Andrei Vlassenko, MD, PhD, *Washington University School of Medicine, St. Louis, MO, USA*
11:30-11:45	Amyloid Deposition, Hypometabolism, and Cognitive Trajectories in the ADNI Population	Susan Landau, PhD, *University of California, Berkeley, CA, USA*
11:45-12:15	**Session 7 Discussion**	Chairs and Presenters
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2:00-2:15	**Award Presentations**	**Keith A. Johnson, MD, *Massachusetts General Hospital, Boston, MA, USA***
	HAI Travel Awards and Young Investigator Award (HAI-YIA)	
2:15-3:45	**Session 8: Multimodal Studies**	**Chairs: Clifford R. Jack, MD, *Mayo Clinic, Rochester, MN, USA* and Christopher C. Rowe, MD, *University of Melbourne, Melbourne, VIC, Australia***
2:15-2:30	Biomarker Correlates in the ADNI AD Population Suggesting Dementia Unlikely Due to AD	Val J. Lowe, MD, *Mayo Clinic, Rochester, MN, USA*
2:30-2:45	Amyloid-Modulated Age-Related Changes in FDG Metabolism in Normal and Medley Impaired Elderly	J. Alex Becker, PhD, *Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA*
2:45-3:00	Diverging PIB and FDG Covariance Patterns across Clinical Variants of AD	Manja Lehmann, PhD, *University of California, San Francisco, CA, USA*
3:00-3:15	Neuroimaging Markers Predict Cognitive Decline in PD	Stephen N. Gomperts, MD, PhD, *Massachusetts General Hospital, Boston, MA, USA*
3:15-3:45	**Session 8 Discussion**	Chairs and Presenters
3:45-4:00	Break	
4:00-5:00	**Session 9: Tau Pet Ligands**	**Chairs: Chester A. Mathis, PhD, *University of Pittsburgh, Pittsburgh, PA, USA* and Sam Gandy, MD, PhD, *Mount Sinai Hospital, New York, NY, USA***
4:00-4:30	In Vivo Tau Imaging	Victor L. Villemagne, MD, *Austin Hospital, Melbourne, VIC, Australia*
4:30-5:00	Discovery of Novel [18F]-PET Agents for Imaging Neurofibrillary Tangles (NFTs)	Hartmuth C. Kolb, MD, *Siemens Molecular Imaging, Culver City, CA, USA*
5:00 PM	**Closing Notes**	**Keith A. Johnson, MD, *Massachusetts General Hospital, Boston, MA, USA***

HAI Program Abstracts

Oral Presentations

Session 1: Genetically At-Risk Populations

Chairs: William E. Klunk, MD, PhD, University of Pittsburgh, Pittsburgh, PA, USA
and Juha Rinne, MD, PhD, University of Turku, Turku, Finland

[11C] PIB, FDG and MR Findings of Preclinical Alzheimer's Disease in the DIAN Cohort
Tammie L.S. Benzinger, MD, PhD, Washington University School of Medicine, St. Louis, MO, USA

Amyloid-Beta Burden and Neuropsychological Test Performance in Cognitively Normal First-Degree Relatives at Varying Genetic Risk for Alzheimer's Disease
Christopher H. Van Dyck, MD, Yale University School of Medicine, New Haven, CT, USA

Florbetapir Imaging in the World's Largest Autosomal Dominant Early-Onset Alzheimer's Disease Kindred: Pilot Data from the Alzheimer's Prevention Initiative Biomarker Project
Adam S. Fleisher, MD, Banner Alzheimer's Institute, Phoenix, AZ, USA

Arctic APP Mutation Carriers Show Low PIB PET Retention in the Presence of Pathological CSF Biomarkers and Reduced FDG Uptake
Agneta Nordberg, MD, PhD, Karolinska Institutet, Stockholm, Sweden

[11C] PIB, FDG and MR Findings of Preclinical AD in the DIAN Cohort

Tammie Benzinger [1], Tyler Blazey [1], Robert Koeppe [2], Clifford Jack [3], Christopher Rowe [4], Adam Brickman [5], Mark Raichle [1], Marcus Daniel [1], Paul Thompson [6], Andrew Saykin [7], Steven Correia [8], Keith Johnson [9], Reisa Sperling [9], Peter Schofield [10], John Morris [11], et al.

[1] *Washington University School of Medicine*
[2] *University of Michigan*
[3] *The Mayo Clinic*
[4] *University of Melbourne*
[5] *Columbia University*
[6] *University of California, Los Angeles*
[7] *University of Indiana*
[8] *Butler University*
[9] *Brigham and Women's Hospital*
[10] *University of New South Wales*
[11] *Washington University*

Background: The DIAN Study (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's Disease (ADAD). Imaging studies acquired in this cohort include [11C]PIB, FDG PET and MRI. Mutations represented in this cohort include presenilin 1 and 2 and amyloid precursor protein (PSEN1, PSEN2, APP).

Methods: 120 participants representing a mix of non-carrier and carriers in both the presymptomatic and symptomatic stages of AD underwent 11C]PIB, FDG PET and MRI. All modalities were transformed and processed in a common atlas space. FreeSurfer parcellation of cortical and subcortical grey and white matter was performed. These regions of interest were applied to volumetric MRI, FDG and [11C]PIB data. Diffusion tensor imaging (DTI) was processed using FSL. Cohorts were determined based on genetic status, dementia severity (Clinical Dementia Rating, CDR), and anticipated age of dementia onset.

Results: Differences in [11C]PIB binding appeared to become statistically significant up to ~25 years before anticipated age at dementia onset (based on parental age at onset).Non-demented carriers were significantly different from the non-carrier cohort in the deep grey matter structures of the caudate, putamen, and thalamus and in every cortical grey matter structure (Figure 1). "Early" areas of significant amyloid deposition appear to involve the caudate, the occipital lobe, and the frontal lobe. In carriers, abnormal DTI anisotropy was identified in the deep white matter structures, particularly the fornix. [AMB1] Significant findings for grey matter volumes, cortical thickness, and FDG were predominantly limited to carriers with dementia symptoms.

Discussion: DIAN represents the largest cohort of families with ADAD studied to date. Similar to sporadic AD, [11C]PIB precedes atrophy and metabolic changes by decades. Unlike sporadic AD, there is particular involvement of the caudate, occipital lobe/visual cortex, the orbito frontal lobes.

Presented by: **Benzinger, Tammie**

Amyloid-Beta Burden and Neuropsychological Test Performance in Cognitively Normal First-Degree Relatives at Varying Genetic Risk for Alzheimer's Disease

Christopher van Dyck [1], *Nicole Barcelos* [1], *Anna Brück* [2], *Beata Planeta-Wilson* [1], *Amanda Benincasa* [1], *Martha MacAvoy* [1], *Joel Gelernter* [1], *Richard Carson* [1]

[1] *Yale University School of Medicine*
[2] *University of Turku*

In Alzheimer's disease (AD) there is strong evidence that brain amyloid deposition precedes the emergence of dementia by many years. This study investigated the relationship between *APOE*-e4 genotype, amyloid deposition, and neuropsychological test performance in pre-symptomatic individuals at varying genetic risk for AD.

Methods: Cognitively normal subjects aged 50-66 with a first-degree family history for AD were genetically screened to select three groups: *APOE*genotype e4e4 (n=15), e3e4 (n=15), and e3e3 (n=15), matched for age and sex. Subjects were then studied with C-11-Pittsburgh Compound B ([C-11]PiB) PET, MRI, and neuropsychological testing. PET and MR images were co-registered for application of a ROI template (AAL for SPM2) to generate regional time-activity curves with cerebellum as reference region. Parametric BPND images were then generated using SRTM2 such that BPND=0 reflected no specific binding. BPND was computed for a mean cortical ROI consisting of frontal, posterior cingulate-precuneus, lateral parietal, and lateral temporal ROIs.

Results: *APOE*-e4 carriers demonstrated significantly greater BPND (.16±.19) in comparison to non-carriers (.04±.09; F=7.00, p=.012, ANCOVA controlling for age and sex), with no dosage effect between e4e4 (.19±.13) and e3e4 (.14±.23) groups (Figure 1). Significant cortical [C-11]PiB uptake was observed in *APOE*-e4 carriers throughout the age range studied (as young as age 51 in a e4e4 subject, Figure 2). There was no significant effect of *APOE*genotype on neuropsychological test performance. There were also no significant associations between mean cortical [C-11]PiB BPND and neuropsychological test performance in the overall sample.

Figure 1

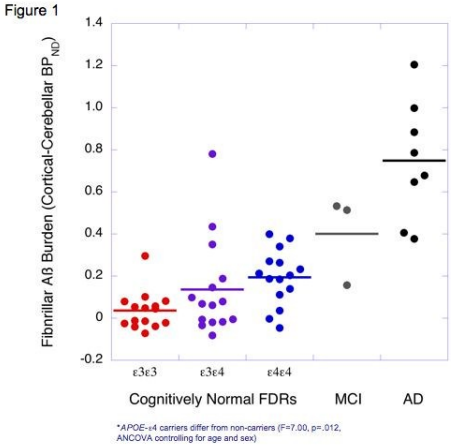
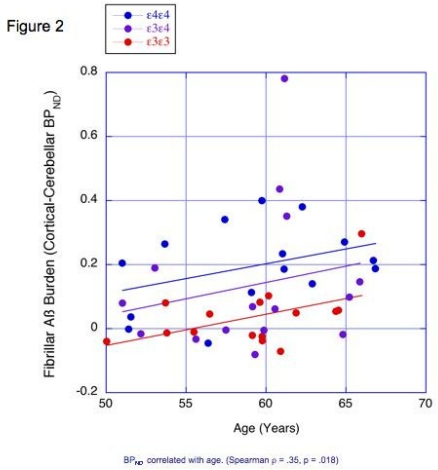


Figure 2



Conclusions: In cognitively normal individuals at high-risk for AD, significant amyloid deposition begins earlier than has been previously reported. Neuropsychological test results suggest minimal cognitive consequences of amyloid burden in these middle-aged “at risk” subjects. Detection of AD pathogenesis at a fully presymptomatic stage of disease may be necessary to enable the earliest therapeutic intervention for prevention trials.

Presented by: **van Dyck, Christopher**

Florbetapir Imaging in the World's Largest Autosomal Dominant Early-Onset Alzheimer's Disease Kindred: Pilot Data from the Alzheimer's Prevention Initiative Biomarker Project

Adam Fleisher [1,4,6], *Kewei Chen* [1,2,6], *Laura Jakimovich* [1], *Madelyn Gutierrez-Gomez* [1,8], *Jessica Langbaum* [1,6], *Auttawut Roontiva* [1,6], *Pradeep Thiyyagura* [1,6], *Xiaofen Liu* [1,6], *Wendy Lee* [1,6], *Napatkamon Ayutyanont* [1,6], *Mark Nishimura* [1,6], *Stephanie Parks* [1,6], *Adriana Ruiz* [8], *Yakeel Quiroz* [7,8], *Kenneth Kosik* [9], *Pierre Tariot* [1,3,6], Francisco Lopera [8], Eric M. Reiman [1,3,5,6]

[1] *Banner Alzheimer's Institute and Banner Good Samaritan PET Center, Phoenix, AZ*
[2] *Department of Mathematics and Statistics, Arizona State University, Tempe, AZ*
[3] *Department of Psychiatry, University of Arizona, Phoenix, AZ*
[4] *Department of Neurosciences, University of California, San Diego, San Diego, CA*
[5] *Division of Neurogenomics, Translational Genomics Research Institute, Phoenix, AZ*
[6] *Arizona Alzheimer's Consortium, Phoenix, AZ*
[7] *Center for Memory and Brain, Psychology Department, Boston University, Boston, MA, USA*
[8] *Grupo de Neurociencias, Universidad de Antioquia, Medellín, Colombia*
[9] *Research Institute, Department of Molecular Cellular Developmental Biology, University of California, Santa Barbara, CA, USA*

Background: In preparation for the Alzheimer's Prevention Initiative's (API) first pre-symptomatic Alzheimer's disease (AD) treatment trial, and in an effort to characterize and compare the trajectory of biomarker changes associated with the preclinical course of AD, we have been conducting cerebrospinal fluid and plasma biomarker, magnetic resonance imaging, as well as fluorodeoxyglucose and florbetapir positron emission tomography (PET) studies in members of the world's largest known autosomal dominant early-onset AD (EOAD) kindred. Located in Antioquia, Colombia, this kindred includes about 5,000 living members, approximately 30% of whom have a presinilin1 (PS1 E280A) mutation that causes EOAD with a median age of 44 at clinical onset. Here, we report preliminary findings from our florbetapir PET studies.

Methods: Fifty family members from Colombia were flown to Phoenix, AZ between September and December, 2011, for florbetapir PET imaging. Here we report cerebral-to-pontine standardized uptake value ratio (SUVR) from this cohort, including 11 symptomatic carriers (7 with MCI, 4 with AD dementia), 19 cognitively normal 35-50 year-old adults (9 carriers), and 20 cognitively normal 18-34 year-old adults (10 carriers).

Results: Compared to non-carriers, patterns of fibrillar amyloid accumulation in both symptomatic and cognitively normal adult PS1 E280A mutation carriers are similar to that found in late-onset AD, characterized by significantly greater florbetapir SUVRs in both cortical and striatal regions. Mean cortical amyloid appears to increase after age 30 and plateau in early symptomatic disease. Striatal florbetapir PET binding is seen early, but not prior to mean cortical or other AD-associated regions.

Conclusions: Florbetapir PET findings in this kindred promise to help inform our understanding of pre-symptomatic AD and the performance of these measures in pre-symptomatic EOAD trials.

Presented by: **Fleisher, Adam**

Arctic APP Mutation Carriers Show Low PIB PET Retention in the Presence of Pathological CSF Biomarkers and Reduced FDG Uptake

Agneta Nordberg [1], Michael Schöll [1], Anders Wall [2], Steinunn Thordadottir [1], Daniel Ferreira [1], Nenad Bogdanovic [1], Bengt Långström [2], Ove Almkvist [3], Caroline Graff [1]

[1] Karolinska Institutet
[2] Uppsala University
[3] Karolinska Institutet, Stockholm University

Background: The dominantly inherited early-onset familial AD (eoFAD) has been proposed as a model to study early disease mechanism of Alzheimer´s disease (AD).
Positron emission tomography (PET) using ^{11}C-PIB and ^{18}F-Flouro-deoxyglucose (^{18}F-FDG) were used to characterize the pathological changes of Arctic APP(APParc) early-onset familial AD in comparison to other AD mutations and sporadic AD disease (sAD) and healthy controls (HCs). All subjects underwent neuropsychology tests as well as magnet resonance imaging (MRI) and cerebrospinal fluid (CSF) sampling.
Seven member of the APParc family (two carriers and five non-carriers), seven sAD patients, one carrier of presenilin (PSEN1) mutation, one carrier of Swedish APP(APPswe) mutation and seven healthy controls (HCs) were examined. Low cortical PIB retention was observed in APParc mutation carriers which was in contrast to the high PIB retention measured in PSEN1 ,and APPswe carriers and sAD patients. Pathological CSF biomarkers (including low Aß42) and decreased cerebral glucose metabolism were observed in carriers of APParc as well as in other eo FAD mutation carriers.

The lack of fibrillar amyloid, measured by ^{11}C-PIB in brain of APParc mutation carriers, combined with reduced Aß42 in CSF and decreased glucose metabolism underline the importance of non-fibrillar forms of Aß (oligomers, protofibrils) for the pathological processes leading to clinical AD.

Presented by: **Nordberg, Agneta**

Session 2: Neuropathology Correlations

Chairs: Vahram Haroutunian, PhD, Mount Sinai School of Medicine, New York, NY, USA
and Claudia Kawas, MD, University of California, Irvine, CA, USA

Neuropathological Evaluation of [C-11]PIB PET Imaging Detection Threshold
Milos Ikonomovic, MD, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence of Florbetapir-PET and Beta-Amyloid Pathology: Analysis of 59 Subjects Who Came to Autopsy
Daniel Skovronsky, MD, PhD, Avid Radiopharmaceuticals, Philadelphia, PA, USA

PIB+ Scans in Dementia Patients are Associated with High Post-Mortem Amyloid Burden
Gil D. Rabinovici, MD, University of California, San Francisco, CA, USA

[18F]-Flutemetamol PET Amyloid Imaging and Cortical Biopsy Histopathology in Normal Pressure Hydrocephalus: Pooled Analysis of Four Studies
Juha Rinne, MD, PhD, University of Turku, Turku, Finland

Neuropathological Evaluation of [C-11]PIB PET Imaging Detection Threshold

Milos Ikonomovic [1], Eric Abrahamson [1], Julie Price [1], Chester Mathis [1], William Paljug [1], Manik Debnath[1], Anne Cohen [1], Steven DeKosky [1], Oscar Lopez [2], William Klunk [1]

[1] University of Pittsburgh
[2] University of Virginia

Amyloid-beta (Abeta) deposits are detectable in the brain in vivo using positron emission tomography (PET) and [C-11]-labeled Pittsburgh Compound-B ([C-11]PiB), however the sensitivity of this technique is not well understood. In this postmortem study, we quantified Abeta pathology in sixteen brain areas from an individual who had clinical diagnoses of probable dementia with Lewy bodies and possible Alzheimer's disease (AD) but with no detectable [C-11]PiB PET retention ([C-11]PiB(-)) when imaged 17 months prior to death. Brain samples were processed in parallel with region-matched brain tissue samples from an individual with a clinical diagnosis of probable AD and a positive [C-11]PiB PET scan ([C-11]PiB(+)) when imaged 9 months prior to death. In both cases neocortical plaques were evident using Abeta immunohistochemistry, Bielschowsky silver staining, and histofluorescent amyloid-binding compounds. However, cortical plaques were sparse to only focally frequent in the [C-11]PiB(-) case, while frequent plaques were observed uniformly across all cortical areas in the [C-11]PiB(+) case. The [C-11]PiB(-) case had low levels of [H-3]PiB binding (<100 pmol/g) and Abeta1-42 concentrations (<500 pmol/g) except in the frontal cortex where Abeta1-42 values (788 pmol/g) approached cortical values in the [C-11]PiB(+) case (800-1,700 pmol/g). Abeta histopathology correlated strongly with both antemortem [C-11]PiB PET retention and postmortem [H-3]PiB binding in the [C-11]PiB(+) case, but there was only a weak correlation in the [C-11]PiB(-) case. The low ratios of [H-3]PiB binding:Abeta concentration and PiB:Abeta plaque labeling indicate that Abeta in the [C-11]PiB(-) brain is primarily nonfibrillar. Our results indicate that threshold levels of Abeta1-42 between 500-800 pmol/g tissue and [H-3]PiB binding levels between 200-350 pmol/g tissue are required for a positive [C-11]PiB PET signal.

Presented by: **Ikonomovic, Milos**

Correspondence Of Florbetapir-PET And Beta-Amyloid Pathology: Analysis Of 59 Subjects Who Came To Autopsy

Christopher Clark [1], Michael Pontecorvo [1], Thomas Beach [2], Edward Coleman [3], Murali Doraiswamy [3], Adam Fleisher [4], Keith Johnson [5], Eric Reiman [4], Marwan Sabbagh [2], Carl Sadowsky [6], Julie Schneider[7], Reisa Sperling [8]

[1] Avid Radiopharmaceuticals
[2] Banner Sun Health Research Institute
[3] Duke University Medical Center
[4] Banner Alzheimer's Institute
[5] Massachusetts General Hospital, Harvard Medical School
[6] Nova Southeastern University
[7] Rush University Medical Center
[8] Brigham and Women's Hospital and Massachusetts General Hospital, Harvard Medical School

Background: Previous studies have shown correlations between amyloid PET imaging and beta-amyloid pathology. However, most studies have been relatively small and have not established sensitivity or specificity of these tracers against a defined pathology reference standard.

Methods: This study extended the correlations reported by Clark (211) to a larger cohort, and tested the sensitivity and specificity of florbetapir PET scans vs the neuropathological diagnosis at autopsy. The primary analysis included 59 patients who came to autopsy within two years of PET imaging with 370 MBq florbetapir F18. Three nuclear medicine physicians provided a semiquantitative (0-4) score for each image, and five different physicians classified each scan in a binary fashion as either amyloid positive or amyloid negative. Amyloid burden at autopsy was evaluated postmortem by both quantitative immunohistochemistry (IHC) and modified CERAD neuritic plaque score (neuropathology positive = moderate or frequent neuritic plaques; negative = sparse or no neuritic plaques).

Results: A correlation was observed between florbetapir-PET imaging and postmortem amyloid burden, regardless of which index of PET activity (semiquantitative visual read or SUVR) or pathology (neuritic plaque score or IHC) was evaluated (p's <0.0001). The median sensitivity and specificity among the 5 readers was 92.3% and 95.0%, respectively, for cases that came to autopsy within two years, and 96% and 94%, respectively, for cases that came to autopsy within one year of the PET scan. Fleiss' kappa for the binary reads was 0.75, showing high inter-reader reliability.

Conclusions: Florbetapir-PET correlated significantly with postmortem amyloid burden in this cohort of 59 subjects. Visual reads using the binary method showed high reader to reader reliability and showed significant concordance with neuropathological assessment, with sensitivity and specificity for detection of moderate/frequent neuritic amyloid plaques of 92.3% and 95.0% respectively.

Presented by: **Skovronsky, Daniel**

PIB+ Scans in Dementia Patients are Associated with High Post-Mortem Amyloid Burden

Gil Rabinovici [1], Pia Ghosh [1], Cindee Madison [2], Chiara Corbetta [2], Elizabeth Mormino [2], Bruce Miller [1], Lea Grinberg [1], William Seeley [1], William Jagust [2]

[1] UCSF Memory & Aging Center, Dept of Neurology
[2] Helen Wills Neuroscience Instititue, UC Berkeley

Objective: To compare PIB-PET signal during life with post-mortem amyloid burden in patients with dementia.

Methods: 16 dementia patients underwent PIB-PET (age 66.2 ± 11.4, 38% ApoE4+) and autopsy (2.2 ± 1.3 years after PET, range 0.7-4.7). PIB DVR images were visually assessed as PIB+/PIB- blinded to clinical diagnosis. Global amyloid burden was measured with a PIB Index, and scans were quantitatively classified using 2 thresholds - one derived from young controls (YC, age 24.7 ± 3.3, PIB Index ≥ 1.08) and a second from older controls (OC, age 74.8 ± 6.7, PIB Index ≥ 1.16) (Mormino 2011). Post-mortem assessment of amyloid included Aβ immunohistochemistry in 14/16 patients and Bielschowsky staining in the other two. Neuritic plaques (NPs) were graded prospectively as CERAD absent, sparse, moderate or frequent, unadjusted for age. Diffuse plaques (DPs) and amyloid angiopathy were noted as present/absent based on retrospective review of autopsy reports.

Results: Primary pathologic diagnoses included: high-likelihood AD (4), mixed FTLD-Tau/AD (1), FTLD-Tau (3), FTLD-TDP (6), argyrophilic grain disease (1) and genetic prion disease (1). NPs were present in 63%, DPs in 79% and amyloid angiopathy in 38% of patients. All CERAD-frequent patients were visually rated PIB+ (Figure), 4/5 were PIB+ based on the YC threshold and 3/5 were PIB+ applying the OC threshold. All patients with CERAD absent to moderate NPs were visually and quantitatively rated PIB-negative. All PIB+ patients had Braak Stage V-VI neurofibrillary pathology. In CERAD absent to moderate subjects, there was no difference in PIB Index between those with and without NPs (Mann-Whitney, p=0.72), DPs (p=0.44) or amyloid angiopathy (p=1.00).

Conclusion: PIB+ scans were associated with a high burden of pathology, corresponding to NIA-Reagan high-likelihood AD. These findings suggest high specificity when applying PIB for differential diagnosis, and potentially in preclinical detection of AD.

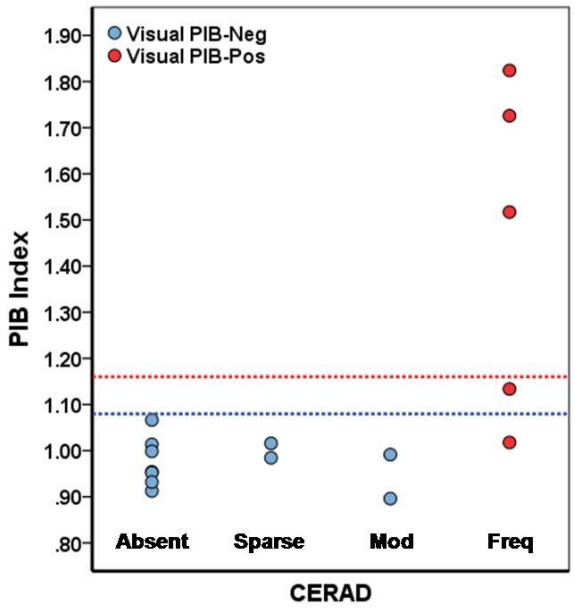


Figure. PIB Index versus CERAD (unadjusted for age). Scans were visually read as PIB+ (red circles) or PIB- (blue circles), and classified using quantitative thresholds from young controls (DVR 1.08, blue hatched line) and older controls (DVR 1.16, red hatched line).

Presented by: **Rabinovici, Gil**

[18F]-Flutemetamol PET Amyloid Imaging and Cortical Biopsy Histopathology in Normal Pressure Hydrocephalus: Pooled Analysis of Four Studies

Juha Rinne [1], Dean Wong [2], David Wolk [3], Ville Leinonen [4], Steven Arnold [5], Chris Buckley [6], Adrian Smith [7], Richard McLain [8], Paul Sherwin [9], Gil Farrar [10], Marita Kailajärvi [11], Igor Grachev [9]

[1] *Turku PET Centre, University of Turku, Finland*
[2] *Johns Hopkins University, Baltimore, MD, USA*
[3] *Department of Neurology, University of Pennsylvania, Philadeplhia, PA, USA*
[4] *Department of Neurosurgery, University of Eastern Finland, Kuopio, Finland*
[5] *Penn Memory Center, University of Pennsylvania, Philadelphia, PA, USA*
[6] *Imaging Technology, Medical Diagnostics, GE Healthcase, Amersham, UK*
[7] *Discovery Biology, Medical Diagnostics, GE Healthcare, Amersham UK*
[8] *PFP Statistical consulting, LLC, Livonia, MI, USA*
[9] *Clinical Development, Medical Diagnostics, GE Healthcare, Princeton, NJ, USA*
[10] *Program and project management, Medical Diagnostics, GE Healthcare, Amersham, UK*
[11] *Clinical Development, Medical Diagnostics, GE Healthcare, Turku, Finland*

Background: The development of molecular imaging techniques to 'visualize' amyloid in vivo represents a major achievement in the study of Alzheimer's disease (AD).

Objective: To determine the level of association between uptake of the amyloid positron emission tomography (PET) imaging agent [18F]-flutemetamol and the level of beta-amyloid measured by immunohistochemical (IHC) and histochemical (HC) staining in a frontal or parietal cortical region biopsy site.

Design/Methods: Forty nine patients with suspected Normal Pressure Hydrocephalus (NPH) underwent prospective (n=27) or retrospective (n=22) [18F]-flutemetamol PET and cortical brain biopsy during intracranial pressure measurement or ventriculo-peritoneal shunting. [18F]-Flutemetamol uptake was quantified using standardized uptake value ratio (SUVR) with cerebellar cortex as a reference region. Tissue beta-amyloid was evaluated using the monoclonal antibody 4G8, Thioflavin-S and Bielschowksy silver stain, and an overall pathology result.

Results: [18F]-Flutemetamol SUVRs from the biopsy site were significantly associated with biopsy specimen beta-amyloid levels using 4G8 (Pearson's r=0.41, p=0.005). There was also good correlation between the biopsy specimen beta-amyloid level and uptake of [18F]-flutemetamol in the region contralateral to the biopsy site (r=0.42, p=0.004), or with composite cortical [18F]-flutemetamol uptake (r=0.44, p=0.002). Blinded visual assessment (BVA) of images showed a high level of agreement between all readers (κ=0.86). Using the overall pathology result as the standard of truth, BVA of PET images showed by-reader sensitivities of 100%, 71%, and 93%; specificity was 100% for each reader. Overall sensitivity and specificity by majority read were 93% and 100%, accordingly.

Conclusions: [18F]-Flutemetamol PET imaging demonstrates strong concordance with histopathology irrespective of timing and sequence of examinations in prospective and retrospective settings, and shows promise as a valuable tool to study and possibly facilitate diagnosis of AD both in patients with suspected NPH, and among the wider population.

Study Supported by: The study was funded by GE Healthcare, Princeton, NJ

Presented by: **Rinne, Juha**

Keynote Lecture

Dementia and Aging-Associated Changes in the Human Brain Transcriptome

Vahram Haroutunian

The Mount Sinai School of Medicine and JJ Peters VA Medical Center

Most studies of gene expression in the aged brain have focused on disease related changes including those associated with Alzheimer's disease. In addition to insights into disease processes, the study of global gene expression in multiple regions of the normal human brain and comparison of gene expression in young-old (<85 years) and oldest-old persons (>85 years) can provide insights into mechanisms that contribute to successful cognitive aging.

Genome-wide gene expression was studied across 17 brain regions of 130 non-demented individuals and persons dying at different stages of dementia and Alzheimer's disease progression.

Gene expression changes in the temporal and prefrontal cortices are more closely related to disease severity than other regions examined; the degree of gene expression change in a given region varied depending on the disease severity classification scheme used; the classification of cases by CDR provides a more orderly gradient of gene expression change in most brain regions than groupings based on neuropathological indices. In non-demented persons, 332 probe sets showed significantly altered expression in the oldest-old (older than 85 years) relative to cognitively intact young-old persons. Strikingly, all transcripts among genes whose expression was altered by dementia and aging were upregulated in cognitively intact oldest-old persons relative to cognitively intact young-old persons. Gene ontology classification of these common probe sets from the two age categories showed them to be linked to canonical immune function pathways.

The results suggest that gene expression varies with brain region, dementia severity and severity of AD neuropathology. Successful aging to advanced old-age is associated with a robust and preserved CNS immune response system. It is possible that persons who survive to advanced old age with intact cognition are those individuals whose CNS immune system is able to respond to and defend against physiological insults (e.g., amyloidogenic, cardiovascular) effectively.

Presented by: **Haroutunian, Vahram**

Keynote Lecture

Studies in the Oldest Old: The 90+ Study

Claudia Kawas

University of California, Irvine

In most of the world, the oldest old comprise the fastest growing segment of the population. As the leading consumers of healthcare and the individuals most affected by dementia, these pioneers of aging present public health challenges and research opportunities to better understand aging and dementia.

The 90+ Study, a population-based sample of more than 1,600 people aged 90 years and older (Laguna Woods, California), comprises one of the largest studies of oldest old in the world. Participants (76% women; mean age 97 years) are followed longitudinally every 6 months with neuropsychological and neurological examinations, medical record review, informant questionnaires and interviews. DNA and brain donation are also requested.

Initial results in this population-based sample show a very high prevalence and incidence of dementia and cognitive impairment in the oldest old. However, typical neuropathological lesions associated with dementia, including amyloid plaques and neurofibrillary tangles (Alzheimer disease), cerebrovascular lesions, and other typical abnormalities associated with dementia, are not necessarily present. Moreover, risk factors associated with dementia and AD in younger old individuals do not appear to be operant in the oldest old. Data from our epidemiological, clinical, radiological, and pathological studies will be presented, and implications for the study of dementia in younger individuals will be discussed.

Presented by: **Kawas, Claudia**

Session 3: Normal Aging

Chairs: Victor L. Villemagne, MD, Austin Hospital, Melbourne, VIC, Australia and
Reisa A. Sperling, MD, Brigham and Women's Hospital, Boston, MA, USA

Predictors of Amyloid Accumulation in a Population-Based Study of Cognitively Normal Elderly Controls
Michelle M. Mielke, PhD, Mayo Clinic, Rochester, MN, USA

Fibrillar Amyloid-Beta Burden in Cognitively Normal Middle-Aged Adults Enrolled in the Wisconsin Registry for Alzheimer's Prevention
Ozioma C. Okonkwo, PhD, University of Wisconsin, Madison, WI, USA

Beta-Amyloid Deposition and White Matter Hyperintensities Both Contribute to Age-Related Decline in Cognition In Healthy Adults
Gerard N. Bischof, MS, University of Texas at Dallas, Dallas, TX, USA

Maternal Dementia Age of Onset In Relation to Amyloid Burden in Non-Demented Offspring
Jacqueline E. Maye, BS, Massachusetts General Hospital, Boston, MA, USA

Predictors of Amyloid Accumulation in a Population-Based Study of Cognitively Normal Elderly Controls

Michelle Mielke, Heather Wiste, Stephen Wiegand, David Knopman, Val Lowe, Rosebud Roberts, Dana Swenson-Dravis, Bradley Boeve, Ronald Petersen, Cliff Jack

Mayo Clinic

Background: Secondary Alzheimer's disease (AD) prevention trials in preclinical subjects are now being designed. Documentation of brain amyloidosis for subject enrollment is a requirement of some trials. Approximately 60% of elderly individuals are expected to be amyloid negative. The identification of inexpensive and non-invasive screening variables that could help predict which individuals have significant amyloid accumulation would greatly reduce screening costs for preclinical AD trials.

Methods: A population-based sub-sample of 483 cognitively normal (CN) individuals, aged 70-93, from the Mayo Clinic Study of Aging underwent PIB-PET imaging. Logistic regression was used to determine whether age, APOE genotype, family history, or cognitive performance increased the odds of having PIB SUVR>1.5. Area under the receiver operating characteristic curve (AUROC) was used to evaluate discrimination between PIB positive and negative subjects. Positive (PPV) and negative (NPV) predictive value was defined based on an estimated probability >0.50 who were PIB>1.5.

Results: Of the 483 CN individuals, 151 (31%) had PIB>1.5. Each five-year increase in age (OR 1.6, 95% CI: 1.3, 1.9) and presence of an APOE E4 allele (OR 3.7, 95% CI: 2.3, 5.7) were independently associated with PIB>1.5. Adding family history of dementia/AD, subjective memory complaints, and cognitive performance did not appreciably improve the classification of persons with PIB>1.5 (AUROC=0.69, PPV=60%, and NPV=73% with age and APOE genotype vs. AUROC=0.71, PPV=61%, and NPV=74% with additional variables).

Conclusion: Age and APOE genotype are useful predictors of PIB>1.5. However, cognitive performance in any domain and subjective memory complaints did not improve classification. Prediction using age and APOE genotype was only fair. However, a PPV of 60% versus 31% (expected baseline rate) means these two inexpensive and non-invasive measures could reduce, by half, the number of CN subjects that must be screened in order to identify a given number of amyloid positive subjects.

Presented by: **Mielke, Michelle**

Fibrillar Amyloid-B Burden in Cognitively Normal Middle-Aged Adults Enrolled in the Wisconsin Registry for Alzheimer's Prevention

Ozioma Okonkwo [1], Jennifer Oh [1], Bradley Christian [2], Guofan Xu [1], Caitlin Cleary [1], Sandra Harding [1], Dustin Wooten [2], Ansel Hillmer [2], Dhanbalan Murali [2], Todd Barnhart [2], Catherine Gallagher [1], Barbara Bendlin [1], Sanjay Asthana [1], Mark Sager [1], Sterling Johnson [1]

[1] Wisconsin Alzheimer's Disease Research Center and Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Madison, WI
[2] Waisman Brain Imaging Laboratory, University of Wisconsin, Madison, WI

Background: Aggregation of amyloid-beta (Aβ) is a core neuropathological feature of Alzheimer's disease (AD). However, it is unknown how early in the disease process this aggregation begins. We present initial data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) addressing this question.

Methods: Participants (mean age=59 years, 68% female) were cognitively-healthy middle aged adults with (FH+, n=108) or without (FH-, n=48) parental family history of AD. Participants underwent neuroimaging including an SPGR MRI (GE 3T) and a dynamic 70-minute PiB PET (Siemens HR+), and comprehensive neuropsychological examination including the Rey Auditory Verbal Learning Test (RAVLT). PiB images were co-registered to the MRI images, and Logan distribution volume ratios (DVRs) were computed utilizing a cerebellar reference derived from FreeSurfer. FreeSurfer parcellations were also used to quantify PiB retention in 34 regions of interest (ROI), with specific focus on the inferior parietal lobule, the cingulate isthmus, the precuneus, the rostral middle frontal gyrus, and the superior temporal gyrus. Participants were designated as PiB+ if the mean DVR in any ROI was ≥ 1.2.

Results: Twenty-eight percent (n=44) of the participants were PiB+. Compared to PiB- participants, PiB+ participants were more likely to be APOE4 positive (55% vs. 28%, p=.002) and women (80% vs. 63%, p=.052). Surprisingly, we found significant positive correlations between RAVLT Total, Short Delay, and Long Delay scores and PiB retention in the precuneus and cingulate isthmus (r's ranging from .16 to .27, p<.05).

Conclusion: We found evidence for Aβ aggregation in 28% of cognitively-healthy late-middle aged adults and this was significantly influenced by APOE status and gender. The positive association with scores on cognitive tests of memory suggests that a compensatory process may be occurring. We are investigating associations between PiB amyloid burden and CSF markers of Aβ, as well as concurrent associations with FDG metabolism and BOLD signal.

Presented by: **Okonkwo, Ozioma**

Beta-Amyloid Deposition and White Matter Hyperintensities Both Contribute To Age-Related Decline in Cognition in Healthy Adults

Gerard Bischof [1], Karen Rodrigue [1], Kristen Kennedy [1], Michael Devous [2], Jenny Rieck [1], Denise Park [1]

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

White matter hyperintensities (WMH) increase with age and are an important marker of cerebrovascular health. Beta amyloid (AB) deposition also increases with age and is a key biomarker of Alzheimer's disease (AD) pathology. Surprisingly, 20% of cognitively-normal adults show significant AB deposition.

In this study, we examined the effect of WMH and AB burden on a range of cognitive tasks in a large sample of healthy adults (N=89; aged 50-89; 71.16±11.44) from the Dallas Lifespan Brain Study (DLBS). Participants underwent 1) high-resolution T1 MRI scanning, 2) FLAIR imaging and 3) a ^{18}F-Florbetapir PET scan. Mean cortical AB was computed by extracting AB counts across 8 ROIs, normalized to cerebellum. WMH were reliably traced. Additionally, we traced hippocampal volume (HCV), which has been hypothesized to be negatively affected later in the cascade of AD-related neuropathology. We applied stepwise regression to examine the effects of WMH, AB and HCV (in that order) on domains of cognition including processing speed, working memory, executive functioning, reasoning and episodic memory.

Results show that both WMH and AB deposition make independent negative contributions in explaining variance associated with age-related declines in measures of processing speed, working memory, and executive function. Reasoning and episodic memory were primarily affected by WMH but not AB. After controlling for AB and WMH, HCV affected only executive function.

The findings suggest that WMH burden is a strong predictor of age-related variance in cognition. Furthermore, AB burden predicts processing speed, working memory and executive function. Memory and reasoning were less sensitive to the effects of AB and suggest that this may be related to buffering effects of knowledge on higher order cognition. We conclude that it is important to measure both WMH and AB burden in individuals as differential sources of cognitive decline with varying implications for intervention.

Supported in part by NIH grants 5R37AG-006265-25, 3R37 AG-006265-25S1, and Alzheimer's Association grant IIRG-09-135087. Radiotracer was generously provided to the study by Avid Radiopharmaceuticals.

Presented by: **Bischof, Gerard**

Maternal Dementia Age of Onset in Relation to Amyloid Burden in Non-Demented Offspring

Jacqueline Maye [1], Christopher Gidicsin [1], Lesley Pepin [1], J. Alex Becker [2], Deborah Blacker [2], Dorene Rentz [3], Joseph Locascio [2], Gad Marshall [3], Rebecca Amariglio [3], Natacha Lorius [1], Lauren Wadsworth [1], Reisa Sperling [3], Keith Johnson [3]

[1] Massachusetts General Hospital
[2] Massachusetts General Hospital, Harvard Medical School
[3] Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School

Family history of dementia (FH) is a significant risk factor for sporadic, late-onset Alzheimer's disease (AD), particularly when the FH is maternal and when the age of dementia onset (AO) is younger. Non-demented individuals have greater amyloid burden regardless of age, gender, and APOE carrier status when there is a maternal FH of dementia (mFH) compared to either those with a paternal FH (pFH) or those without a FH. We hypothesized that younger parental AO of dementia would relate to greater beta-amyloid burden and that the effect would be greater in those with a maternal history of dementia.

Detailed family history and PIB PET was acquired in 143 non-demented individuals participating in the Harvard Aging Brain Study with mean ±SD age 74 ±8. Forty-one subjects were excluded, e.g., because one parent died before age 63. Of the remaining 102 individuals (CDR0, N=73; CDR0.5, N=29), 46 reported a single-parent history of dementia, 32 mFH+ and 14 pFH+. PiB retention (DVR, cerebellar reference) was measured in a global cortical region and its relation to AO was evaluated with general linear models.

Parental dementia AO (range 54 – 90 y) did not differ between mothers (78 ±8y) and fathers (73 ±9y; $p>0.1$). Higher prevalence of dementia in mothers was not accounted for by parental longevity (Kaplan-Meier analysis). Similar to previous reports, PiB retention in this sample was greater in mFH+ subjects compared to subjects with no FH ($p<0.05$). Controlling for child's age, gender, CDR status, APOE status, and education, higher PiB retention was associated with maternal AO ($p<0.005$) but not paternal AO ($p>0.9$).

Our results suggest that greater amyloid burden in offspring is associated with younger age at dementia onset when the affected parent was female, not when the affected parent was male, and that the effect is independent of APOE status.

Presented by: **Maye, Jacqueline**

Session 4: Amyloid Imaging in the Clinic *(Panel Discussion)*

Moderator: William J. Jagust, MD, University of California, Berkeley, CA, USA

Christopher C. Rowe, MD, University of Melbourne, Melbourne, VIC, Australia

Jason H. Karlawish, MD, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Ranjan Durara, MD, Mount Sinai Medical Center, Miami Beach, FL, USA

Session 5: Technical Emphasis

Chairs: Chester A. Mathis, PhD, University of Pittsburgh, Pittsburgh, PA, USA, and Robert A. Koeppe, PhD, University of Michigan, Ann Arbor, MI, USA

Effect of White Matter Binding on Florbetapir and PIB Image Classification
Suzanne Baker, PhD, Lawrence Berkeley National Lab, Berkeley, CA, USA

The Use of an Adaptive Template for Spatial Normalization of [18F]Flutemetamol Amyloid Imaging Data
Lennart Thurfjell, PhD, GE Healthcare, Uppsala, Sweden

Classification of Amyloid-Positivity in Controls: Comparison of Approaches
Ann D. Cohen, PhD, University of Pittsburgh, Pittsburgh, PA, USA

Evaluation of a Binary Read Methodology for Florbetapir-PET Images
Mark A. Mintun, MD, Avid Radiopharmaceuticals, Philadelphia, PA, USA

Effect of White Matter Binding on Florbetapir and PIB Image Classification

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

[1] *Lawrence Berkeley National Lab*
[2] *University of California, Berkeley*

Different PET tracers for in vivo detection of β-amyloid have different binding characteristics, but it is unclear how these characteristics are reflected in diagnostic performance. We explored the effects of gray and white matter binding on quantitative metrics for [18F]Florbetapir and [11C]PIB. All comparisons used SUVRs obtained with data acquired between 50-70 min for PIB and florbetapir using cerebellar gray as the reference region. In 22 subjects scanned with both tracers, a composite gray matter region showed a broader range of values in PIB (1.67+/-0.50) than florbetapir (1.42+/-0.33). No correlation was found (r^2=0.01) in white matter uptake between PIB (2.14+/-0.28) and florbetapir (2.22+/-0.31). We modeled the effect of these ranges using a segmented MR template. All voxels in the gray matter mask=x, all voxels in the white matter mask=y, and all remaining voxels=0. This was repeated for 51x51 images stepping through values (x,y) from 0-5 at 0.1 intervals. Each image was smoothed to 8mm^3, we then calculated the smoothed gray and white matter values. A subset of the 51x51 images was found in which the measured gray and white matter values were within two standard deviations of the mean for PIB (gray=0.66-2.67, white=1.59-2.69). For any “true” value of x, a range of 0.47 smoothed gray matter values was possible, reflecting the ambiguity caused by varying white matter values. For florbetapir parameters (gray=0.78-2.07, white=1.61-2.83) the same approach resulted in a range of 0.52 smoothed gray matter values. As a result of florbetapir’s diminished gray matter uptake and increased white matter variability, 44% of the modeled data was ambiguous and the false positive/negative rate=12%. In comparison, 28% of PIB modeled data was ambiguous with a false positive/negative rate=7%.

Presented by: **Baker, Suzanne**

The Use of an Adaptive Template for Spatial Normalization of [18F]Flutemetamol Amyloid Imaging Data

Lennart Thurfjell [1], Roger Lundqvist [1], Johan Lilja [1], Benjamin A. Thomas [2], Victor L. Villemagne [3], Christopher C. Rowe [3], David J. Brooks [4]

[1] GE Healthcare, Uppsala, Sweden
[2] University College London, London, UK
[3] Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Australia
[4] GE Healthcare, London, United Kingdom; Imperial College, London, United Kingdom.

Background: Spatial normalization of amyloid imaging is challenging because of the different uptake patterns in *Aβ-* and *Aβ+* scans and there is a risk for systematic bias if a standard method is used. We propose the use of an adaptive template registration method to overcome this problem.

Methods: Data from the [^{18}F]flutemetamol Phase II study (n=72) was used to model amyloid deposition. Linear regression of voxel intensities on the SUVR value in a neocortical composite region for all scans gave an intercept image and a slope image. We devised a method where an adaptive template image spanning the range from the most *Aβ-* to the most *Aβ+* can be generated through a linear combination of these two images and where the optimal template is selected as part of the registration process. We applied the method to the [^{18}F]flutemetamol Phase II data and used a fixed VOI template to compute SUVR values. For comparison, we used FreeSurfer to segment each subject's MRI scan and the parcellations were applied to the co-registered PET scans. We then correlated SUVR values for a composite neocortical region obtained with both methods. Furthermore, to investigate whether the [^{18}F]flutemetamol model could be generalized to [^{11}C]PIB, we applied the method to AIBL [^{11}C]PIB scans downloaded from ADNI (n=226) and compared the PET-based neocortical composite score with the corresponding score obtained using a semiautomatic method that made use of the subject's MR for positioning of regions (Villemagne et al., 2011).

Results: Spatial normalization was successful on all scans. For [^{18}F]flutemetamol, there was a strong correlation between the PET-only and FreeSurfer SUVRs (Pearson's *r*=0.96). We obtained a similar correlation for the AIBL data (Pearson's *r*=0.94).

Conclusion: The derived adaptive template registration method allows for robust, accurate and fully automated quantification of [^{18}F]flutemetamol and [^{11}C]PIB scans without the use of MRI.

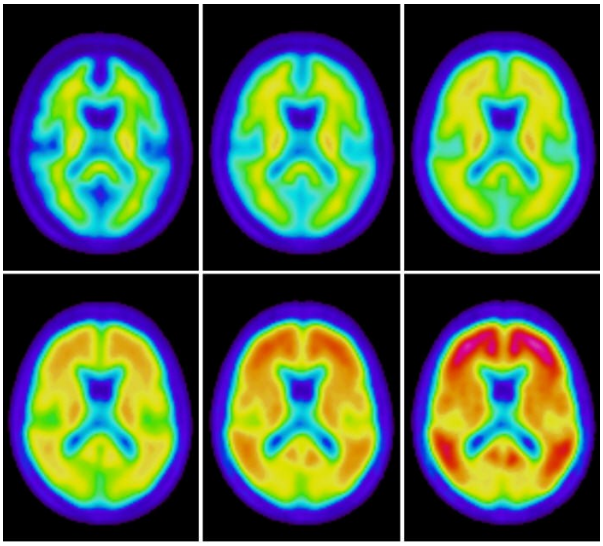


Figure 1. Template images showing typical Flutemetamol patterns going from fully normal Aβ- (upper left) to severely Aβ+ (lower right). The value of x (range 0-1) controlling the linear combination of the intercept and the slope image is increased in steps by 0.2 going from left to right, top to bottom.

Presented by: **Thurfjell, Lennart**

Classification of Amyloid-Positivity in Controls: Comparison of Approaches

Ann Cohen [1], Wenzhu Bi [2], Lisa Weissfeld [2], Howard Aizenstein [1], Eric McDade [3], James Mountz [4], Robert Nebes [1], Judith Saxton [3], Beth Snitz [3], Julie Price [4], Chester Mathis [4], William Klunk [1]

[1] University of Pittsburgh, Department of Psychiatry
[2] University of Pittsburgh, Department of Biostatistics
[3] University of Pittsburgh, Department of Neurology
[4] University of Pittsburgh, Department of Radiology

The focus of PiB-PET imaging studies is shifting increasingly towards detection of amyloid pathology in cognitively normal individuals, generating a need to define cutoffs for the earliest signs of amyloid deposition. We previously reported the iterative-outlier method (IO) using dynamic DVR data for generation of cutoffs in a group of 62 controls. Here, we examine the generalizability of the IO method when extended to late-summed (SUVR) data and alternative subject cohorts and compare IO to sparse k-means clustering (SKM). Finally, we compare the objective methods to consensus visual reads.

62 cognitively normal controls were utilized, 54 elderly (72.9 ± 7.2yrs), 8 aged 35-55yrs. An alternative cohort was generated by adding data representative of 62 very elderly (>85yrs) subjects. The objective IO and SKM methods were compared to each other and to visual reads by five experienced readers.

The IO and SKM methods identified an identical set of 16 subjects (26%) as PiB(+) using DVR data and similar results were observed using SUVR summed 50-70min post-injection. When SUVR(40-60min) data or the alternative cohort were used, the classification of these original 62 controls by IO differed significantly from SKM and from the original IO classifications using DVR data. Readers agreed with SKM classifications in 15/16 (94%) of PiB(+) and in 40/46 (87%)of PiB(-) cases. Of the 6 visually rated PiB(+) but PiB(-) by SKM, 3 were classified as PiB(+) by SKM at 2-3yr follow-up. These data suggest the SKM method is much more generalizable than the IO method and will be a useful objective approach to classify subjects as amyloid positive. Visual reads may be more sensitive to early amyloid deposition, but this may reflect that this method visualizes voxels throughout brain, as compared to the region-of-interest based approach of the IO and SKM methods, applied thus far.

Presented by: **Cohen, Ann**

Evaluation of a Binary Read Methodology for Florbetapir-PET Images

Mark Mintun , Christopher Clark , Michael Pontecorvo , Ming Lu , Michael Krautkramer , Anupa Arora, Abhinay Joshi , Catherine Veeraraj , Daniel Skovronsky

Avid Radiopharmaceuticals

The report by Clark et al (JAMA, 2011) showed increased florbetapir uptake by visual analysis correlated to increased beta-amyloid deposition. To better define the procedure for determining whether a florbetapir-PET scan is normal or abnormal, a specific binary read methodology using visual analysis was defined and tested. This methodology specified an inverted gray scale, the manner of review of the images and the specific criteria for determination of a positive image. To evaluate readers using this methodology a series of example cases and practice cases were chosen and the training tested with cases in which the subject had come to autopsy and the neuropathology was known. For these autopsy cases a CERAD neuritic plaque count of 'frequent' or 'moderate' was considered positive, while "none" or "sparse" was considered negative. A total of 19 nuclear medicine physicians were trained and evaluated. 14 readers underwent in-person training while 5 readers underwent "not-in-person" training via slides and recorded video. All readers had access to the training cases. All 19 readers interpreted the 35 autopsy cases from Phase III study reported by Clark et al and the median sensitivity was 95% and specificity was 94%. Their agreement with each other as measured by a Fleiss' kappa was 0.82. Ten readers (5 with in-person and 5 with not-in-person training) interpreted cases from an expanded set of 59 autopsies yielding a median sensitivity of 87% and specificity of 95%. In this group, there were 46 cases that came to autopsy within 12 months. In this subset, the median sensitivity was 91% and the specificity of 94%.The 5 readers with not-in-person training also interpreted an additional 92 cases without autopsy validation that consisted of cognitively healthy controls, subjects with a diagnosis of probably AD, and those with MCI. The Fleiss' kappa was 0.88 in these cases.

Presented by: **Mintun, Mark**

Session 6: Invited Didactic Lecture

Basic Principles and Controversies in PET Amyloid Imaging

Robert A. Koeppe

University of Michigan, Ann Arbor, MI

The talk will focus on some of the technical issues of amyloid imaging using positron emission tomography (PET) with an emphasis on image analysis, data extraction and interpretation. With the huge increase in interest over the past decade around [11C]PiB and now several new [18F]-labeled compounds for measuring amyloid burden, there has been considerable effort by many groups in assessing not only how well these tracers work and why, but also on the optimal ways to perform analyses and extract quantitative data. This has led to a variety of issues in the field, some still being quite controversial in regard to what are the most important areas of amyloid imaging methodology and how to implement these methods. Topics covered will include: 1) choice of reference tissue -- theoretical vs. practical issues; 2) differences between [11C]PiB and [18F]florbetapir (AV-45) and how they effect choices in methodology; 4) thresholds for amyloid positivity and how these vary with radiotracer and methods; 5) considerations for longitudinal versus cross-sectional analyses, and 6) partial volume correction -- help or hindrance.

Presented by: **Koeppe, Robert**

Session 7: Longitudinal Studies

Chairs: Keith A. Johnson, MD, Massachusetts General Hospital, Boston, MA, USA and Susan Resnick, PhD, National Institute on Aging, Bethesda, MD, USA

A Two-Year Longitudinal Assessment of A-Beta Deposition in Late MCI with 18F-Florbetaben
Christopher C. Rowe, MD, University of Melbourne, Melbourne, VIC, Australia

Use of Florbetapir-PET to Assess Progression of Amyloid Burden over Time
Michael J. Pontecorvo, PhD, Avid Radiopharmaceuticals, Philadelphia, PA, USA

Tracking Fibrillar Amyloid Accumulation and Estimating Prevention Trial Sample Sizes in Cognitively Normal APOE E4 Homozygotes, Heterozygotes and Non-Carriers
Jessica Langbaum, PhD, Banner Alzheimer Institute, Phoenix, AZ, USA

Conversion to Preclinical Alzheimer's Disease in Cognitively Normal Adults: the Characteristics from Longitudinal [11C] PIB PET Study
Andrei Vlassenko, MD, PhD, Washington University School of Medicine, St. Louis, MO, USA

Amyloid Deposition, Hypometabolism, and Cognitive Trajectories in the ADNI Population
Susan Landau, PhD, University of California, Berkeley, CA, USA

A Two-Year Longitudinal Assessment of Aβ Deposition in Late MCI with 18F-Florbetaben

Kevin Ong [1], Victor L Villemagne [1], Alex Bahar-Fuchs [1], Fiona Lamb [1], Cornelia Reininger [2], Barbara Putz [2], Beate Rohde [2], Colin L Masters [3], Christopher C Rowe [1]

[1] Centre for PET, Austin Health, Melbourne, Australia
[2] Bayer Healthcare, Berlin, Germany
[3] The Mental Health Research Institute, Melbourne, Victoria

Objective: Assess Aβ deposition longitudinally in subjects with Mild Cognitive Impairment (MCI) and explore its relationship with cognition and disease progression.

Methods: Forty-five MCI subjects were followed up for 24 months after their first ^{18}F-Florbetaben PET (FBB-PET) scan. Every participant underwent a comprehensive clinical and neuropsychological examination every 6 months and a FBB-PET scan every year. Aβ burden was quantified using SUVR employing the cerebellar cortex as reference region.

Results: At baseline, 24/45 (53%) of the MCI participants presented with high neocortical FBB retention. There was a strong relationship between neocortical SUVR and composite memory scores (r=-0.60, p<0.0001), as well as MMSE (r = -0.41, p < 0.008). At 24-month follow-up, small but significant increases in neocortical FBB SUVR were observed in MCI with high-FBB retention at baseline (+2.4%, p=0.02). Progression to AD occurred in 79% of MCI with high-FBB, with 24% of the low-FBB MCI subjects progressing to other dementias. One low-FBB MCI developed mixed dementia.

Conclusions: Aβ deposition is a slow process that precedes severe cognitive impairment. Extensive Aβ deposition is associated with a significant higher risk of progression from MCI to AD over 2 years. ^{18}F-Florbetaben-PET is a sensitive technique to longitudinally assess Aβ deposition in the brain.

Presented by: **Rowe, Christopher**

Use of Florbetapir-PET to Assess Progression of Amyloid Burden over Time

Abhinay Joshi , Michael Pontecorvo , Christopher Breault , Ming Lu , Mark Mintun , Alan Carpenter , Daniel Skorvonsky

Avid Radiopharmaceuticals

Objective: To evaluate the change in beta-amyloid deposition in mild cognitive impairment (MCI) and cognitively normal elderly controls (CN) over 2-years of follow-up.

Method: 85 subjects comprised of 49 CNs (MMSE ≥ 29; age 71±11) and 36 MCI (CDR 0.5, MMSE >24; age 71±10) underwent florbetapir-PET scans at baseline and approximately two years later (23±4 months). Scans were independently spatially normalized to a standard florbetapir PET template in Talairach space. Standard uptake value (SUVr) ratios were calculated using the mean of pre-defined anatomically relevant cortical regions (precuneus, posterior cingulate, anterior cingulate, frontal, temporal and parietal), relative to entire cerebellum. The relationship between change in SUVr and baseline PET SUVr and diagnostic group was examined.

Results: SUVr values from baseline and follow-up scans were highly correlated (Pearson correlation, r=0.96). Using an SUVr cut-off of 1.10, 44% (16/36) of MCI subjects and 20 % (10/49) of CN subjects had scans at baseline that were considered positive for amyloid. The group of subjects that were positive at baseline (mean SUVr= 1.37) had a significant change in SUVr (mean delta= +0.06; $p< 0.05$) while the subjects that were negative at baseline (mean SUVr=0.98) did not (mean delta = +0.005; p=0.40). Interestingly, among the 59 subjects that were amyloid negative at baseline, 4 subjects (6.8%) had converted to amyloid positive on the follow-up scan for a conversion rate of 3.5 % per year. None of the subjects who were amyloid positive at baseline converted to amyloid negative on follow-up.

Conclusion: These florbetapir-PET results suggest non-demented subjects with evidence of beta-amyloid deposits have continued increase in amyloid. Those subjects without evidence of beta-amyloid show no mean increase at two years. However, a small number of subjects may convert from negative to positive during this time.

Presented by: **Pontecorvo, Michael**

Tracking Fibrillar Amyloid Accumulation and Estimating Prevention Trial Sample Sizes in Cognitively Normal APOE E4 Homozygotes, Heterozygotes and Non-Carriers

Adam Fleisher [1], Jacquelin Esque [1], Kewei Chen [1], Candy Monarrez [1], Xiaofen Liu [1], Wendy Lee [1], Auttawut Roontiva [1], Pradeep Thiyyagura [1], Jessica Langbaum [1], Daniel Bandy [1], Richard Caselli [2], Eric Reiman [1]

[1] Banner Alzheimer's Institute, Phoenix, AZ
[2] Department of Neurology, Mayo Clinic, Scottsdale, AZ

Background: We previously used Pittsburgh Compound B positron emission tomography (PiB PET) to characterize and compare baseline fibrillar amyloid measurements in cognitively normal late middle-aged and older adult *apolipoprotein-E4 (APOE4*) homozygotes, heterozygotes and non-carriers (Reiman et al, 2009). Here, we used PiB PET to track the 24-month accumulation of fibrillar amyloid in these genetic groups and estimate the number of at-risk persons needed to detect attenuation in amyloid accumulation in 24-month pre-symptomatic Alzheimer's disease (AD) trials.

Methods: 90 min dynamic PET scans were acquired at baseline and 24-month follow-up. Cerebral-to-cerebellar PiB distribution volume ratios (DVR) were calculate in twenty-nine 63±4 year-old cognitively normal participants, including 8 *APOE4* homozygotes, 8 heterozygotes, and 13 non-carriers. SPM8 was used to characterize and compare brain maps of 24-month PiB DVR increases, as well as increases in six automatically labeled regions-of-interest (ROIs). The number of cognitively normal homozygotes and/or heterozygotes needed per group to detect a 25% slowing in amyloid accumulation with two-tailed p=0.05, 80% power was estimated.

Results: While the *APOE4* homozygotes were slightly younger (p=0.05), the three genetic groups did not differ in their gender distribution, educational level, clinical ratings or neuropsychological test scores, or in their 24-month cognitive test ratings and changes scores. The APOE4 homozygotes and heterozygotes had significant 24-month PiB DVR increases compared to non-carriers, evident in the statistical brain maps, ROIs, and mean cerebral measurements ($p<0.001$). We estimate the need for 75 heterozygotes, 78 homozygotes, or 76 carriers per treatment arm to detect 25% slowing in amyloid accumulation in24-months.

Conclusions: This study demonstrates increased rates of amyloid accumulation in cognitively normal adults at three levels of genetic risk for AD. A relatively small number of at-risk subjects may be needed to detect amyloid-modifying treatment effects in pre-symptomatic AD trials, as we have proposed in the Alzheimer's Prevention Initiative (API).

Presented by: **Langhbaum, Jessica**

Conversion to Preclinical Alzheimer's Disease in Cognitively Normal Adults: The Characteristics from Longitudinal [11C] PIB PET Study

Andrei Vlassenko [1], Tyler Blazey [1], Yi Su [1], Chengjie Xiong [2], Alison Goate [3], Tammie Benzinger [1], Mark Mintun [4], John Morris [5]

[1] Department of Radiology, Washington University School of Medicine
[2] Division of Biostatistics, Washington University School of Medicine
[3] Department of Psychiatry, Washington University School of Medicine
[4] Avid Radiopharmaceuticals
[5] Department of Neurology, Washington University School of Medicine

The concept of preclinical Alzheimer's disease (AD) implies that beta-amyloid (Aβ) deposits may accumulate in the brain years prior to the clinical manifestations. Cognitively normal individuals with preclinical AD as detected by increased uptake of [^{11}C] PIB have a greater risk of progression to symptomatic AD. However the conversion to preclinical AD in cognitively normal individuals has not been characterized yet. In this study, we evaluated Aβ accumulation in 146 cognitively normal older adults who underwent two [^{11}C] PIB PET scans about 2.6 years apart. Global Aβ deposition was estimated using mean cortical binding potential (MCBP) from gyrus rectus, prefrontal cortex, precuneus and lateral temporal cortex, and MCBP > 0.18 was considered abnormal representing PIB-positive state or preclinical AD. Of the 146 participants, 115 individuals were PIB-negative and 21 individuals were PIB-positive on both [^{11}C] PIB scans. Ten of the 125 individuals (7 females, mean age 65.5 ± 8.3 years), who were PIB-negative at the first [^{11}C] PIB scan, converted to PIB-positive state, with an incidence of conversion of 3.1% per year. At the second [^{11}C] PIB scan, converters demonstrated substantially greater Aβ deposition in many cortical and subcortical regions compared to PIB-negative individuals. The magnitude of Aβ accumulation was dependent on the duration of follow-up, with greater changes in Aβ levels resulting from longer follow-up. The mean annual rate of change in Aβ deposition in converters was similar to that in individuals PIB-positive at both scans. Seven of the 10 converters were APOE4 positive. The incidence of conversion to preclinical AD in APOE4 positive individuals was 7.0%. The youngest participant to convert was 56 years old at the second PIB scan and he was a carrier of two APOE4 alleles. Our findings suggest that conversion to preclinical AD is associated with continuous and widespread progression in AD pathology.

Presented by: **Vlassenko, Andrei**

Amyloid Deposition, Hypometabolism, and Cognitive Trajectories in the ADNI Population

Susan Landau, William Jagust

Helen Wills Neuroscience Institute, UC Berkeley

A greater understanding of the relationship between amyloid deposition and cognitive performance is critical for determining the utility of amyloid imaging for identifying individuals likely to progress to AD.

We examined associations between amyloid deposition, hypometabolism, and cognitive function in a large sample of ADNI participants (N = 325; Normal=102, early MCI = 129, MCI = 64, AD = 30) with recent florbetapir F18 scans. Subjects were categorized as florbetapir +/- based on uptake in cortical grey matter relative to cerebellar grey matter, and using a threshold derived from a previously validated PiB threshold. A concurrent FDG-PET scan was available for most subjects (N = 294), and subjects were also categorized as hypometabolic or not (+/-) using a previously determined set of regions of interest and threshold. Longitudinal episodic memory performance was assessed at regular intervals prior to and concurrently with the florbetapir scans (average followup time = 4.4 years) for a subset of participants (N = 155).

Proportions of florbetapir+ individuals were comparable to those reported previously for PiB [Normal 31/102(30%), EMCI 55/129(43%), MCI 42/64(66%)], with the exception of a low proportion of florbetapir+ AD patients in this sample [22/30(73%)].

We carried out mixed effects regression to determine whether florbetapir (+/-) and FDG (+/-) status were associated with longitudinal cognitive trajectories. Florbetapir+ normals and MCI subjects had greater episodic memory decline than florbetapir- subjects. When FDG status was added to the model, florbetapir status remained a significant predictor for normals but not for MCI subjects.

Our findings indicate that subclinical change in cognitive performance is associated with amyloid deposition and hypometabolism in normals. Tracking changes in cognitive function, particularly in normal and mildly impaired individuals, will help clarify the predictive role of amyloid PET imaging.

Presented by: **Landau, Susan**

Session 8: Multimodal Studies

Chairs: Clifford R. Jack, MD, Mayo Clinic, Rochester, MN, USA and
Christopher C. Rowe, MD, University of Melbourne, Melbourne, VIC, Australia

Biomarker Correlates in the ADNI AD Population Suggesting Dementia Unlikely Due to AD
Val J. Lowe, MD, Mayo Clinic, Rochester, MN, USA

Amyloid-Modulated Age-Related Changes in FDG Metabolism in Normal and Medley Impaired Elderly
J. Alex Becker, PhD, Massachusetts General Hospital/Harvard Medical School, Boston, MA, USA

Diverging PIB and FDG Covariance Patterns Across Clinical Variants of AD
Manja Lehmann, PhD, University of California, San Francisco, CA, USA

Neuroimaging Markers Predict Cognitive Decline in PD
Stephen N. Gomperts, MD, PhD, Massachusetts General Hospital, Boston, MA, USA

Biomarker Correlates in the ADNI AD Population Suggesting Dementia Unlikely Due to AD

Val Lowe [1], Clifford Jack [1], Patrick Peller [1], Nirubol Tosakulwong [2], Stephen Weigand [2], Heather Wiste [2], Lennon Jordan [1], Ronald Petersen [3]

[1] Radiology, Mayo Clinic, Rochester
[2] Biostatistics, Mayo Clinic, Rochester
[3] Neurology, Mayo Clinic, Rochester

Objective: ADNI includes subjects categorized with the clinical diagnosis of probable AD. Data from these subjects have been used as the basis for determining the utility of biomarkers in AD research. Recently, published modifications have been proposed to the clinical diagnostic characterization of AD by incorporating new biomarkers, especially in data used for research. We assessed the ADNI probable AD population to determine if any subjects are included that fit the proposed diagnostic classification of "Dementia unlikely to be due to AD" based on negative AB and neuronal injury biomarkers.

Methods: The ADNI AD population was searched for subjects with FDG PET and amyloid biomarkers. FDG was used as a neuronal biomarker surrogate. The subgroup was interrogated by searching for FDG findings that were negative for AD. Specifically, FDG patterns were assessed as being AD-like, FTD-like or other by blinded readers using Cortex ID. In addition we searched the sub-population for those who had negative AB biomarkers (CSF and/or Amyloid PET).

Results: Of the 92 subjects we reviewed, 58 (63%) had positive amyloid biomarkers and an AD pattern on FDG. Seven subjects (8%) were identified who had negative amyloid biomarkers. Of these 7, FDG PET demonstrated an AD pattern in 3, an FTD pattern in one and an "other" pattern in 3. Two (2/7) had both negative CSF and PiB. FDG PET findings uncharacteristic for AD were seen in an additional 27 subjects with positive amyloid studies.

Conclusion: Several subjects within the ADNI AD population fit the recently proposed characterization of "Dementia unlikely to be due to AD" based on negative AB and neuronal injury biomarkers. Several others have a single biomarker that is negative. These findings raise important considerations in research analysis of ADNI AD population data particularly with respect to the specificity of biomarkers and clinical diagnosis.

Presented by: **Lowe, Val**

Amyloid-Modulated Age-Related Changes in FDG Metabolism in Normal and Mildly Impaired Elderly

J. Alex Becker [1], Christopher Gidicsin [2], Jacqueline Maye [2], Lesley Pepin [2], Reisa Sperling [3], Keith Johnson [3]

[1] Massachusetts General Hospital, Harvard Medical School
[2] Massachusetts General Hospital
[3] Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School

An increase in cerebral amyloid-beta (Ab) accumulation has been postulated as one of the initiating events in Alzheimer's disease that leads to a cascade of sequelae including neurodegeneration and declining glucose metabolism.

Objective: To evaluate the association of cerebral amyloidosis with longitudinal change in FDG metabolism in cognitively normal (CN; CDR=0) older individuals and individuals with MCI (CDR=0.5).

One hundred-five CN and 166 MCI subjects with known amyloid status and at least two FDG PET time-points available (mean acquisition interval ~2.5yr) were identified in the ADNI1 and Harvard Aging Brain Study samples (68 Ab- and 37 Ab+ CNs, 46/120 MCIs). FDG and PiB volumes were spatially normalized using SPM8, resampled in AAL regions, and scaled to pons (FDG) or cerebellum (PIB). FDG change was modeled in CN and MCI groups separately as a function of baseline age, time since baseline, amyloid status (Ab+/-) and Ab-by-time interaction using mixed-effect regression.

Significant within-subject FDG decline with age was identified in Ab- CNs most prominently in the anterior and posterior cingulate ($p<0.02$), superior temporal pole ($p<10^{-4}$) and hippocampus ($p<0.005$). Ab+ CNs exhibited no regions with significantly different baseline FDG or with significantly different rates of within-subject FDG decline compared to Ab- subjects. Among Ab- MCIs , within-subject decline of metabolism with age remained significant in the hippocampus ($p<10^{-3}$), posterior cingulate ($p<0.03$) and superior temporal pole ($p<10^{-4}$), while Ab+ MCIs exhibited significantly decreased baseline metabolism globally ($p<10^{-3}$), and specifically in the inferior parietal and lateral temporal cortices, and in the precuneus/posterior cingulate ($p<10^{-3}$). Ab+ MCIs had significantly greater rates of decline in hippocampus ($p<0.02$), inferior temporal ($p<0.04$), and posterior cingulate ($p<0.02$).

These results suggest that dynamics of FDG metabolism differ by clinical stage, such that MCI subjects exhibit steeper within-subject declines than CN subjects. We were not able to demonstrate with regional data steeper FDG declines in Ab+ vs Ab- CNs.

Presented by: **Becker, J. Alex**

Diverging PIB and FDG Covariance Patterns across Clinical Variants of AD

Manja Lehmann [1,2], Pia Ghosh [1,2], Cindee Madison [2], Chiara Corbetta [2], Andrea Long [3], Bruce Miller [1], William Jagust [1,2,3], Gil Rabinovici [1,2,3]

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

The current study aimed to assess patterns of covariance of PIB and FDG uptake in regions that are implicated in specific clinical presentations of AD.

The study included 49 patients with probable AD (24 amnestic (AD-MEM), 11 language (AD-LANG) and 14 visual variants (AD-VIS), age = 65.0 (9.4) years, 55% male). In a previous study, 3 peak atrophy voxels that showed selective grey matter atrophy in each AD variant compared with the other two were identified in: the right middle frontal gyrus in AD-MEM, the left superior temporal sulcus in AD-LANG, and the right middle occipital gyrus in AD-VIS. 6mm spheres were drawn around these voxels, and FDG and PIB values were extracted for each ROI. Multiple regressions were performed in SPM to assess correlations between FDG and PIB uptake in the ROIs with uptake at each voxel across the brain. Analyses were conducted with all subjects pooled together, adjusting for age, gender and education.

FDG uptake in the three ROIs produced distinct patterns of covariance (Figure A), with the regions involved for each ROI greatly overlapping with specific functional networks. Regions found to correlate with FDG in the AD-MEM region greatly overlapped with the default-mode network, whilst FDG uptake in the AD-LANG ROI mainly correlated with hypometabolism in left hemisphere regions typically associated with the language network, and FDG in the AD-VIS ROI correlated with regions of the ventral and dorsal visual processing networks. In contrast, PIB uptake in the three ROIs showed diffuse covariance patterns across the brain, with great overlap between the three correlation maps (Figure B).

Regions targeted in AD clinical variants showed distinct FDG covariance patterns that corresponded with expected functional networks, whereas PIB uptake covaried diffusely across the brain. We hypothesize that AD syndromes are associated with degeneration of specific networks, and that anatomic differences between AD variants are not explained by distinctions in the regional deposition of amyloid.

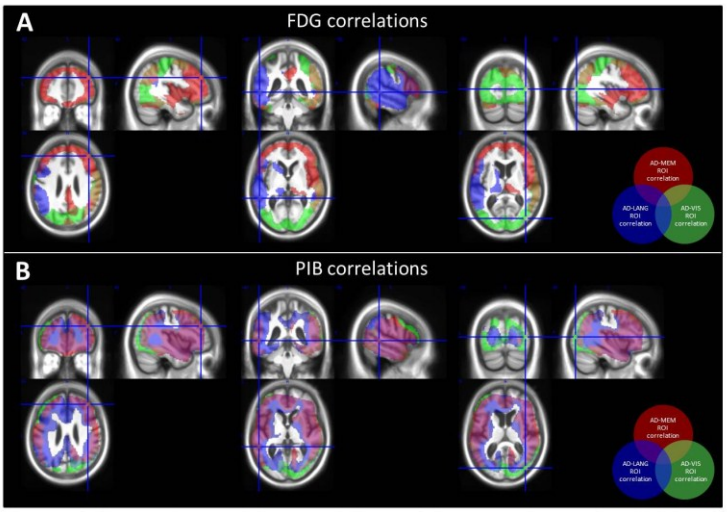


Figure: Overlap between **A)** FDG correlation maps and **B)** PIB correlation maps. Overlap maps show correlations with FDG/PIB in the AD-MEM ROI (red), AD-LANG ROI (blue), and AD-VIS ROI (green). Shown are statistically significant t scores after multiple comparisons correction (FWE at p<0.05). Crosshairs are set to MNI coordinates of peak atrophy voxel for AD-MEM ROI (left, 40 42 30), AD-LANG ROI (middle, -56 -40 1), and AD-VIS ROI (right, 39 -88 10).

Presented by: **Lehmann, Manja**

Neuroimaging Markers Predict Cognitive Decline in PD

Stephen Gomperts, Andrea Santarlasci, Joseph Locascio, Marta Marquie-Sayagues, Dorene Rentz, Keith Johnson, John Growdon

Massachusetts General Hospital

Background: Cognitive impairments are common in Parkinson disease (PD), and the increase in severity and number over time often leads to frank dementia. Brain amyloid accumulation is an early pathogenic event leading to Alzheimer disease, and we hypothesized that amyloid deposition may contribute to cognitive impairment in PD.

Specific Aims: To determine whether amyloid deposition, as indexed by Pittsburg Compound B (PiB) uptake using Positron Emission Tomography (PET), predicts cognitive decline in a cohort of non-demented PD subjects.

Methods: We examined 47 non-demented subjects with PD, of whom 36 had normal cognition (PD-nl) and 11 met criteria for PD-MCI (PD with Mild Cognitive Impairment). All subjects underwent baseline standardized neurological and neuropsychological examinations and PiB PET scans, and annual clinical examinations for up to 5 years. PiB amyloid deposition was measured in the precuneus region (Distribution Volume Ratios) and its topography assessed by SPM (Statistical Parametric Mapping). Data were analyzed using mixed random and fixed effects and Cox proportional hazards models.

Results: PiB uptake did not distinguish baseline diagnoses of PD-MCI and PD-nl, but correlated with worsening CDR sum of box score for the entire cohort. Those with a diagnosis of PD-MCI at their most recent visit had higher PiB values than those who remained PD-nl, adjusting for age. Of the original 36 PD-nl, 6 progressed to PD-MCI and 2 to PD dementia (PDD); of the original 11 PD-MCI, 4 converted to PDD. Patients above the median PiB value converted to a more severe diagnosis significantly ($p=0.04$) faster than those who were below it. In contrast to progression of cognitive impairment, increased PiB uptake did not affect progression of motor signs.

Conclusions: Although amyloid deposition is not required for the development of cognitive impairment in PD, our data suggest that amyloid contributes to cognitive decline in non-demented PD subjects.

Presented by: **Gomperts, Stephen**

Session 9: Tau PET Ligands

Chairs: Chester A. Mathis, PhD, University of Pittsburgh, Pittsburgh, PA, USA, and Sam Gandy, MD, PhD, Mount Sinai Hospital, New York, NY, USA

In Vivo Tau Imaging
Victor L. Villemagne, MD, Austin Hospital, Melbourne, VIC, Australia

Discovery of Novel [18F]-PET Agents for Imaging Neurofibrillary Tangles (NFTs)
Hartmuth C. Kolb, MD, Siemens Molecular Imaging, Culver City, CA, USA

In Vivo Tau Imaging

Victor L Villemagne [1], Shozo Furumoto [2], Michelle T Fodero-Tavoletti [3], Svetlana Pejoska [1], Yukitsuka Kudo [4], Rachel Mulligan [1], John Hodges [5], Colin L Masters [6], Kazuhiko Yanai [2], Christopher C Rowe [1], Nobuyuki Okamura [2]

[1] Centre for PET, Austin Health, Melbourne, Australia
[2] Dept Pharmacology, Tohoku University School of Medicine, Sendai, Japan
[3] Dept Pathology, Bio21 Institute, University of Melbourne, Australia
[4] Div of Radiopharmaceutical Chemistry, Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan
[5] Neuroscience Research Australia, Sydney, Australia
[6] The Mental Health Research Institute, Melbourne, Victoria

Definitive diagnosis of tauopathies such as Alzheimer's disease (AD), some variants of frontotemporal lobe degeneration, (FTLD) progressive supranuclear palsy and corticobasal degeneration, is still reliant upon post-mortem examination of the human brain. Furthermore, these diseases are often difficult to differentiate clinically due to overlapping phenotypes, especially at early stages of their development. In vivo imaging with PET will allow new insights into tau deposition in the human brain, facilitating research into causes, diagnosis and treatment of taupathies, as is now available for Aβ. We have characterized ^{18}F-THK523, a novel tau imaging agent developed at Tohoku University in Sendai, Japan, demonstrating its selectivity and specificity for tau pathology both in vitro and in vivo. In vitro binding studies demonstrated that ^{18}F-THK523 binds with higher affinity to a greater number of binding sites on recombinant tau compared with $A\beta_{1-42}$ fibrils. Autoradiographic and histofluorescence analysis of human AD hippocampal brain sections, demonstrated that THK523 co-localized with immunoreactive tau pathology, but failed to highlight Aβ plaques. In small animal PET studies, there was a significantly higher (48%) brain retention of ^{18}F-THK523 in tau transgenic (rTg4510) mice compared with their wild-type littermates or APP/PS1 mice. The preclinical examination of THK523, with its high affinity and selectivity for tau pathology both in vitro and in vivo, along with toxicity studies, indicated that ^{18}F-THK523 fullfilled criteria for human PET studies. Initial human PET studies comparing ^{18}F-THK523 and ^{11}C-PiB have shown that ^{18}F-THK523 does not bind to Aβ in AD. While no cortical retention was observed in healthy controls and Semantic Dementia (SD) patients, higher retention, albeit much lower than the observed with ^{11}C-PiB, was detected in AD. Further studies are needed to confirm these initial findings.

Presented by: **Villemagne, Victor L**

Discovery of Novel [18F]-PET Agents for Imaging Neurofibrillary Tangles (NFTs)

Hartmuth Kolb, Janna Arteaga, Dan Cashion, Gang Chen, Umesh Gangadharmath, Felipe Gomez, Dhanalakshmi Kasi, Qianwa Liang, Katrin Szardenings, Joseph Walsh

Siemens

Background: There are two main neuropathologic hallmarks in AD, senile neuritic plaques around an amyloid beta core and neurofibrillar protein aggregates containing tau protein. In AD patients tau is abnormally phosphorylated and loses its normal function.

Methods: In order to screen many compounds as potential tau binders, we developed a competitive autoradiography screening method utilizing human AD brain sections. Selectivity of tau binding compounds was determined by competition experiments in tau rich or Aβ rich brain sections. Grey and white matter binding was measured for each candidate. Brain uptake of [F18]-labeled tracers was measured in rodents and non-human primates. Metabolism and pharmacokinetic studies were performed in mice.

Results: We have discovered several novel, small molecule tau binding compounds that show high selectivity for native tau aggregates in human AD brain sections over β-amyloid. Several of these candidates were further optimized and shown to have a high brain uptake/fast clearance in mice, rats, and primates. White matter distribution in non-human primates is very low. Metabolism studies of our lead candidates show very good stability in plasma and no metabolite presence in mouse brains.

Conclusions: We have identified several novel small heterocyclic compounds that bind to human PHF-tau. Our in vitro and in vivo studies confirm that our lead candidates [F18]-T807 and T808 bind to PHF-tau selectively over β-amyloid, shows good PK and metabolic properties, and exhibits excellent brain uptake/washout kinetics in rodent and non-human brains.

Presented by: **Kolb, Hartmuth**

HAI Poster Abstracts

Subjective Cognitive Complaint is Associated with Increased Amyloid Burden in Cognitively Normal Individuals

Rebecca Amariglio [1], Lauren Wadsworth [2], Natacha Lorius [1], Alex Becker [2], Keith Johnson [2], Reisa Sperling [1], Dorene Rentz [1]

[1] BWH
[2] MGH

Background: Accumulating evidence suggests that subjective cognitive complaint (SCC) may represent one of the earliest behavioral changes heralding risk for future cognitive decline due to Alzheimer's disease (AD). Furthermore, associations between SCC and a variety of AD biomarkers have been found in cognitively normal (CN) individuals but not with amyloid imaging and standardized measures of SCC.

Objective: We sought to determine whether SCC is associated with cortical amyloid burden using Positron Emission Tomography with Pittsburgh Compound B (PiB PET) in CN individuals and with more extensive behavioral measures than used previously.

Methods: Ninety four CN individuals (CDR = 0, MMSE ≥27) underwent PiB PET imaging and behavioral assessments of SCC including the Everyday Cognition Scale (E-Cog), Memory Function Questionnaire (MFQ), the seven subjective questions (7 Questions) that were previously reported as identifying cognitive impairment in SCC, as well as the Selective Reminding Test (SRT) and Geriatric Depression Scale (GDS). Amyloid deposition was assessed using PiB PET DVR with an aggregate of cortical regions. Multivariate models related PiB retention to the three different SCC questionnaires separately, each controlling for age. Secondary analyses covarying for SRT, GDS, and APOE status were also performed.

Results: Higher PiB retention was associated with greater SCC in two of the behavioral measures (E-Cog: beta=5.11, p=0.01; 7 Questions: beta=1.55, p=0.012) and at trend level for the third (MFQ: beta= -0.81, p=0.06). The relationship between PiB and SCC for the E-Cog and 7 Questions remained significant when SRT and GDS were included as covariates. APOE status did not mediate the relationship between SCC and PiB.

Conclusions: These results suggest that SCC is associated with greater amyloid burden, unrelated to objective memory performance or depressive symptoms in CN. SCC may assist detection of the earliest cognitive changes in preclinical AD, particularly when more extensive and targeted instruments are used.

Presented by: **Amariglio, Rebecca**

1

A New Method for Automated Regional and Voxelwise Quantification of Brain Beta-Amyloid Load as Imaged by Florbetaben PET

Henryk Barthel [1], Daniel Butzke [1], Markus Diemling [2], Michio Senda [3], George Zubal [4], John Seibyl [4], Hermann-Josef Gertz [1], Martin Pessel [5], Cornelia Reininger [5], Osama Sabri [1]

[1] University of Leipzig, Leipzig, Germany
[2] Hermes Medical Solutions, Stockholm, Sweden
[3] IBRI, Kobe, Japan
[4] Institute of Neurodegenerative Disorders, New Haven, USA
[5] Bayer Healthcare, Berlin, Germany

Florbetaben is a promising beta-amyloid-targeted PET tracer currently in global clinical development (Barthel et al., Lancet Neurol 2011). In the beta-amyloid PET community there is a growing understanding that standardization of image data analysis is of importance. For florbetaben PET, in addition to visual scan interpretation, quantification via standardized uptake value ratios (SUVRs) and total brain volume affected by beta-amyloid may be of significant value. Recently, we identified the HERMES BRASS module as a potential tool to operator-independently determine both of these quantitative parameters. Here, we evaluated the diagnostic performance of this tool when analyzing multi-center data.

A BRASS database was generated from florbetaben PET scans of 93 cognitively normal, beta-amyloid-negative healthy volunteers (HVs). Using this normal database, 145 florbetaben PET scans (77 patients with probable AD, 68 HVs) obtained from the multi-center phase 2A trial were analyzed in a voxel-based and volume of interest (VOI)-based manner. The VOI analysis resulted in composite SUVRs which were compared to those obtained by the reference technique.

The BRASS analysis of the florbetaben datasets was possible with minimal operator-interventions within 41±4 sec. The composite SUVRs as determined by BRASS correlated significantly with those determined by the reference method ($r=0.85$, $p<0.001$). Both SUVR datasets discriminated equally well between ADs and HVs ($p<0.001$, Cohen's $d = 1.37$ for both approaches). In the ADs and HVs, 3.2±2.7 vs. 0.1±0.4 ($p<0.001$, Cohen's $d = 1.61$) neocortical regions were defined by BRASS as pathologic (z-score > 2.5). The total brain volume affected by beta-amyloid was 18.6±25.7 vs. 0.8±3.7ml for the ADs and HVs ($p<0.001$).

The BRASS tool customized for florbetaben PET demonstrated excellent ability in discriminating between ADs and HVs. Thus, this software has great potential in supporting the visual interpretation of florbetaben PET image data in a rapid, user friendly and operator-independent manner.

Research support: Bayer Healthcare

Presented by: **Barthel, Henryk**

2

A Global Phase 2B Efficacy and Safety Trial to Investigate Florbetaben Beta-Amyloid Brain Positron Emission Tomography in Alzheimer's Disease

Osama Sabri [1], Hermann-Josef Gertz [1], Keiichi Ischihara [2], Amane Tateno [2], Alexander Drzezga [3], Timo Grimmer [3], Michio Senda [4], Yasuji Yamamoto [5], Cornelia Reininger [6], Henryk Barthel [1]

[1] *University of Leipzig, Leipzig, Germany*
[2] *Nippon Medical School, Tokyo, Japan*
[3] *Technical University Munich, Munich, Germany*
[4] *IBRI, Kobe, Japan*
[5] *Kobe University Hospital, Kobe, Japan*
[6] *Bayer Healthcare, Berlin, Germany*

The efficacy, safety and biological relevance of florbetaben PET in detecting/excluding cerebral beta-amyloid was recently demonstrated in a phase 2A trial (Lancet Neurol 2011). The present open-label, non-randomized, multicenter (21 PET sites, four continents), phase 2B trial was designed to prospectively confirm those results using an expert consensus panel clinical diagnosis as the standard of truth.

272 subjects, 147 patients with probable Alzheimer's disease ([AD], MMSE = 18–26, CDR = 0.5–2) and 125 age-matched healthy volunteers ([HV], MMSE ≥28, CDR = 0) underwent florbetaben brain PET. For quantitative assessment, SUV ratios (reference: cerebellar cortex) were determined. The co-primary efficacy variables were the sensitivity and specificity of the visual assessment of images 90–110 min p.i. (majority read).

>95% of the PET images visually assessed were considered high quality. The consensus panel verified the onsite diagnosis in 83.5% of the probable ADs and 100% of the HVs. Optimized reader training (transverse orientation; gray scale; 4 target VOIs; gray matter signal intensity compared to maximum white matter intensity; one target region "positive" → entire brain "positive") resulted in test read (150 phase 2 datasets) results of 95% sensitivity and specificity, respectively. SUV ratios were higher in the ADs as compared to the HVs in frontal and other neocortical VOIs ($p<0.001$). No safety concerns were observed.

The consensus panel findings verify that, even among experts, the clinical AD diagnosis remains challenging. Florbetaben PET imaging provided high-quality data across multiple centers, with high discriminative power to separate between AD patients and HVs. These results of this confirmatory 2B trial are in concordance to those of the exploratory 2A trial. Taken together, florbetaben PET has a great potential to supplement the routine diagnostic toolbox in AD.

Research support: Bayer Healthcare

Presented by: **Sabri, Osama**

3

Reference Tissue Normalization in Autosomal Dominant AD: Comparison of Cerebellar Versus Brainstem Referencing for [11C]PIB in the DIAN Cohort

Tammie Benzinger [1], Robert Koeppe [2], YI Su [1], Tyler Blazey [1], Clifford Jack [3], Paul Thompson [4], Andrew Saykin [5], Steven Correia [6], Reisa Sperling [7], Peter Schofield [8], Christopher Rowe [9], Nicholas Fox [10], Adam Brickman [11], Keith Johnson [7]

[1] *Washington University School of Medicine in Saint Louis*
[2] *The University of Michigan*
[3] *The Mayo Clinic*
[4] *University of California, Los Angeles*
[5] *University of Indiana*
[6] *Butler University*
[7] *Brigham and Women's Hospital*
[8] *University of New South Wales*
[9] *University of Melbourne*
[10] *University College London*
[11] *Columbia University*

Background: The DIAN Study (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's Disease (ADAD). Imaging studies acquired in this cohort include [11C]PIB, FDG PET and MRI. Mutations represented in this cohort include presenilin 1 and 2 and amyloid precursor protein (PSEN1, PSEN2, APP). [11C]PIB processing for sporadic AD (sAD) has traditionally used a cerebellar region of interest as a reference tissue. However, in ADAD participants may be positive for [11C]PIB in the cerebellum, so an alternative tissue reference may be needed.

Methods: 120 participants underwent 11C]PIB, FDG PET and MRI. All modalities were transformed and processed in a common atlas space. FreeSurfer parcellation of cortical and subcortical grey and white matter was performed. As there is no standard FreeSurfer region for the pons/brainstem that would reliably be covered by the scans collected in this study, manual pontine/brainstem regions were outlined on each individual scan.

Results/Discussion: Using cerebellar referencing, non-demented carriers were significantly different from the non-carrier cohort in the deep grey matter structures of the caudate, putamen, globus pallidus, and thalamus and in every cortical grey matter structure. Similar analysis using the pointine/brainstem reference is ongoing. The DIAN study represents the largest cohort of families with ADAD studied with imaging to date. It may be helpful to the field to compare approaches for data normalization and processing, especially when traditional reference regions may show elevated signal.

Presented by: **Benzinger, Tammie**

4

Intensity Anchors for Reading [18F]Flutemetamol Amyloid Images

Chris Buckley [1], *Gil Farrar* [1], *David Brooks* [2], *Kerstin Heurling* [1]

[1] *GE Healthcare*
[2] *GE Healthcare/Imperial College London*

The visual review of F18 amyloid-tracer PET images and their classification requires a judgement on whether cortical levels of tracer binding are normal or abnormal. To make this classification consistently and reliably a methodology for working with intensity anchors has been established and implemented.

The ratio of the SUV in grey matter to that in the sub cortical white matter (SCWM) and also to the pons was measured in [18F]flutemetamol PET scans of healthy volunteers. The variation was low with an SD/mean of 7% in grey matter SUV to SCWM SUV ratio and 6% in grey matter SUV to PONS SUV ratio.

This low level of variation provides confidence in using white matter rich regions as an intensity reference for scaling images for visual inspection. For [18F]flutemetamol, the pons provides a high-end intensity anchor. Images are scaled using regular workstation controls such that they are displayed with zero at the minimum and with the pons at 90%. This reliably places the grey matter of the cerebellum at 30% intensity and abnormal levels are easily identified in the grey matter with this scaling methodology.

The methodology is assisted by using a color scale in which has clearly identified intensity bands:

90% for Pons scaling,
20% to 40% for normal grey matter,
>60% for abnormal grey matter.

Using this methodology in phase II studies, Inter reader consistency was measured as 98% (k=0.96), intra-reader self consistency 100% and consistency with automated SUVR based classification to HV levels in HV & pAD 100%.

Presented by: **Buckley, Chris**

5

Molecular Imaging of Protein Conformation Changes in Human Amyloid Diseases

Ina Caesar [1], K. Peter R. Nilsson [2], Patrick R. Hof [1], Stefan Prokop [3], Vahram Haroutunian [1], Frank L. Heppner [3], David M. Holtzman [4], Michelle E. Ehrlich [1], Sam Gandy [1]

[1] *Mount Sinai School of Medicine*
[2] *Linköping University*
[3] *Charité-Universitätsmedizin Berlin*
[4] *Washington University in St Louis*

Luminescent Conjugated Oligothiophenes (LCOs) show promise as tools for the investigation of protein conformation in amyloidosis and other protein misfolding diseases. The fluorescent spectra emitted by LCOs differ as a function of the conformation of the protein aggregates. This property allows LCOs to distinguish between different structures of a broad range of amyloidogenic proteins, and thereby potentially identify the toxic conformers associated with proteinopathies. In this study, we used LCOs to study the molecular mechanisms underlying how protein aggregation state(s) influence the clinical and molecular pathophysiology of Alzheimer's disease (AD) and Huntington's disease (HD).

The *APOE* ε4 allele is the most common identified genetic risk factor for developing typical late-onset sporadic AD. The molecular mechanisms underlying how the apoE protein isotype influences AD onset and disease progression are largely unknown. Human AD postmortem brain samples were analyzed for structural differences in the amyloid aggregates of senile plaques and neurofibrillary tangles as a function of apoE protein isotype. To determine if LCOs are promising for "amyloid-like" aggregates, transgenic mouse models of HD were analyzed for structural differences in the aggregates associated with polyglutamine (polyQ) amplification in the huntingtin (htt) protein encoded by the different transgenes. The length of the polyQ expansion in the huntingtin protein is directly linked to the disease progression and the age of onset in humans.

In human AD brain, we observed differences in LCO spectra as a function of apoE protein isotype indicating the existence of apoE-isotype-associated structural differences in both senile plaques and neurofibrillary tangles. In mice overexpressing mutant htt, we observed polyQ-length-dependent and aging-dependent changes in LCO spectra. Further studies are underway aimed at identifying which components of each structure contribute to the unique properties of each unique LCO spectral pattern.

This work was supported by postdoctoral salary award from Swedish Research Council (Caesar).

Presented by: **Caesar, Ina**

6

[18F] AZD4694 PET Quantification for the Assessment of Fibrillar Amyloid-B Deposition

Auttawut Roontiva [1], Kewei Chen [2], Adam Fleisher [3], Xiaofen Liu [1], Pradeep Thiyyagura [1], Ayutyanont Napatkamon [1], Jessica Langbaum [1], Anita Prouty [1], Daniel Bandy [1], Michelle Perkins [1], Nicole Richter [1], Laura Jakimovich [1], Zsolt Cselenyi [4], Lars Farde [5], Reiman Eric [6]

[1] Banner Alzheimer's Institute, Phoenix, Arizona, USA; Arizona Alzheimer's Consortium, Phoenix, Arizona, USA
[2] Banner Alzheimer's Institute, Phoenix, Arizona, USA; Arizona Alzheimer's Consortium, Phoenix, Arizona, USA; Arizona State University, Tempe, Arizona, USA
[3] Banner Alzheimer's Institute, Phoenix, Arizona, USA; Arizona Alzheimer's Consortium, Phoenix, Arizona, USA; University of California San Diego, San Diego, California, USA;
[4] AstraZeneca R&D, Södertälje, Sweden
[5] AstraZeneca R&D, Södertälje, Sweden; Karolinska Institutet, Stockholm, Sweden
[6] Banner Alzheimer's Institute, Phoenix, Arizona, USA; Arizona Alzheimer's Consortium, Phoenix, Arizona, USA; Translational Genomics Research Institute, Phoenix, Arizona, USA; Univeristy of Arizona, Tucson, Arizona, USA

Background and Objective: [F18] AZD4694, a second-generation PET ligand developed by AstraZeneca, has been suggested for use in the examination of fibrillar abeta burden in the study of AD. This study aims to determine an analysis setting feasible for examining the differential fibrillar abeta burden between patients with mild AD and elderly controls, between elderly controls and young controls, and between patients with mild AD and young controls.

Methods: Using a data set comprising 90-minute dynamic PET scan of 10 patients with probable mild AD, 10 healthy elderly adults, and 4 healthy younger adults, we examined the Fibrillar abeta burden with 1) original Logan Graphic Analysis (LGA) estimated distribution volume ratio (DVR), a modified LGA (T0-Logan) which does not require the early PET frames and semi-quantitative Standardized Uptake Value ratio (SUVr), 2) cerebellum and pons reference regions, and 3) various early/late scan time intervals and 4) pre- or post-injection transmission scan for attenuation correction,

Results: We found that assessment of differential fibrillar abeta burden is feasible for all three pair-wise comparisons ($p<0.05$) using 1) a 15-minute scan starting from 30 minutes, 2) 6-minute post-injection transmission for attenuation correction, 3) T0-Logan DVR or SUVr, and 4) cerebellum reference region.

Conclusion: [18F] AZD4694 PET assessment of fibrillar abeta deposition in the study of AD is feasible and relatively straightforward with common analysis methodologies. Additional studies are needed to compare it to other ligands and validate the feasibility with larger sample size.

Presented by: **Roontiva, Auttawut**

7

Standard and Novel PET Measurements of Amyloid Burden, Relationships to Clinical Severity, and Relationships to an AD-Related Hypometabolic Convergence Index in Early MCI

Hillary Protas [1], Kewei Chen [1], Auttawut Roontiva [1], Napatkamon Ayutyanont [1], Xiaofen Liu [1], Stephanie Parks [1], Mark Nishimura [1], Cole Reschke [1], Jagust William [2], Norman Foster [3], Michael Weiner [4], Adam Fleisher [1], Eric Reiman [1]

[1] Banner Alzheimer's Institute; Arizona Alzheimer's Consortium
[2] University of California, Berkeley
[3] University of Utah
[4] University of California, San Francisco

Background & Objective: We previously introduced a "hypometabolic convergence index (HCI)" to characterize the extent to which the magnitude and spatial pattern of hypometabolism in a person's FDG PET image corresponds to that in an Alzheimer's disease (AD) dementia group. We subsequently developed an "amyloid convergence index (ACI)" to characterize the extent to which a person's amyloid PET image corresponds to that in an AD dementia group, and we have begun to evaluate its ability to detect and track AD-related amyloid accumulation. Here, we demonstrate the ability of the florpetapir PET-derived ACI and SUVR measurements of fibrillar amyloid to distinguish probable AD dementia, mild cognitive impairment (MCI), early MCI (eMCI), and cognitively normal adult (NC) groups. Using thresholds to categorize these amyloid PET measurements as positive or negative, we demonstrate their ability to distinguish between eMCI patients with higher or lower HCIs.

Methods: Florbetapir PET and FDG PET images from 215 ADNI participants (29 probable AD dementia, 40 MCI, 88 eMCI, and 58 NCs) were analyzed. ACIs and mean cerebral SUVRs were characterized using a whole cerebellum reference region. Thresholds were established using ROC analyses of probable AD dementia versus NC data.

Results: ACI and SUVR amyloid measurements distinguished each patient group from NCs, probable the AD dementia group from MCI and eMCI groups, but not between MCI and eMCI groups. While significance levels were greater using ACIs than SUVRs, they were not significantly different. eMCI patients with higher amyloid burden had higher HCIs than those with lower amyloid burden (ACI/SUVR defined amyloid positivity p=0.037/0.064).

Conclusions: AmyloidPET measurements are associated with greater clinical severity (AD dementia>MCI&eMCI.>NC) and greater FDG PET evidence of disease severity in eMCI patients. Additional studies are needed to evaluate the ACI's power to detect and track AD-related amyloid accumulation.

Presented by: **Protas, Hillary**

8

How Well Do PIB, Cortical Thickness, and FDG PET Match Behavior in AD and Logopenic PPA?

Howard Chertkow, Jim Nikelski, Alan Evans

McGill University

Background: In Primary Progressive Aphasia (PPA), language problems can be the primary or sole deficit. In a particular subgroup, termed Logopenic variant Primary Progressive Aphasia (PPA-LV), Alzheimer's Disease (AD) is often the underlying pathology despite the "focality" of the cognitive deficit. We wondered whether multi-modal imaging would point in the direction of typical AD (bilateral deficits) vs.PPA (strictly left temporal/frontal deficits).

Methods: Thirteen subjects with typical AD and 13 with PPA-LV were studied. MRI was assessed visually and with quantitative grey matter cortical thickness in 48 cortical regions of each hemisphere. Flouro-deoxyglucose PET (FDG) and C-11 amyloid PET imaging with Pittsburgh B Compound (PIB) were assessed as typical AD [ie., bitemporo-parietal decreased glucose uptake] or left predominant pattern of decreased metabolism, on visual rating as well as quantitative SUVR analysis with "Beagle" software pipeline. PIB PET amyloid imaging was considered positive if there was SUVR > 1.5 for association cortex regions, corresponding to medium or large PIB uptake on visual inspection.

Results: All subjects were PIB positive, with no significant difference between mean SUVR (mean 1.7). On MRI , 6/13 ADs and 7/13 PPA-LVs showed predominantly left sided cortical atrophy of visual rating, and four left fronto-temporal regions showed significantly greater left sided cortical thinning. On FDG PET , 1/13 ADs and 9/13 PPA-LVs showed predominantly left sided hypometabolism on inspection, and five regions showed significantly greater hypometabolism. On PIB PET, there was no visual or SUVR difference between left sided uptake between the two groups. There was no significant left PIB predominance in either group.

Conclusion: Amyloid imaging with PIB showed no particular differences between those clinically labeled as PPA-LV, and from typical AD individuals Supported by CIHR(Canadian Institutes of Health Research), and the FRSQ Quebec Aging Network (RQRV).

Presented by: **Chertkow, Howard**

9

PIB Binding in APP-Transgenic Mice Exogenously Seeded with AD-brain Extract

Amarallys Cintron [1], *Rebecca Rosen* [1], *Brian Ciliax* [1], *Lary Walker* [1], *Harry LeVine III* [2]

[1] *Emory University*
[2] *University of Kentucky*

The misfolding and aggregation of β-amyloid (Aβ) is one of the earliest events in the pathogenesis of Alzheimer's disease. The induction and spread of these lesions may involve corruptive protein templating (seeding), similar to the molecular mechanism underlying prion disease. Experimentally, Aβ deposition can be induced in Aβ-precursor protein- (APP) transgenic mice by the intracerebral injection of dilute brain extracts that contain misfolded, aggregated Aβ seeds. Radiolabeled Pittsburgh compound B (PIB) binds with high affinity and specificity to cerebral Aβ deposits in patients with Alzheimer's disease. However, PIB high-affinity binding sites are very rare on Aβ deposits in APP-transgenic mice and aged nonhuman primates, even though these models express human-sequence Aβ. We asked whether high-affinity PIB binding sites can be generated on Aβ deposits that have been seeded by AD-brain extracts in APP-transgenic mice. Using autoradiography of ^{3}HPIB binding to tissue sections, we found that PIB binding is augmented in seeded deposits of Aβ in this model, suggesting that the seed can influence the characteristics of the resulting protein aggregates *in vivo*. Establishing an understanding of corruptive protein templating and the strain-like features of Aβ structure in Alzheimer's disease will provide new insights into the characteristics of proteopathic lesions that are specific to Alzheimer's disease.

Presented by: **Cintron, Amarallys**

10

Beta Amyloid Imaging: A Comparative Study of Homeopathic Treatment versus Donepezil and Galantamine

Claudia De Rosa, Ciara O'Brien, Sara O'Reilly

EOLAS

Background: The aim of our study was to demonstrate effectiveness of homeopathic medicine in Alzheimer's disease treatment versus Donepezil and Galantamine allopathic drugs through PET Beta-amyloid imaging.

Method: Controlled single-blinded method and PET imaging comparison. The study was conducted in Ireland between March 2009 and December 2010 (21 months).

112 patients (aged 65-82, both females and males) with mild to moderate symptoms of Alzheimer's disease were considered. They all completed the protocol.

The group was divided in two smaller group of 66 patients each, a Homeopathic Group and a Allopathic Group.

The Homeopathic group was treated with the following constitutional remedies according to their symptoms: Anacardium, Alumina, Conium, Baryta carbonica, Mercurius and Secale cornutum.

The Allopathic group was treated with Donepezil and Galantamine.

General decreased energy, minor and mild memory loss, mood swings, withdrawn behaviour, confusion, impaired communication both verbal and written, impaired memory, speech problems, development of
skin infections and respiratory problems were considered as inclusion criteria.

Therapeutic success within 30 days (phase I), 60 days (phase II), 90 days (phase III), 6 months (phase IV), 9 months (phase V), 12 months (phase VI), 18 months (phase VII) and 21 months (phase VIII), of treatment was considered as evaluation criteria.

Results: All 112 cases were analysed through PET imaging. The homeopathic medicine was not therapeutically inferior to the allopathic reference drug.

Conclusions: Although Homeopathic Medicine is an "individualized" therapy and although a number of remedies is considered by homeopaths to be effective in homeopathic treatment of Alzheimer's disease, our study had proved that the data obtained demonstrate that the efficacy and tolerability of the homeopathic drug in treating Alzheimer's symptoms have been confirmed in phase IV (6 months period of treatment) of the clinical trial.

Presented by: **De Rosa, Claudia**

11

The Flutemetamol in Flanders' Aging Population (FLUFLAG) Study: Prevalence of a Positive Scan in Cognitively Intact Elderly Individuals

An-Sofie De Weer [1], Mathieu Vandenbulcke [2], Natalie Nelissen [1], Gill Farrar [3], Lennart Thurfjell [4], Koen Van Laere [5], Rik Vandenberghe [6]

[1] Laboratory for Cognitive Neurology, Catholic University Leuven, Leuven, Belgium
[2] Psychiatry Department, University Hospitals Leuven, Leuven, Belgium
[3] GE Healthcare, London, UK
[4] GE Healthcare, Uppsala, Sweden
[5] Division of Nuclear Medicine, University Hospitals Leuven, Leuven, Belgium
[6] Laboratory for Cognitive Neurology, Catholic University Leuven, Leuven, Belgium; Neurology Department, University Hospitals Leuven, Leuven, Belgium

Increased Aβ-amyloid levels without cognitive deficits could be a marker of preclinical Alzheimer disease (AD). In the phase 2 18F-flutemetamol study 1 out of 15 healthy elderly controls (mean age = 68.7, s.d. = 7.61) showed AD-like tracer uptake. Here, we report results from a longitudinal, community-recruited, prospective cohort study to estimate prevalence and predictive value of a positive 18F-flutemetamol scan in Flemish healthy elderly volunteers.

Recruitment was stratified for age (50-80 years) and genotype: apolipoprotein E (e4-carriers versus non-carriers) and BDNF (met-carriers versus non-carriers). Exclusion criteria were below-normal neuropsychological test scores, significant vascular lesions on MRI and significant neurological or psychiatric history. Of the 279 subjects screened, 67 met all criteria (mean age = 66, s.d. = 5.63, range 52-80). The 30-minute PET started 90 minutes after injection of 150 MBq of 18F-flutemetamol. Scans were categorized following two approaches: 1) Visual assignment to a 'raised' versus 'normal' uptake category by three blinded independent readers. 2) Quantitative assessment using composite cortical VOI Standardized Uptake Value Ratios (SUVR) and a cut-off of 1.56, based on previous studies. The readers assigned three FLUFLAG cases to the 'raised' category (ages 65, 68 and 72, all heterozygous ε4-carriers). Quantitative assessment classified seven subjects as positive (SUVR mean = 1.78, s.d. = 0.23). SUVR-values were significantly higher in e4-carriers ($p < 0.05$) and correlated significantly with total encoding and delayed recall on the Rey Auditory Verbal Learning test ($r = -0.24$, $p = 0.05$; $r = -0.24$, $p = 0.05$). We confirm the low prevalence of positive 18F-flutemetamol scans in healthy controls as seen in the phase 2 study but in a larger cohort. Factors like recruitment strategies, analysis methodologies, or the ligand used, may explain differences between cohorts. Quantitative assessment may be more sensitive for mild amyloid increases in healthy elderly than visual reads.

Presented by: **De Weer, An-Sofie**

12

Plasma Aβ and PET PIB Binding are Inversely Related in Mild Cognitive Impairment

D. Devanand [1], Nicole Schupf [1], Ramin Parsey [1], Yaakov Stern [1], Gregory Pelton [1], Pankaj Mehta [2], Richard Mayeux [1]

[1] Columbia University
[2] NYS Institute for Developmental Disabilities

Objective: To evaluate the relations between Positron Emission Tomography Pittsburgh compound B (PIB-PET) binding (amyloid imaging) and plasma Aβ in patients with mild cognitive impairment (MCI) and similarly aged controls.

Methods: In 20 patients with MCI and 19 cognitively intact controls (case-control study), PIB binding potential (BPnd) was assessed in four regions, and total brain excluding cerebellum, referenced to cerebellar binding. The mean of plasma Aβ levels measured in duplicate was analyzed.

Results: Plasma Aβ42/Aβ40 ratio was decreased in MCI compared to controls (mean 0.15 SD 0.04 versus mean 0.19 SD 0.07, p=0.03) but Aβ40 (p=0.3) and Aβ42 (p=0.06) levels did not differ between the two groups. PIB BPnd was increased in MCI compared to controls in the cingulate (p=0.02), parietal (p=0.02) and total brain (p=0.03), but not in prefrontal cortex (p=0.08) or parahippocampal gyrus (p=0.07). Linear regression analyses adjusting for age, sex and cognitive test scores showed that low Aβ42/Aβ40 ratio was associated with high cingulate, parietal and total brain PIB binding ($0.01 < p \leq 0.05$). These associations between PIB binding and the Aβ42/Aβ40 ratio were strongest in PIB positive subjects and within the MCI group.

Conclusions: Though cross-sectional, the findings support the “sink” hypothesis that increased brain Aβ is accompanied by lower peripheral levels of Aβ, particularly the Aβ42/Aβ40 ratio in patients with MCI. The association between PIB binding and the plasma Aβ42/Aβ40 ratio suggests possible use of plasma Aβ combined with PIB binding as a risk biomarker with potential clinical application.

Presented by: **Devanand, D.**

13

Beta-Amyloid Burden Alters Default Mode and Salience Network Connectivity in a Manner that Predicts Impaired Cognition in a Lifespan Sample of Healthy Adults

Michael Devous [1], *Kristen Kennedy* [2], *Karen Rodrigue* [2], *Andrew Hebrank* [2], *Denise Park* [2]

[1] *Nuclear Medicine Center, UT Southwestern Medical Center*
[2] *Center For Vital Longevity, University of Texas at Dallas*

Increasing evidence suggests amyloid burden (AB) alters functional connectivity in Alzheimer's Disease, Mild Cognitive Impairment, and healthy elderly. We examined the relationship between AB and functional connectivity in relation to cognitive performance in a lifespan sample of healthy participants (Dallas Lifespan Brain Study). BOLD at rest was measured within a continuous age sample of healthy adults (N = 137; 30-89 years old), and functional connectivity was determined as z-score-normalized temporal correlation coefficients, with seeds in posterior cingulate to represent Default Mode Network (DMN) and anterior cingulate to represent Salience Network (SN). Participants underwent PET using ^{18}Florbetapir to measure AB, and the standardized uptake value ratio to cerebellum from a precuneus ROI was extracted. Relationships between AB and functional connectivity were examined as continuous variables and by contrasting high AB subjects against age- and gender-matched low AB subjects (N=25 each). The impact of AB-induced alterations in connectivity on cognitive performance was also assessed. Elevated AB was associated with decreased connectivity in the DMN in multiple bilateral frontal areas and precuneus, and increased connectivity in bilateral middle temporal gyrus. In contrast, impaired connectivity of the SN (in the resting state) was restricted to middle frontal gyrus, while increased connectivity was seen in bilateral insula, dorsolateral prefrontal cortex, and superior temporal gyri. AB-impaired DMN function predicted poorer processing speed and working memory (weaker connectivity associated with poorer cognitive function). Interestingly, *increased* superior frontal and inferior fronto-opercular SN connectivity was associated with poorer processing speed, fluid reasoning and working memory. Thus, high AB in healthy adults is associated with decreased connectivity in the Default Mode Network, but with enhanced connectivity in the Salience Network. It is particularly noteworthy that connectivity measures show a direct relationship to cognitive performance. Increased SN connectivity may be an attempt to compensate for amyloid burden or represent failed SN suppression.

Presented by: **Devous, Michael**

14

Amyloid-PET and MR Imaging in the Classification of Prodromal and Probable AD in the ADNI Study

Ranjan Duara, David Loewenstein, Qian Shen, Warren Barker, Daniel Varon

Wien Center for Alzheimer's Disease and Memory Disorders, Mount Sinai Medical Center

Objective: To evaluate individual and combined contributions of amyloid positive status (Am+) and MRI positive status (MRI+) based on measures of medial temporal atrophy (MTA) in the classification of aMCI and probable Alzheimer's Disease (AD) among subjects in the ADNI study.

Methods: Amyloid PET scans using [C-11] PiB and volumetric MRI scans were used to classify 18 elderly normals (EN) (mean age: 77yrs), 59 aMCI (mean age: 74yrs) and 15 AD subjects (mean age: 73 yrs), using established cutpoints for Am+ status (SUVR=1.5+) and MRI+ status [bilateral hippocampal volume (HP-v) <0.39% of intracranial volume, or visually rated MTA score of 1.17+ (mean rating of 3 bilateral structures on a 0-4 scale)].

Results: Among EN, aMCI and AD subjects, Am+ rates were:50%, 68% and 93%, MRI+ rates (MTA scores best separated the groups) were 37.5%, 75% and 100%, and either Am+ or MRI+ rates were 67%, 86% and 100%. The ROC areas distinguishing EN from AD were 0.71 (for SUVR), 0.84 (for HP-v) and 0.89 (for MTA). MRI+ and Am+ status were not additive for distinguishing EN from aMCI or AD. Alternative SUVR and MRI cut scores did not provide better classification rates. Correlations between SUVR scores and episodic memory scores (AVLT-D) (r=-0.34) and Category Fluency scores (r= -0.31) remained significant after controlling for MTA scores (which were also significantly correlated with memory and fluency scores; r=0.50 and 0.33, respectively).

Conclusions: MRI+ rates were numerically more sensitive and specific than AM+ rates for classifying aMCI and AD, although the combination appears to be most effective. Amyloid PET may be most effective for classifying pre-clinical AD. It remains to be determined what SUVR cut scores should be used for classifying subjects as Am+ and how specific MRI+ status is in detecting AD pathology, as compared to other degenerative and vascular pathologies.

Presented by: **Duara, Ranjan**

15

Flutemetamol is related to Practice Effects on Cognitive Testing

Kevin Duff [1], John Hoffman [1], Norman Foster [1], Kathryn Dennett [1], Lennart Thurfjell [2], Angela Wang [1], Kathryn Morton [1], Lauren Zollinger [1], Kim Gallagher [2]

[1] University of Utah
[2] GE Healthcare

Objective: To examine the relationship between amyloid plaque burden measured with flutemetamol and PET imaging and practice effects, a possible marker of early cognitive decline, in non-demented seniors.

Method: Six non-demented community-dwelling older adults (3 males, M age = 75, M MMSE = 28) participated. PET imaging of the brain was performed 90 minutes after the injection of 5 mCi of flutemetamol and analyzed via standard semi-quantitative techniques to yield: 1. blinded visual assessments of flutemetamol uptake categorized as increased or normal uptake and 2. a semi-quantitative global composite of standardized uptake value ratios (cortex to cerebellum). Practice effects were collected via repeated administration of a visual memory test across one week and analyzed via regression-based reliable change indices to yield: 1. dichotomous categorization of "high" or "low" practice effects, and 2. a continuous practice effects value. Increased/normal flutemetamol uptake was compared to high/low practice effects with chi-square, and the composite uptake was compared to the continuous practice effects with Pearson correlation.

Results: No adverse events were reported during flutemetamol injection or the uptake period of the tracer. Only one participant was categorized on visual assessement as having increased uptake, and this participant was in the low practice effects group. An additional participant with low practice effects was rated as having normal flutemetamol uptake. All participants with high practice effects had normal flutemetamol uptake. Medium to large correlations were observed between the composite measure of flutemetamol uptake and the continuous practice effects (r=-0.47 to 0.61).

Conclusion: Although needing replication in larger samples, our findings provide preliminary evidence that flutemetamol uptake is inversely related to cognitive functioning in non-demented older adults.

Presented by: **Duff, Kevin**

16

Regional Brain Differences in Flutemetamol Uptake and Practice Effects

Kevin Duff [1], Norman Foster [1], John Hoffman [1], Kathryn Dennett [1], Lennart Thurfjell [2], Angela Wang [1], Lauren Zollinger [1], Kathryn Morton [1], Kim Gallagher [2]

[1] University of Utah
[2] GE Healthcare

Objective: To examine regional differences in brain uptake of 18F-flutemetamol and practice effects in non-demented older adults.

Method: Six non-demented community-dwelling older adults (3 males, M age = 75, M MMSE = 28) participated. PET imaging of the brain was performed 90 minutes after the injection of 5 mCi of flutemetamol and analyzed via standard semi-quantitative techniques. Amyloid plaque burden imaging with flutemetamol and analyzed with automated techniques to yield normalized standardized uptake value ratios (brain region to cerebellum) for 16 brain regions. Practice effects were collected via repeated administration of a visual memory test across one week and analyzed via regression-based reliable change indices. Pearson correlations were used to examine associations between flutemetamol uptake in different brain regions and practice effects.

Results: No adverse events were reported during flutemetamol injection or the uptake period of the tracer. Flutemetamol uptake ratios and practice effects associations were observed across multiple brain regions (r = -0.45 to -0.75). The largest associations occurred in the right medial temporal lobe (r = -0.75) and left parietal lobe (r = -0.69).

Conclusion: These preliminary findings are among the first to demonstrate associations between regional brain amyloid pathology measured with flutemetamol PET and cognitive functioning in non-demented seniors. This suggests amyloid pathology can have direct significant cognitive consequences. The strongest association occurred in the right medial temporal lobe, which would be expected given our use of a visual memory test to calculate practice effects.

Presented by: **Duff, Kevin**

17

Diagnostic Classification with Amyloid PET and FDG-PET among Clinically Diagnosed Alzheimer's Disease Patients in the Alzheimer's Disease Neuroimaging Initiative

Norman Foster [1], Richard King [1], Angela Wang [1], Susan Landau [2], William Jagust [2], Kewei Chen [3], Eric Reiman [3]

[1] Center for Alzheimer's Care, Imaging and Research, Department of Neurology, University of Utah, Salt Lake City, Utah
[2] University of California, Berkeley, Berkeley, California
[3] Banner Alzheimer's Institute, Phoenix, Arizona

Objective: To determine the degree of diagnostic concordance between amyloid PET and FDG-PET scans in subjects diagnosed with probable Alzheimer's disease (AD) based on clinical history and examination in the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods: Initial amyloid PET was performed between 4/07-10/11 in 62 subjects with mild probable AD at the time of their scans (38 men, 24 women) using either 11C-PIB (19 subjects) or 18F-florbetapir (43 subjects). Preliminary analysis was performed on 22 of these subjects. Amyloid binding in cortical gray matter relative to cerebellar gray matter was calculated and scans were categorized as either AD-like or not AD-like based upon this ratio using threshold values derived from our previously published studies of 11C-PIB. Concurrent FDG-PET scans on these subjects were analyzed using 3-dimensional stereotactic surface projection (3D-SSP) mapping. Two experienced raters independently reviewed the metabolic and statistical 3D-SSP maps and classified them based upon visual interpretation using our previously published criteria. We then evaluated the degree of concordance of amyloid PET and FDG-PET scan classifications in each subject.

Results: Among the 22 clinically probable AD subjects evaluated in this preliminary analysis, 5 (23%) had amyloid scans classified as negative and 3 (14%) had FDG-PET scans with a pattern of hypometabolism that was not AD-like. In only 1 of these cases was there correspondence between amyloid PET and FDG-PET classification.

Conclusions: The results of both FDG-PET and amyloid PET scans raise concerns about the accuracy of clinical diagnosis in ADNI AD subjects. Additional analyses are needed to understand the source of this unexpected discrepancy, which could include analytic techniques, variability in image acquisition and choice of diagnostic thresholds. This will be critical for implementing these techniques as diagnostic biomarkers. FDG-PET and amyloid PET contribute different and complementary information that can be exploited in clinical trials.

Presented by: **Foster, Norman**

18

Brain Amyloid and Self-Reported History of Cognitive and Physical Activity

Christopher Gidicsin [1], Jacqueline Maye [1], Lesley Pepin [1], J. Alex Becker [2], Lauren Wadsworth [1], Natacha Lorius [1], Aaron Schultz [1], Rebecca Amariglio [3], Gad Marshall [4], Dorene Rentz [4], Reisa Sperling [4], Keith Johnson [4]

[1] Massachusetts General Hospital
[2] Massachusetts General Hospital, Harvard Medical School
[3] Brigham and Women's Hospital, Harvard Medical School
[4] Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School

Brain amyloid pathology, a central component of Alzheimer's disease, gradually accumulates over many years and has a highly variable prevalence among normal elderly. Some evidence suggests that variability in lifelong cognitive or physical activity patterns could modify the level of amyloid accumulation and contribute to disease prevention. We hypothesized that greater self-reported cognitive or physical activity would be associated with lower levels of amyloid deposition.

Clinically normal individuals (N=90; age 74 ±6 years) participating in the Harvard Aging Brain Study underwent clinical and cognitive assessments, genotyping and PiB PET imaging (DVR, cerebellar reference). We evaluated responses on 42 items from an autobiographical questionnaire in which participants subjectively rated their past and current levels of cognitive activity and current levels of physical activity. The association of PiB retention with activity scores was evaluated with regression models covarying age, APOE status, and estimated IQ (AMNART) or education.

Cognitive activity scores were correlated with estimated IQ ($r=0.5$, $p<0.0001$), education ($p<0.05$), performance on selective reminding ($p<0.05$), and visual discrimination tests ($p<0.05$). However, the primary hypothesis was not affirmed: greater PiB retention was weakly ($r\text{-}sq<0.1$), positively associated with more reported cognitive activity with marginal statistical significance depending on the cognitive activity test item. PiB retention was not related to any current physical activity score.

In summary, we did not find evidence of a protective effect of either cognitive activity or recent physical activity on amyloid deposition. However, cognitive activity history did relate to IQ and performance on neuropsychological test performance. These findings suggest that while a history of lifelong cognitive activity may support better cognitive performance, this relation is not mediated by brain amyloid burden. However, objective measures of past and current cognitive and physical activity, and a larger sample size are needed to fully test these hypotheses.

Presented by: **Gidicsin, Christopher**

19

Brain Amyloid and Cognition in Lewy Body Diseases

Andrea Santarlasci [1], Joseph Locascio [1], Marta Marquie-Sayagues [1], Stephen Gomperts [1], Dorene Rentz [2], Jackie Maye [1], Keith Johnson [1], John Growdon [1]

[1] Massachusetts General Hospital
[2] Brigham and Women's Hospital

Background: Many patients with Parkinson disease (PD) develop dementia (PDD), a syndrome that overlaps clinically and pathologically with dementia with Lewy bodies (DLB); PDD and DLB differ chiefly in the relative timing of dementia and parkinsonism. Brain amyloid deposition is an early feature of DLB and may account in part for its early dementia. We sought to confirm this hypothesis and also to determine whether amyloid accumulation contributes to cognitive impairment and dementia in the broad range of parkinsonian diseases.

Methods: 29 cognitively normal PD, 14 PD subjects with mild cognitive impairment (PD-MCI), 18 with DLB, 12 with PDD and 85 healthy control subjects (HCS) underwent standardized neurologic and neuropsychological examinations and PiB imaging with PET. Apolipoprotein (APOE) genotypes were obtained in 65 of the 74 parkinsonian patients. PiB retention was expressed as the distribution volume ratio using a cerebellar tissue reference.

Results: PiB retention was significantly higher in DLB than in any of the other diagnostic groups. PiB retention did not differ across PDD, PD-MCI, PD, and HCS. Amyloid burden increased with age and with the presence of the APOEe4 allele in all patient groups. Only in the DLB group was amyloid deposition associated with impaired performance on the MMSE.

Conclusions: DLB subjects have higher amyloid burden than subjects with PDD, PD-MCI, PD or HCS; amyloid deposits are linked to cognitive impairment only in DLB. Early amyloid deposits in DLB relative to PDD may account for their difference in the timing of dementia and parkinsonism.

Presented by: **Santarlasci, Andrea**

20

Influence of APOE2 Genotype on Global and Regional Amyloid Deposition

Eisuke Haneda [1], Kenji Ishii [1], Muneyuki Sakata [1], Keiichi Oda [1], Jun Toyohara [1], Kiichi Ishiwata [1], Michio Senda [2], Kengo Ito [3], Ryozo Kuwano [4], Takeshi Iwatsubo [5], the Japanese Alzheimer's Disease Neuroimaging Initiative, the Alzheimer's Disease Neuroimaging Initiative, the AIBL Research Group

[1] Positron Medical Center, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan
[2] Molecular Imaging Research Group, Institute of Biomedical Research and Innovation, Kobe, Japan
[3] Department of Clinical and Experimental Neuroimaging, National Center for Geriatrics and Gerontology, Obu, Japan
[4] Department of Molecular Genetics, Brain Research Institute, Niigata University, Niigata, Japan
[5] Department of Neuropathology and Neuroscience, Tokyo University Graduate School of Medicine, Tokyo, Japan

Apolipoprotein E (APOE) e2 allele has been implicated in reduced risk for Alzheimer's disease (AD). However, the details of APOE2 role are mostly unknown. In this study, we evaluated the influence of APOE2 on the global and the regional brain accumulation of ^{11}C-Pittsburgh compound B (PiB) in three nation-wide prospective imaging studies of AD; Alzheimer's Disease Neuroimaging Initiative (US-ADNI), Austrarian Imaging Biomarker and Lifestyle (AIBL), and Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI).

We analyzed the baseline ^{11}C-PiB scan data acquired 50-70 min post-injection in all the studies. The PET images were coregistered to individual MRI data, and automated VOI analysis were performed using DARTEL template, standard set of volumes of interest, and cerebrospinal fluid volume correction. The regional (precuneus, frontal, temporal and parietal cortices) uptake was evaluated in reference to that of the cerebellum. The mean cortical uptake (mcSUVR) was regarded as the representative value of individual global cortical amyloid deposition. The cut-off mcSUVR value for PiB-positivity was set at 1.5 for all the studies. Among all the studies, the number of subjects in each APOE genotype with PiB positive or negative (PiB+/PiB-) were; e2e2 (0/1), e2e3 (4/20), e2e4 (7/3), e3e3 (71/106), e3e4 (110/31) and e4e4 (14/19).

In the PiB-positive subjects, ^{11}C-PiB uptake level in e2e4 genotype was significantly lower in mean cortical area (17.5%, $p<0.01$) and precuneus (17.1%, $p<0.005$) relative to those in e4e4 genotype. In contrast, no significant difference was observed in other regions (frontal, temporal and parietal) between the groups of e2-positive and e2-negative genotype.

These results suggest the possibility that ApoE e2 allele might be implicated in the suppression of AD risk via the inhibition of amyloid deposition in the brain especially in precuneus.

Presented by: **Haneda, Eisuke**

21

Mild Cognitive Impairment Due to Alzheimer's Disease Associated with Beta-Amyloid Deposition and Neuronal Injury on PET Imaging

Shizuo Hatashita, Hidetomo Yamasaki

Shonan-Atsugi Hospital

Objective: We investigated to define "mild cognitive impairment (MCI) due to Alzheimer's disease (AD)" using beta-amyloid deposition and neuronal injury as biomarkers, and the transition point of MCI conversion to AD. Methods: Thirty-six MCI patients who met Core Clinical Criteria for MCI, 20 AD and 14 healthy control (HC) subjects underwent cognitive testing, 60-min dynamic [11C]-PIB PET and 15-min static [18F]-FDG PET at baseline, 12 months and 24 months, Regions of interest were defined on co-registered MRI. PIB distribution volume ratios (DVR) were calculated using Logan graphical analysis, and quantitative analysis for [18F]-FDG used the standardized uptake value ratio (SUVR) on the same regions. Results: Thirty-two of 36 MCI patients were above the greatest value of PIB DVR in HC and below the greatest value of FDG SUVR in AD. Of these, 24 (75.0%) converted to AD over 24 months: 15 (46.9%) converted to AD at 10.2 ± 2.6 months (faster), and 9 (28.1%) converted at 22.2 ± 1.9 months (slower). Eight (25.0%) did not convert during 24 months (stable). The delayed recall score (WMS-R Logical Memory) was 1.2 ± 1.8 for faster converters and 1.3 ± 1.8 for slower converters, significantly lower than that of stable patients. In each group, there were no significant differences in mean DVR values of different cortical regions. In contrast, faster converters had a reduced glucose metabolism in parietal, lateral temporal, frontal and precuneus cortices at baseline while slower converters had in lateral temporal cortex and precuneus. Stable patients had a hypometabolism only in precuneus. Conclusion: MCI in individuals, who meet the Core Clinical Criteria and have biomarkers for Aβ deposition and glucose metabolism, is defined as "MCI due to AD". These individuals are more likely to convert to AD in a short period.

Presented by: **Hatashita, Shizuo**

22

Influence of Aging and Amyloid Pathology on Associative Memory Retrieval Networks

Trey Hedden [1], Koene R.A. van Dijk [2], Emily Shire [3], Reisa A. Sperling [4], Keith A. Johnson [1], Randy L. Buckner [5]

[1] Massachusetts General Hospital, Harvard Medical School
[2] Massachusetts General Hospital
[3] Massachusetts General Hospital, Harvard University
[4] Massachusetts General Hospital, Brigham & Women's Hospital, Harvard Medical School
[5] Harvard University, Massachusetts General Hospital, Harvard Medical School

Advanced aging is associated with alterations in neuronal activity related to memory retrieval (Velanova 2007) and with changes in connectivity of memory-related brain networks (Andrews-Hanna 2007). Substantial amyloid burden occurs among a subset of cognitively normal older adults and has been linked to alterations in memory-related activity (Sperling 2009) and declines in functional connectivity (Hedden 2009). We examined the relationship of task-induced activity during an associative memory paradigm and the integrity of functionally connected networks during rest in 51 younger and 62 older adults. Participants underwent functional MRI (fMRI) scanning while retrieving previously learned arbitrary word pairs. Word pairs were either old (i.e., originally paired), repaired, or new. fMRI resting state data were collected while participants passively viewed a fixation cross. Two distinct memory-related networks were identified. One network was related to memory retrieval for old versus new items and included the hippocampal formation, posterior cingulate cortex, and inferior parietal cortex. A second network was related to controlled memory retrieval and included lateral prefrontal cortex, superior parietal cortex, and dorsal anterior cingulate cortex. Older adults performed more poorly than younger adults and exhibited decreased modulation of activity in both networks relative to younger adults. Among older adults, amyloid burden was not associated with changes in activity in the old-new retrieval network, but was associated with changes in activity in the controlled retrieval network. Functional connectivity within each network during rest was associated with task-related activity in that network. Age and amyloid burden influenced the relationship between functional connectivity during rest and activity during the task. The results suggest that network metrics during rest may reflect an individual's ability to modulate activity in response to a task, and that this relationship is disrupted by aging and amyloid pathology.

Presented by: **Hedden, Trey**

23

Postmortem Correlations of Flutemetamol and Pittsburgh Compound-B Binding in Eight [C-11]PIB Imaged Brains

Milos Ikonomovic, Julie Price, Eric Abrahamson, Chester Mathis, William Paljug, Manik Debnath, Lan Shao, Carl Becker, Ronald Hamilton, William Klunk

University of Pittsburgh

Flutemetamol is a new in vivo amyloid imaging agent labeled with fluorine-18 which has a longer half-life than [C-11]PiB. Whether flutemetamol and Pittsburgh Compound-B (PiB) have comparable binding in Alzheimer;s disease (AD) brains and similar ability to identify cortical Abeta deposits is unknown. The goal of the current study was to determine the extent to which flutemetamol binding reflects the extent of AD pathology and how it compares to PiB binding quantified in both postmortem brain tissues and antemortem in [C-11]PiB imaged brains. Eight subjects underwent [C-11]PiB imaging and later came to autopsy. Plaque load was quantified in fixed tissue sections using highly fluorescent derivatives of flutemetamol (6-CN-flutemetamol) and PiB (6-CN-PiB) and Abeta immunohistochemistry. Fresh frozen autopsy brain tissue homogenates from four [C-11]PiB imaged subjects were processed for [H-3]flutemetamol and [H-3]PiB binding assays and Abeta1-42 concentration was determined by an ELISA. Postmortem data were compared to region-matched in vivo [C-11]PiB PET retention data recorded antemortem in the same subjects. 6-CN-flutemetamol labeling was comparable to 6-CN-PiB (r=0.93) and Abeta plaque load (r=0.88), while it did not detect neurofibrillary tangles. [H-3]flutemetamol binding correlated directly with [H-3]PiB binding (r=0.86) and Abeta1-42 peptide concentration (r=0.37) across all brain areas. There was a direct correlation between antemortem [C-11]PiB DVR values and postmortem [H-3]flutemetamol binding (r=0.58) or [H-3]PiB binding (r=0.73). Direct correlations were also observed between [C-11]PiB DVR values and 6-CN-flutemetamol plaque load (r=0.31) or 6-CN-PiB plaque load (r=0.35) across all brain regions. Our results demonstrate that in autopsy brains of [C-11]PiB PET imaged subjects, flutemetamol binding reflects Abeta plaque load in a manner comparable to PiB. These results indicate that [F-18]flutemetamol is comparable to [C-11]PiB in its ability to detect brain Abeta pathology in living subjects.

Presented by: **Ikonomovic, Milos**

24

Amyloid Imaging of Brain Tumors

Geoffrey Johnson [1], Mark Nathan [2], Joseph Parisi [3], Wilma Lingle [3], Vivian Negron [3], Christopher Hunt [2], Patrick Peller [2], Stephen Broski [2], Abdul Fauq [4], Clifford Jack [2], Ronald Petersen [5], William Klunk [6], Chester Mathis [7], Val Lowe [2]

[1] *Mayo Clinic, Rochester, Depts. of Radiology and Immunology*
[2] *Mayo Clinic, Rochester, Dept. of Radiology*
[3] *Mayo Clinic, Rochester, Dept. of Laboratory Medicine and Pathology*
[4] *Mayo Clinic, Jacksonville, Depts. of Pharmacology and Neuroscience*
[5] *Mayo Clinic, Rochester, Dept. of Neurology*
[6] *University of Pittsburgh, Depts. of Psychiatry and Neurology*
[7] *University of Pittsburgh, Dept. of Pharmacology and Chemical Biology*

Background: Pittsburgh compound B (PiB) was designed to bind fibrillar amyloid-beta (Ab). However, unexpectedly, we observed that meningiomas accumulate PIB as seen on positron emission tomography (PET). Meningiomas are predominantly benign and are the most common intracranial tumor. Meningiomas can be confused with many other tumors on imaging, including malignant metastases. We evaluated the ability of PiB PET/CT to detect meningiomas. Furthermore, we evaluated whether intracranial metastases and other tumors accumulate PiB.

Methods: 834 adults who underwent MRI, [F-18]FDG PET/CT and [C-11]PiB PET/CT imaging as part of the Mayo Clinic Study of Aging were retrospectively reviewed. Presumed meningiomas and other intracranial tumors detected on MRI were selected and all available imaging was reviewed.

Results: All 16 meningiomas identified by strict imaging criteria showed PiB activity greater than normal adjacent tissues. All other intracranial tumors in this population showed PiB activity less than meningiomas. Other tumors seen in the population included 8 tumors commonly confused with meningiomas on imaging; metastases, pituitary macroadenomas, schwannomas and an ependymoma.

Conclusions: Meningiomas accumulate PiB, and can therefore be identified with PET. PiB PET/CT may prove helpful for differentiating meningiomas from tumors that mimic meningiomas. This discovery could lead to an advance in medical care, especially for patients with a history of cancer who undergo brain imaging for staging. The exact molecular substrate for PiB binding to meningiomas (i.e., Ab vs. non-Ab) is currently a target of investigation.

Presented by: **Johnson, Geoffrey**

25

Atypical Presentation is Associated with Greater Amyloid Burden among Patients with Early-Onset Alzheimer's Disease

William Kreisl, Meghan McGwier, Cheryl Morse, Yi Zhang, Jinsoo Hong, Victor Pike, R. Turner, Robert Innis

Molecular Imaging Branch, National Institute of Mental Health

Background: Patients with early age-of-onset Alzheimer's disease (AD) have more severe cortical atrophy and glucose hypometabolism than late-onset patients at similar disease stages. There is conflicting evidence as to whether early-onset patients also have greater amyloid plaque burden. Patients with early-onset AD sometimes present with an atypical cortical syndrome rather than typical amnestic symptoms. We sought to compare amyloid burden in early-onset AD patients with typical and atypical presentations using [11C]Pittsburgh Compound B (PIB) PET.

Methods: Twenty-two patients with early-onset (< 65 years) AD were included. Eleven patients had an atypical cortical presentation (dysexecutive syndrome, logopenic progressive aphasia, or posterior cortical atrophy). Eleven patients presented with episodic memory impairment typical of AD. Ten late-onset AD patients matched for clinical severity and 12 healthy controls (age 54 – 70 years) were also included for comparison. PIB ratio images (cerebellar reference) were compared using statistical parametric mapping (SPM) and on a region-of-interest (ROI) basis.

Results: SPM analysis showed atypical early-onset patients had greater PIB binding than typical early-onset patients in left parietal, right temporo-parietal, and bilateral occipital cortex ($p < 0.05$, FDR corrected). ROI analysis showed atypical early-onset patients had greater PIB binding than typical early-onset patients in left occipital cortex ($p = 0.025$, one-way ANOVA), and greater binding than both typical early-onset and late-onset patients in right temporal and bilateral occipital cortex ($p < 0.05$). No difference was seen between typical early-onset and late-onset patients on SPM or ROI analysis. Each AD subgroup had greater PIB binding than controls in frontal, temporal, parietal, and occipital cortex ($p < 0.001$).

Conclusions: Atypical early-onset patients may contribute the increased amyloid deposition seen in some studies comparing early and late-onset AD. Greater cognitive reserve and preservation of memory may make atypical early-onset patients more tolerant of amyloid plaque deposition before clinical symptoms become apparent.

Presented by: **Kreisl, William**

26

Multivariate Data Analysis of FDG-PET and PIB-PET in Three Conditions with Underlying Alzheimer's Pathology

Robert Jr Laforce [1], Duygu Tosun [2], Pia M Ghosh [3], Cindee M Madison [1], Michael W Weiner [2], Bruce L Miller [3], William J Jagust [4], Gil D Rabinovici [4]

[1] Helen Wills Neuroscience Institute, University of California Berkeley
[2] Center for Imaging of Neurodegenerative Diseases; Department of Radiology and Biomedical Imaging, University of California, San Francisco
[3] UCSF Memory and Aging Center
[4] Helen Wills Neuroscience Institute, University of California Berkeley; Lawrence Berkeley National Laboratory

The goal of this study was to apply parallel independent component analysis (ICA) to FDG-PET and PIB-PET data from a clinically heterogeneous population of patients with underlying AD in order to: (1) identify specific components from each modality that correlate with clinical presentation; (2) identify relationships between spatial patterns of PIB and FDG across the population. The population included patients with amnestic AD (ADmem, n=27), visuospatial AD (posterior cortical atrophy (PCA), n=9) and language AD (logopenic variant primary progressive aphasia (lvPPA), n=10). All patients were PIB-positive, 59% were female, mean age was 63.0 (7.7) and MMSE 22.0 (4.8). All data were Z transformed and FDG data inverted. Parallel ICA was applied using Fusion ICA Toolbox (Calhoun et al., 2006). Relationship to clinical diagnosis was examined using a Receiver Operator Characteristic approach including age, gender, education and ApoE4 as covariates. Four significant components were identified for FDG (Figure). These included a left inferior frontal and temporal component correlated with lvPPA (AUC 0.90, p=0.009), a bilateral inferior frontal (low metabolism) and PCC/precuneus (high metabolism) component correlated with ADmem (0.83, p=0.039) and two components correlated with PCA (bilateral occipito-temporal (0.88, p=0.012) and right PCC/lateral parietal (0.78, p=0.05)). None of the 4 significant PIB components (left PCC/lateral parietal, right parieto-temporal, bilateral inferior frontal, bilateral PCC/precuneus) correlated with diagnosis. A significant mixed FDG-PIB coefficient was found in which decreased frontal and increased PCC/precuneus FDG uptake was correlated with the inverse pattern (increased frontal, decreased PCC/precuneus) of PIB uptake (partial r=0.76, p<0.0001). In conclusion, we found that three clinical phenotypes of AD (ADmem, PCA, LPA) correlated with independent components of FDG but not with PIB. PIB and FDG showed inverse relationships in frontal cortex and PCC/precuneus. Parallel ICA may help better understand the relationships between clinical phenotype, glucose metabolism and amyloid.

Presented by: **Laforce, Robert Jr.**

27

[18F] AZD4694 PET in the Assessment of Fibrillar Amyloid-B Deposition: Performance Characteristics

Jessica Langbaum [1], Kewei Chen [1], Adam Fleisher [1], Auttawut Roontiva [1], Xiaofen Liu [1], Pradeep Thiyyagura [1], Daniel Bandy [1], Michelle Perkins [1], Nicole Richter [1], Laura Jakimovich [1], Anita Prouty [1], Zsolt Cselenyi [2], Lars Farde [2], Samantha Budd [2], Eric Reiman [1]

[1] Banner Alzheimer's Institute
[2] AstraZeneca

Background & Objective: Fibrillar amyloid-beta (Aβ) PET ligands offer great promise in the scientific study, early detection, tracking, and differential diagnosis of Alzheimer's disease (AD) and the evaluation of Aβ-modifying treatments. [F18]AZD4694, a second-generation ligand developed by AstraZeneca, is used in the present study to characterize fibrillar Aβ burden in patients with mild AD, healthy elderly and healthy young controls.

Methods: 90min dynamic PET scans were acquired following the administration of [18F]AZD4694 10 mCi IV in 10 patients with probable mild AD (5 apolipoprotein E (*APOE*) ε4 carriers, 5 non-carriers), 10 healthy elderly adults (5 *APOE ε*4 carriers, 5 non-carriers), and 4 healthy young *APOE ε4* non-carriers. Fibrillar Aβ burden was quantified with cerebellum as the reference region over the 30-45min versus 0-90min frames, blind visual ratings, and gray matter, white matter, and cerebellar time-activity curves (TACs). Test-retest was determined in the AD and young controls.

Results: Our findings provide additional support of the following observations: 1) [18F]AZD4694 reaches equilibrium relatively quickly (about 27 min following radiotracer administration). 2) There is higher specific bindingrelative to cerebellumin AD than in elderly controls whose were higher than that in young controls, and easy assessment of fibrillar Abeta burden using visual ratings. 3) Quantified fibrillar Aβ burden can distinguish between AD and healthy elderly and young normal control subject groups, with the best differentiation between AD and young controls. 4) [18F]AZD4694 has high test-retest reliability.

Conclusion: [18F]AZD4694 PET offers promise in the assessment of fibrillar Aβ deposition. Additional studies are needed to compare it to other ligands and determine the extent to which it offers improved sensitivity for the presymptomatic detection and tracking of AD.

Presented by: **Langbaum, Jessica**

28

Contribution of Vascular Brain Injury and Brain Abeta to Cognitive Function

Natalie Marchant [1], Bruce Reed [2], Nerses Sanossian [3], Cindee Madison [1], Roxana Dhada [1], Stephen Kriger [4], Charles DeCarli [2], Michael Weiner [4], Helena Chui [3], William Jagust [1]

[1] UC Berkeley
[2] UC Davis
[3] USC
[4] UCSF

Background: Vascular brain injury (VBI) and brain Abeta deposition frequently co-occur and both may induce cognitive decline in aging. This study evaluated the relative contribution of VBI and Abeta to cognitive function in a cognitively diverse population.

Methods: 61 participants (female = 18, mean age = 77.8), enrolled in a vascular-focused study of aging that recruits cognitively normal and impaired participants (Clinical Dementia Rating [CDR] 0: N = 30; .5: N = 25; >.5: N = 6), underwent MRI, PIB-PET imaging, and cognitive testing. MRI images were visually rated for presence and location of infarct (VBI+: 34; VBI-: 27). PIB-PET DVRs (Logan plotting, 35-90min post-injection, grey matter cerebellar reference) were used to create a PIB index by averaging DVRs across frontal, posterior cingulate, precuneus, parietal and lateral temporal cortices. Participants with a PIB index 2 SDs greater than the mean PIB index of a young control group (N = 11, mean age = 24.5 ± 3.5) were classified as PIB positive (PIB+: N = 29; PIB-: N = 32). Standardized composite tests of cognition included measures of Global cognition, Memory, and Executive Functioning.

Results: VBI, particularly when located in subcortical grey matter, was associated with lower cognitive performance in all domains (p's < 0.08); inclusion of PIB as either a continuous or categorical (PIB+/PIB-) variable did not alter these findings and showed no interaction with VBI.

Conclusions: In this sample of cognitively diverse older adults, VBI played a more influential role than Abeta in cognitive function, and remained a significant predictor of cognition after controlling for the possible influence of Abeta.

Presented by: **Marchant, Natalie**

29

Standardization of Amyloid Imaging Methodology for Clinical Trials of Disease-Modifying Treatments for Alzheimer's Disease

Richard Margolin [1], *Mark Schmidt* [2], *Dawn Matthews* [3], *Enchi Liu* [1]

[1] *Janssen Alzheimer Immunotherapy*
[2] *Janssen Research and Development*
[3] *Abiant, Inc.*

Amyloid brain imaging (ABI) is being increasingly used in clinical trials of putative disease-modifying (DM) agents for Alzheimer's disease (AD), both for sample enrichment and as an endpoint. The successful implementation of ABI involves a series of steps in the image acquisition and quantitative analysis domains which must be carefully specified and thoroughly monitored in order to achieve the quality necessary for the data generated to be used effectively for either enrichment or as an endpoint. Yet, the methodology of ABI is not currently standardized, and variability exists in several areas which may impair the interpretability and comparability of the data reported for clinical trials using this method, particularly large multi-center studies. Here we consider areas of problematic variability in image acquisition and analysis. An important acquisition challenge is imposed by the need to use multiple scanners with differing resolutions, scatter correction software and reconstruction methods. Mobile scanners and change of scanner during a trial may be particular concerns. Tracer-specific differences (e.g., in white matter retention) are also potentially significant, and the ability to compare (and even integrate) data from different tracers is increasingly important. Enrichment paradigms include both visual and quantitative methods to segregate amyloid-positive and negative individuals. Variability considerations in this area include the specific visual assessment methodology and the comparability of this approach to quantitative (SUVR-based) methods. In using a quantitative approach to enrichment or for ABI as an endpoint, one notable source of variability is the nature of the reference region (e.g., the whole cerebellum, cerebellar gray matter, or pons). Beyond cataloging sources of variability, we discuss potential vehicles for addressing their impact and working toward standardization and Best Practices.

Presented by: **Margolin, Richard**

30

Glucose Metabolism, But Not Amyloid Deposition, Differentiates PD-MCI from PD without Cognitive Impairment

Marta Marquie-Sayagues, Stephen N. Gomperts, Joseph J. Locascio, Andrea L. Santarlasci, Doreen M. Rentz, John H. Growdon, Keith A. Johnson

Massachusetts General Hospital

Background: Mild cognitive impairment (MCI), a transitional stage between normal cognition and dementia, is a common feature in Parkinson disease (PD-MCI), but its underlying pathophysiology is not well known. We sought to determine whether PD-MCI could be differentiated from PD with normal cognition (PD-nl) by glucose metabolism using ^{18}F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) and by amyloid deposition using Pittsburgh Compound B (PiB) PET.

Methods: 43 PD patients without dementia (35 PD-nl (mean CDR-SOB=0.27) and 8 PD-MCI (mean CDR-SOB=2.44)) were examined. Subjects underwent neurological and neuropsychological examinations, FDG PET, and PiB PET imaging. FDG and PiB uptake were measured in temporal, occipital, precuneus, prefrontal, inferior parietal, anterior cingulate, posterior cingulate, putamen, thalamus, and caudate Regions-of-interest (ROI), using the Distribution Volume Ratio with cerebellar reference. ANCOVA and Multivariate analyses were performed for comparisons, with age and disease duration as covariates.

Results: PD-nl and PD-MCI groups did not differ in terms of gender, age or education. PD-MCI had lower disease duration and higher motor impairment. ROI analyses revealed significantly decreased glucose metabolism in temporal, occipital, precuneus, inferior parietal and prefrontal cortices in PD-MCI relative to PD-nl ($p<0.05$ for each). In contrast, PiB uptake failed to differentiate PD from PD-MCI in any brain area. FDG and PiB uptake in combination distinguished PD-nl from PD-MCI in temporal and occipital regions. ($p<0.05$ for each). In the PD-nl group, higher global FDG uptake correlated with higher MMSE score ($p<0.05$), while higher caudate FDG uptake was associated with lower UPDRS-III and H&Y scores ($p<0.05$).

Conclusions: PD-MCI showed hypometabolism in cortical brain areas compared to PD-nl. In contrast, amyloid deposition did not differ between both groups. Our results suggest that FDG PET may be a more sensitive marker than PiB PET for MCI in PD, and that decreased glucose metabolism is not due to amyloid deposition in PD.

Presented by: **Marquie-Sayagues, Marta**

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Apathy is Associated with Increased Amyloid Burden in Mild Cognitive Impairment

Gad Marshall [1], Nancy Donovan [2], Natacha Lorius [1], Christopher Gidicsin [3], Jacqueline Maye [3], J. Alex Becker [3], Rebecca Amariglio [1], Dorene Rentz [1], Reisa Sperling [1], Keith Johnson [4]

[1] Brigham and Women's Hospital, Massachusetts General Hospital
[2] Cambridge Health Alliance, Brigham and Women's Hospital, Massachusetts General Hospital
[3] Massachusetts General Hospital
[4] Massachusetts General Hospital, Brigham and Women's Hospital

Background: Apathy is the most common neuropsychiatric symptom in Alzheimer's disease (AD) dementia and mild cognitive impairment (MCI). Apathy has been associated with executive dysfunction and activities of daily living impairment and is a major source of frustration for patients and caregivers alike. Apathy has been shown to relate to hypometabolism and hypoperfusion in the anterior cingulate and orbitofrontal region in mild to moderate AD dementia, as well as to increased anterior cingulate neurofibrillary tangle burden in moderate to severe AD dementia. However, apathy has yet to be linked to amyloid burden.

Objective: We sought to determine whether apathy is associated with cortical amyloid burden and regional hypometabolism in MCI.

Methods: Twenty four MCI subjects participating in an investigator-initiated imaging study underwent clinical assessments and Pittsburgh Compound B (PiB) and 18F-fluorodeoxyglocuse (FDG) positron emission tomography (PET) imaging. FDG metabolism was expressed as the Standardized Uptake Value (cerebellar reference) for each region of interest. Cortical PiB retention was evaluated using the Distribution Volume Ratio (cerebellar reference). The Apathy Evaluation Scale (AES) was used to assess apathy severity based on an informant interview (lower scores indicate greater apathy). Partial Spearman's correlations, controlling for age, were used to assess the association between apathy and an aggregate of cortical PiB regions, as well as anterior cingulate and orbitofrontal FDG metabolism.

Results: There was a significant association between increased apathy (lower AES score) and greater cortical PiB retention (pr_s=-0.46, p=0.03). There was no significant association between apathy and anterior cingulate or orbitofrontal FDG metabolism.

Conclusions: These results suggest that increased apathy is associated with greater amyloid burden in MCI but not with anterior cingulate or orbitofrontal metabolism. Prior studies assessing these relationships at later stages of AD dementia have found associations with metabolism rather than amyloid burden. Future longitudinal studies will help clarify this difference.

Presented by: **Marshall, Gad**

32

Reference Region Quality Control as a Critical Aspect of Amyloid Measurement Using PET

*Dawn Matthews [1,2], Lisa Mosconi [1,2,3], Randolph Andrews [1,2], Richard Margolin [4], Enchi Liu [4], Mark Schmidt [5], the Alzheimer's Disease Neuroimaging Initiative (ADNI)**

[1] Abiant, Inc., Grayslake, IL
[2] ADM Diagnostics, Chicago, IL
[3] New York University School of Medicine, New York, NY
[4] Janssen Alzheimer Immunotherapy, South San Francisco, CA, USA
[5] Janssen Research and Development, Beerse, Belgium

Background: The cerebellar cortex, often used as the primary reference region to evaluate PET amyloid burden, profoundly impacts all region of interest standardized uptake value ratio (SUVR) measures. However, it is vulnerable to numerous sources of artifact that must be considered in obtaining and interpreting results.

Objective: The goal of our study was to identify the frequency of occurrence of sources of reference region artifact in a multi-center data set (ADNI) and the impact upon region of interest results, with the goal of providing practical guidelines for analysis.

Methods: We examined cerebellar attributes of 226 PIB scans from 103 ADNI subjects imaged at 13 imaging sites with 6 different PET scanner models. Scans were co-registered within subject and spatially normalized to a common tissue probability map, and a full gray matter cerebellum volume of interest was applied. Scans were categorized as having truncation within reference region bounds, coincidence of reference region with edge of field-of-view, or location of the reference region at least 1 cm above the image edge. For a subgroup of scans, comparisons were performed between reference region values obtained using successive reductions in reference region bounding box reduction as could be applied to avoid edge effects.

Results: Of the 226 scans, 3.5% had truncation causing sampling outside tissue, and 12% additional scans had reference region overlap with image edge where artifact is known to occur. Sampling of truncated cerebellum without boundary correction altered SUVR values by ≥15%. Use of different degrees of reference region boundary reduction resulted in SUVR variability reaching >20%.

Conclusion: Quality control of reference region sampling, coupled with sampling of a consistent region from scan to scan within subject, is of key importance particularly in threshold cases of PIB positivity and in the measurement of longitudinal progression using limited numbers of subjects.

Presented by: **Matthews, Dawn**

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

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Characterization and Optimized Measurement of Longitudinal PIB Changes for Clinical Trials by Accurate Sampling and Quantitation

Dawn Matthews [1], Lisa Mosconi [2], Randolph Andrews [1], Enchi Liu [3], Mark Schmidt [4], et al.

[1] *Abiant Inc., Grayslake, IL USA; ADM Diagnostics, Chicago, IL USA*
[2] *New York University School of Medicine, New York, NY, USA*
[3] *Janssen Alzheimer Immunotherapy, South San Francisco, CA, USA*
[4] *Janssen Research and Development, Beerse, Belgium*

Objective: The use of Amyloid beta-PET endpoints to evaluate AD therapeutics requires an understanding of amyloid progression rates within the target population, and the impact of sampling methods. The goal of this longitudinal study was to characterize and maximize detection of ^{11}C-PiB changes in a multi-center setting using accurate sampling techniques and optimized reference regions.

Methods: Twenty clinically normal (NL), 45 MCI and 18 AD subjects with n≥2 PiB scans from ADNI were examined. Using an automated technique, cortical PiB standardized uptake value ratios (SUVRs) were calculated using 6 reference regions: our optimized whole cerebellum, cerebellar gray matter, crus gray matter, pons, and centrum ovale, and cerebellum from the AAL template. A mixed model for repeated measures was used to examine PiB change across baseline and outcome clinical groups, and PiB groups (PiB- vs PiB+, defined as baseline PiB>1.4 SUVR). Rates of progression were calculated for each group. Analyses were repeated using general linear models and after additional quality screens.

Results: Baseline PiB retention was higher in AD>MCI>NL. Stable NL (n=17) and MCI (n=29) had significantly lower baseline PiB retention than MCI decliners to AD (n=15) and AD ($P<0.05$). Longitudinally, there were no interaction effects between clinical groups, although NL and MCI showed PiB increases over time while the AD group was stable. Interaction effects were observed when comparing PiB groups among NL ($P\leq0.03$), as PiB+ subjects (n=11) showed higher rates of PiB accumulation compared to PiB- (n=9). Reference regions that maximized detection of longitudinal effects were optimized whole cerebellum and cerebellar gray matter. Results after additional quality control were consistent but impacted progression rate.

Conclusion: These results provide a benchmark for measuring therapeutic impact upon amyloid progression, support robustness of findings across multiple reference regions, and demonstrate the benefit of applying quality control and optimization in data sampling.

Presented by: **Matthews, Dawn**

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Running with the Beagle: A Multi-Modal, Integrative Imaging Pipeline Specialized for the Processing of Elderly Brains

Jim Nikelski [1], *Howard Chertkow* [2], *Alan Evans* [3]

[1] *Lady Davis Institute, Jewish General Hospital*
[2] *McGill University, Lady Davis Institute*
[3] *Montreal Neurological Institute, McGill University*

Purpose: Hitherto, few image analysis approaches have attempted to create an integrative analysis system, capable of leveraging information gleaned from a wide array of imaging modalities. The implementation of such an integrative approach is the primary goal of the Beagle image processing pipeline.

Methods and Results: Processing within the Beagle pipeline is comprised of a number sub-pipelines, which in turn, are dependent upon an external structural analysis pipeline (Civet; MNI, Evans Lab). The structural pipeline, when provided with a high-resolution MRI T1 volume, yields a number of components required by Beagle, including stereotactic space transforms, tissue classification masks, and cortical thickness measures. These products are used by Beagle in the subsequent analysis pipelines, producing individually-targeted voxel or vertex-level results for: VBM, PiB, FDG, and cortical thickness.

The PiB and FDG analyses produce ratio volumes (using cerebellar gray matter as reference), permitting direct visualization of PiB distribution or FDG hypometabolism. SUVR values are also computed. The VBM analysis provides an indicator (voxel-level z-scores) of gray or white matter atrophy, by comparing the subject against 200 normal elderly brains, obtained from the ADNI project. The cortical thickness analysis similarly produces z-scores, compared against the ADNI model, permitting us to visualize areas of significant cortical thinning.

Quantification of results by region of interest (ROI) is made possible through the use of a customized labelling template, based on the AAL template, that is automatically, non-linearly warped onto the subject's brain in both stereotactic and native space.

An automatically generated report summarizes the results, with each modality included as a separate chapter, complete with full details of the analysis methodology. Additionally, files in CSV format are also created for each subject and analysis modality, permitting easy import of ROI-based results into the statistical analysis tool of choice.

Presented by: **Nikelski, Jim**

35

Effects of Age and Beta-Amyloid Deposition on Brain Activity and Functional Connectivity during Episodic Memory Encoding in Cognitively Normal Elderly

Hwamee Oh, Elizabeth Mormino, William Jagust

University of California-Berkeley

Objectives: To examine how brain activity and effective connectivity underlying episodic encoding change as a function of age and amyloid deposition measured by [^{11}C] Pittsburgh compound B (PIB) positron emission tomography (PET).

Method: Eleven young ("YOUNG", mean age=22.8, 7 males), 18 PIB-negative ("PIB−OLD", mean age=76.8, 7 males) and 11 PIB-positive ("PIB+OLD", mean age=77.5, 4 males) older adults performed an episodic encoding task of visual scenes during fMRI scans, followed by a surprise recognition task outside of the scanner where subjects made an old/new judgment. 200 encoding trials were sorted based on recognition judgment as correct recognition with high ("HC") or low ("LC") confidence or incorrect ("INCORRECT") recognition (i.e., misses).

Results: Whole-brain analyses revealed that, for the HC versus INCORRECT, YOUNG showed increased activity in frontal, parietal and visual association areas compared to both PIB−OLD and PIB+OLD. PIB−OLD showed increased activity in hippocampus and medial frontal cortex compared to YOUNG. Psychophysiological interaction (PPI) analyses was performed to evaluate connectivity with a seed region in the right parahippocampal gyrus (rPHG), which is implicated in visual processing and which was defined by a HC-INCORRECT contrast in each subject (mean coordinates X = 27, Y = -26, Z = -18). This revealed stronger coupling between rPHG and the left posterior hippocampus in YOUNG than PIB−OLD while, for the same contrast, PIB−OLD showed stronger coupling than YOUNG between the rPHG seed and the left frontal and parietal cortices, middle temporal cortex and the lateral occipital cortices. Within the older subjects, PIB−OLD showed stronger coupling between the rPHG and frontal and parietal cortices than PIB+OLD.

Conclusion: These preliminary results indicate that activity in prefrontal cortices, hippocampus, and visual association areas undergoes age-related alterations in support of successful visual encoding and that connectivity across these regions are further affected by age and amyloid deposition.

Presented by: **Oh, Hwamee**

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Increased Parietal Amyloid Burden and Metabolic Dysfunction in Alzheimer's Disease with Early Onset

Rik Ossenkoppele, Marissa Zwan, Sofie Adriaanse, Ronald Boellaard, Albert Windhorst, Frederik Barkhof, Adriaan Lammertsma, Philip Scheltens, Wiesje van der Flier, Bart van Berckel

VU University Medical Center

Background: Alzheimer's disease (AD) with an early onset often presents with a distinct cognitive profile compared to late-onset AD, potentially reflecting a different distribution of underlying neuropathology. The purpose of this study was to examine the relationships between age-at-onset with both in vivo fibrillary amyloid deposition and glucose metabolism.

Methods: Dynamic [11C]Pittsburgh compound-B (PIB) (90 minutes) and static [18F]fluorodeoxyglucose (FDG) scans were obtained in 100 AD patients. Parametric non-displaceable binding potential (BPND) images of [11C]PIB and standardized uptake value ratio (SUVr) images of [18F]FDG were generated using cerebellar grey matter as reference tissue. Nine [11C]PIB-negative patients were excluded. The remaining AD patients were categorized into younger (n=45, mean age at diagnosis: 56±4) and older (n=46, mean age at diagnosis: 69±5) groups, based on the median age (62 years) at time of diagnosis.

Results: Although groups did not differ on Mini-Mental State Examination, younger patients showed more severe impairment on visuo-spatial function, attention and executive function composite scores ($p<0.05$) as compared to older patients. In contrast, we found a trend towards poorer memory performance for the older AD group ($p=0.11$). Younger and older patients did not differ in global cortical [11C]PIB BPND ($p=0.29$) or in global cortical [18F]FDG SUVr ($p=0.30$). Regional distributions of both [11C]PIB BPND (p for interaction ><0.01) and [18F]FDG SUVr (p for interaction ><0.05), however, differed between groups. This was largely due to increased [11C]PIB binding and decreased [18F]FDG uptake in the parietal cortex of younger patients. >

Conclusion: These findings suggest that clinical differences between younger and older AD patients are related not only to topographical differentiation in downstream processes, but may originate from distinctive distributions of early upstream events. As such, increased amyloid burden, together with metabolic dysfunction, in the parietal lobe of younger AD patients may explain the distinct cognitive profile in these patients.

Presented by: **Ossenkoppele, Rik**

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Effects of Carotid Atherosclerosis and Cerebral Amyloid on Memory and Executive Function

Bruce Reed [1], Natalie Marchant [2], Neres Sanossian [3], Wendy Mack [3], Charles DeCarli [1], Michael Weiner [4], William Jagust [2], Helena Chui [3]

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

Background: We investigated the hypothesis that atherosclerosis (AS) has negative cognitive effects not mediated by cerebral amyloid or cerebrovascular disease.

Methods: Subjects were 56 people, mean age 78, with CDR scores of 0 or 0.5 (except 3 rated as "1"). AS was quantified by carotid intima-media thickness (CIMT). Infarcts and white matter lesions (WML) were quantified with MRI. Cerebral amyloid was measured with [11C]PIB-PET. DVRs for frontal, posterior cingulate, precuneus, parietal and lateral temporal cortices were averaged to create a cortical PIB index. Cases were designated as "PIB positive" (PIB+) or not (PIB-) using data from young volunteers . Memory (MEM) and executive function (EXEC) were measured using composite scales.

Results: Sequential multiple linear regressions separately evaluated MEM and EXEC, adjusted for age, sex, education, ethnicity and CDR. Because CIMT effects appeared different in PIB+ and PIB- cases, an indicator variable for PIB status was used to create interaction terms.

MEM: Neither PIB index nor CIMT had significant main effects. The interaction CIMT X PIB status was significant ($p < .01$); in PIB- cases, higher CIMT was associated with worse MEM. For PIB+, CIMT had no effect on MEM. The interaction term PIB status X PIB index showed a trend toward significance ($p = .07$), such that higher PIB was associated with worse MEM in PIB+ cases only. Neither infarcts nor WML were significant, and neither attenuated the CIMT X PIB status interaction.

EXEC: PIB index had a significant ($p < .02$), negative effect. Neither the main effect of CIMT nor its interaction with PIB status was significant. MRI infarcts, however, had a relatively large effect, explaining approximately 20% of the variance in EXEC.

Conclusions: The effects of CIMT differ according to cognitive domain and the presence of significant cerebral amyloid. Both atherosclerosis and amyloid may affect the medial temporal lobe, via different mechanisms.Background: We investigated the hypothesis that atherosclerosis (AS) has negative cognitive effects not mediated by cerebral amyloid or cerebrovascular disease.

Presented by: **Reed, Bruce**

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Elevated Beta-Amyloid Burden is Associated with Neural Differences in Face Processing in Healthy, Non-Demented Older Adults

Jenny Rieck [1], Karen Rodrigue [1], Kristen Kennedy [1], Andrew Hebrank [1], Michael Devous, Sr. [2], Denise Park [1]

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

Impaired face recognition is a commonly reported deficit in aging and Alzheimer's disease (AD). The fusiform gyrus is a key region involved in processing facial features (Kanwisher et al., 1997). Previous research provides evidence that this region shows less neural selectivity with normal aging (Park et al., 2004). The current study investigated the role of *in vivo* beta-amyloid deposition, a putative biomarker of AD, in the neural processing of faces in a sample of healthy, non-demented older adults.

Participants underwent ^{18}F-Florbetapir PET imaging to measure beta-amyloid load and also completed a functional MRI task designed to measure neural activation while viewing faces and other categories of objects. A total of 50 cognitively-healthy adults distributed across three groups participated in the study: 14 young adult controls (mean age = 32.7±2.0 years, mean SUVR = 1.08), 18 low beta-amyloid older adults (mean age = 74.0 ± 8.1 years, mean SUVR =1.14) and 18 high beta-amyloid older adults (mean age =74.1 ± 8.7 years, mean SUVR =1.50).

Multivariate pattern analysis of neural activity in the fusiform gyrus revealed that high beta-amyloid adults showed considerably different patterns of neural activation compared to demographically matched low beta-amyloid adults. Our results suggest these differences are driven by reduced neural activity in the fusiform gyrus for the high beta-amyloid group. Furthermore, these differences in neural activity were strongly associated with greater beta-amyloid burden in the precuneus, anterior cingulate, and posterior cingulate regions, but not occipital region.

Overall, elevated beta-amyloid in older adults is associated with a reduced neural response to human faces, compared to both young adults and older adults with a lower beta-amyloid load. We conclude that elevated beta-amyloid deposition, even in healthy adults, may be one of the mechanisms underpinning the neural changes in face processing that occur with aging.

Supported in part by NIH grants 5R37AG-006265-25, 3R37AG-006265-25S1, and Alzheimer's Association grant IIRG-09-135087. Radiotracer was generously provided to the study by Avid Radiopharmaceuticals.

Presented by: **Rieck, Jenny**

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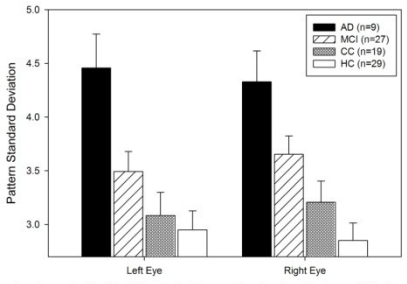
Relationship of Visual Contrast Sensitivity to Amyloid Deposition Assessed by [11C]PIB PET

Shannon Risacher [1], Karmen Yoder [1], John West [1], Darrell WuDunn [2], Tamiko MaGee [1], Brenna McDonald [1], Gary Hutchins [1], Qi-Huang Zheng [1], Andrew Saykin [1]

[1] Department of Radiology and Imaging Sciences, Indiana University School of Medicine
[2] Department of Ophthalmology, Indiana University School of Medicine

Alzheimer's disease (AD) is characterized by extensive amyloid deposition, formation of neurofibrillary tangles, widespread neurodegeneration, and cognitive impairment. Although memory deficits are most commonly reported, AD patients also show impaired visual processing, including deficits in visual contrast sensitivity (Figure 1). We sought to evaluate the relationship between visual contrast sensitivity, evaluated using frequency doubling technology (FDT), and amyloid deposition, assessed using [^{11}C]PiB PET.

Figure 1. Impaired Visual Contrast Sensitivity in Patients with AD and MCI, and Older Adults with Cognitive Complaints



* Increased pattern standard deviation indicates greater visual contrast sensitivity impairment

Adapted from Risacher et al. (submitted)

Participants included patients with AD (n=3) and amnestic mild cognitive impairment (MCI, n=4), older adults with cognitive complaints but no significant cognitive deficits (CC, n=6), and healthy age-matched controls (HC, n=5). All participants received a FDT-2 24-2 visual field test to evaluate contrast sensitivity and a [^{11}C]PiB PET scan. Briefly, PiB scans were collected for 50min after a 40min uptake period. Individual PET frames were motion-corrected and normalized to MNI space. A mean PiB image from 40-90min was generated, normalized using a cerebellar grey matter reference region, and smoothed with an 8mm FWHM kernel. The relationship between visual contrast sensitivity performance (pattern standard deviation, PSD) and PiB SUVR was then evaluated on a voxel-wise basis. Finally, values from the most significant cluster identified in the whole-brain analysis (bilateral precuneus) were extracted to quantitate this correlation between mean PiB SUVR and visual contrast sensitivity.

A significant relationship between impaired visual contrast sensitivity performance (greater PSD) and increased amyloid deposition was observed. In the voxel-wise analysis, significant clusters were observed in the bilateral precuneus and frontal and parietal lobes (Figure 2). The correlation between mean PiB SUVR and PSD in the bilateral precuneus cluster is shown graphically in Figure 3.

Visual contrast sensitivity performance appears to track with amyloid deposition in AD-associated regions, particularly frontal and parietal areas. Further studies are warranted to investigate the relationship of visual contrast sensitivity to amyloid and other biomarkers of AD pathology.

Figure 2. Significant Association between Impaired Visual Contrast Sensitivity and Increased Amyloid Deposition Measured using [11C]PiB PET

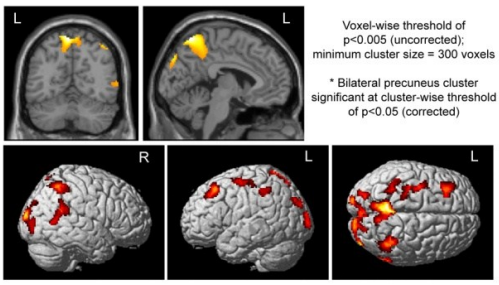
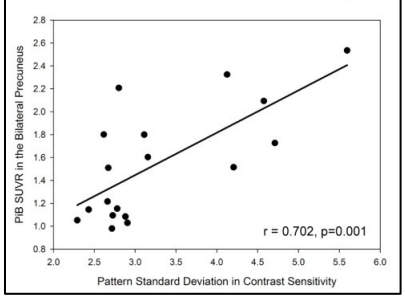


Figure 3. Relationship between Impaired Visual Contrast Sensitivity and Increased PiB SUVR in the Bilateral Precuneus



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Presented by: **Risacher, Shannon**

Comparison Between Anatomically and Probabilistically-Driven Volumes of Interests for Quantifying Amyloidosis in Prodromal AD

Lyiong Wu, Jared Rowey, Sara Mohades, Monica Shin, Sergr Gauthier, Pedro Rosa-Neto

Alzheimer's Disease Research Unit - McGill University

Background: In the prodromal stage of Alzheimer's disease (AD) , amyloidosis progresses without respecting clear anatomical boundaries. Therefore, group classification algorithms derived from purely anatomically-based volumes of interest s (a VOI s) might underestimate [11 C] PIB retention by a dilution effect from areas with low amyloid load. In contrast, probabilistically-driven volumes of interest (pVOIs) containing information of abnormal [11 C]PIB retention in the AD brain might increase the performance of classification algorithms by restricting the estimation of binding parameters to areas of high amyloid load.

Objective: Here, we compared estimation of [11 C]PIB retention using an aVOI and a pVOI approach in prodromal AD. Methods: A total of 103 structural MRI and [11C]PIB scans were obtained from the ADNI database. 52 cases of MCI, 27 of AD and 1 7 of controls were includedin the present study. While 19 MCI converted to AD subsequent to the [11C]PIB scan, 32 of MCI remainedclinically stable (27 months follow - up). MRI images were corrected for non-linearity, classified (white, grey matter and CSF) and automatically segmented into cortical regions. Brain to cerebellum index (BCI) images were calculated in the PET native space. Binary images representing abnormal BCI (>1.5) were obtained from AD subjects and non-linearly resampled to the MNI151 space. Abnormal BCI probabilistic distributions were calculated by compiling individual binary images into a probabilistic map. pVOI encompassed regions with abnormal BCI present in >93% AD patents (Fig 1). pVOI representing abnormal BCI was applied to MCI individuals converters and non converters.

Results: pVOI resulted in increase of median [11C]PIB BCI in all groups compared to aVOIs ($F=5.7$; $df=95$; $p<0.001$). Althoughthe sensitivity of pVOIs to detect prodromal AD has increased 20% (ROC-AUC Zscore=1.83) compared to aVOIs, the specificity of pVOIs has declined 17%.

Conclusion: These results suggest that pVOIs method has higher but modest performance toquantify amyloidloadin prodromalAD.

Presented by: **Wu, Lyiong**

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Evaluation of Voxel Concordance-Discordance Between [11C]PIB and Florbetapir PET Group Difference T-Maps for Amyloid(+) Vs. Amyloid(-) Subject Groups

Bedda Rosario [1], Wenzhu Bi [2], Lisa Weissfeld [2], William Klunk [3], Chester Mathis [1], Cristy Matan [1], Michael Berginc [1], Julie Price [1]

[1] University of Pittsburgh, Department of Radiology
[2] University of Pittsburgh, Department of Biostatistics
[3] University of Pittsburgh, Department of Psychiatry

Objective: Apply a non-parametric multimodal correlation test to explore voxel concordance-discordance in t-maps of amyloid(+) vs. amyloid(-) group differences determined for [11C]PiB (or PiB) and Florbetapir PET.

Methods: PiB and Florbetapir PET (50-70 SUVR) were performed for 22 (6 NC, 16 MCI) ADNI subjects, the largest exploratory sample of baseline PiB scans versus subsequent baseline Florbetapir scans (3.0±0.3 years apart). PET SUVR images were spatially normalized to a MR template using the individual's structural MRI. Subject amyloid retention status (+/-) was based on regional iterative outlier analyses of the PiB data (9 amyloid(-), 13 amyloid(+)). Voxel-wise 2-sample t-tests were performed to generate group difference t-maps for both PiB and Florbetapir (amyloid(+) vs. amyloid(-))**.** The degree of concordance-discordance was summarized using a combining t-value function within a permutation test framework [1]. Clusters of concordance-discordance were projected into normalized space and mapped to anatomical locations ($p<0.05$ FWE corrected). Concordance reflects t-map differences for both PiB and Florbetapir. Discordance reflects significant PiB group differences without Florbetapir differences, and vice versa. A secondary analysis examined a smaller cohort scanned with PiB 1.1±0.2 years before Florbetapir (6 amyloid(-), 10 amyloid(+)).

Results: Concordance was significant in high amyloid retention areas of cortex. Discordance with significant PiB (insignificant Florbetapir) arose in ventral frontal cortex, lateral temporal cortex, hippocampus and anterior cerebellum. Discordance with significant Florbetapir (insignificant PiB) arose in sensory motor cortex, occipital pole and putamen. The secondary analysis revealed a greater concordance-discordance overlap in the cortex, and discordance in the anterior-ventral striatum.

Conclusions: Group differences were highly concordant in amyloid-bearing areas of cortex. Discordance arose in areas with intra- and inter-subject variation (e.g., non-uniform retention, individual anatomical variability, low retention). Changes that may arise during the interval between PiB and Florbetapir scanning (e.g., atrophy, amyloid accumulation) may contribute to discordance.

[1] Hayasaka et al. Neuroimage (2006)

Presented by: **Rosario, Bedda**

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Impaired Cerebrovascular Reactivity is a Potential Biomarker to Assess Vascular Risk Factors in Alzheimer's-Related Diseases

Kevin Sam [1], *Julien Poublanc* [2], *Daniel M. Mandell* [2], *Joseph Fisher* [1], *David Mikulis* [2]

[1] *Department of Physiology, University of Toronto*
[2] *Division of Neuroradiology, University Health Network, Toronto, Ontario*

Purpose: There is abundant evidence supporting a vascular etiology of cerebral amyloid angiopathy (CAA) and Alzheimer's disease and (AD), yet the role of cerebrovascular autoregulation as a contributor to CAA and AD is still not fully determined. A measure of the autoregulatory capacity is cerebrovascular reactivity (CVR). Cerebrovacular disease and amyloid angiopathies have been suggested to work synergistically to cause leukoaraiosis. These white matter abnormalities are also found in genetic amyloid angiopathies, suggesting that amyloid angiopathy is sufficient to cause leukoaraiosis. We propose that impaired CVR may influence the course of CAA and AD due to cerebral hypoperfusion when there is an increased blood flow demand during neural activity. The aim of this study was to determine whether there is a difference in cerebrovascular reactivity between subjects with leukoaraiosis compared to healthy individuals.

Method: 13 consenting subjects with moderate-severe leukoariosis (Fazekas score >2) and 25 healthy individuals were enrolled following IRB approval. BOLD MRI CVR at 3T (GE Healthcare, Milwaukee) was performed during oscillating iso-oxic carbon dioxide (CO_2) manipulation, from 40 to 50 mmHg, with echoplanar-imaging gradient-echo to measure flow related wash-out of deoxyhemoglobin during hypercapnea. Gas manipulations were made using a device that permits precision control of CO_2 (RespirActTM, Thornhill Research, Inc.) The method enables quantitative analysis of CVR since rapid manipulations of the flow stimulus, end-tidal-CO_2 are precisely known.

Results: Subjects with leukoaraiosis and MCI had a significant reduction in CVR compared to healthy individuals ($P<0.01$).

Conclusion: BOLD MRI CVR can be used to quantitate vascular reserve showing a decrease in patients with leukoariosis and MCI. Since MCI is a precursor of vascular dementia and possibly AD as well, this may serve as an imaging biomarker for assessing the vascular contribution to cognitive decline.

Presented by: **Sam, Kevin**

43

PET PIB Utility in Clinical Practice: Learning from the Unexpected Findings

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

[1] University Hospital "Marqués de Valdecilla"
[2] The Memory & Aging Center, University of California San Francisco
[3] University of California Berkeley; Lawrence Berkeley National Laboratory

Background/Aims: Amyloid imaging is poised to enter the clinical arena, yet few studies have examined its impact on clinical diagnosis and management. We evaluated the longitudinal course and clinical decision making in patients seen at our Center who had a PIB result that was discordant with the pre-scan clinical diagnosis.

Methods: 6/69 of clinically diagnosed AD patients were PIB-negative (8.7%), and 9/65 patients with frontotemporal lobar degeneration (FTLD), a non-Aβ dementia, were PIB-positive (13.8%). Median follow up was 7 visits (range 1-10) over 4 years (range 1-11). The clinical course of these patients was retrospectively reviewed by a neurologist and neuropsychologist to assess: (1) longitudinal evolution; (2) change in clinical diagnosis after release of PIB results; (3) changes in prescribed medications.

Results: PIB-negative AD:Two patients showed little cognitive change, and the diagnosis was changed to MCI due to psychiatric and vascular causes. Three patients evolved an FTLD syndrome (PSP, PPA) and clinical diagnosis was changed appropriately. One patient continued to show progressive amnesia with relative sparing of other domains, and the diagnosis remained AD.No changes in medications occurred related to PIB results. PIB-positive FTLD: Four PPA patients (two non-fluent variant and two semantic variant) showed PIB uptake despite typical disease courses. Even though diagnosis was unchanged, cholinesterase inhibitors were added in three cases. Five FTD patients had a positive PIB, which together with their clinical evolution prompted a change in diagnosis to AD. In three cases cholinesterase inhibitors were added.

Discussion: The clinical trajectories of patients with discordant PIB results varied and suggested: (1) non-degenerative cognitive impairment; (2) possibly incidental AD pathology in patients with classical FTLD syndromes; (3) misclassification of AD vs. FTLD. Clinical diagnosis was often affected by PIB results, particularly in PIB-negative AD. Cholinesterase inhibitor treatment was initiated in most patients that were unexpectedly PIB-positive.

Presented by: **Sanchez-Juan, Pascual**

44

Voxel-Wise Investigation of Cerebral Blood Flow and Distribution Volume Ratio (DVR) Maps: Contribution of Blood Flow to DVR, a Measure of B-Amyloid Deposition

Jitka Sojkova [1], Joshua Goh [2], Bennett Landman [3], Xue Yang [3], Yun Zhou [4], Yang An [2], Lori Beason-Held [2], Michael Kraut [4], Dean Wong [4], Susan Resnick [2]

[1] *Johns Hopkins University and NIA/NIH*
[2] *National Institute on Aging/NIH*
[3] *Vanderbilt University*
[4] *Johns Hopkins University*

In mouse models, neuronal activity regulates regional vulnerability to Aβ deposition (Bero et al 2011). We hypothesized that local relationships exist between Aβ accumulation and neuronal activity in nondemented older adults.

Methods: 55 nondemented participants (78.5±6.3 years,7 CDR=0.5) in the Baltimore Longitudinal Study of Aging underwent [^{15}O]-water PET and dynamic [^{11}C]PiB-PET. [^{15}O]-water PET images, which detect regional cerebral blood flow (CBF) and reflect neural activity, were normalized and smoothed in SPM5. A simplified reference tissue model with linear regression and spatial constraint (Zhou et al 2007) was used to generate distribution volume ratio (DVR) images which were then regressed on CBF images on a voxel-by-voxel basis using robust Biomedical Parametric Mapping software (Yang et al 2011), adjusting for age and sex (FDR p=0.5, k=50). DVR images were also regressed on R1 images, a measure of the transport rate constant from vascular space to tissue. All analyses were performed in the whole group as well as by tertiles of mean cortical DVR.

Results: Increased DVR is positively associated with increased CBF in frontal, parietal, temporal, and occipital cortex. However, this association occurs primarily in regions that do not typically show early Aβ deposition. In addition, more robust relationships between CBF and DVR are observed in those with negligible cortical Aβ load compared with those with higher cortical Aβ load. Finally, the spatial distribution of the DVR-CBF relationship is similar to that of the DVR-R1 relationship. No reliable negative voxel-wise relationship between CBF and DVR was found.

Conclusion: Robust DVR-CBF associations at low levels of Aβ together with similar spatial distributions of DVR-CBF and DVR-R1 relationships suggest that especially in those with minimal Aβ load, DVR images reflect blood flow rather than Aβ deposition. This finding has implications for voxel-wise correlations with external variables in individuals with varying amounts of Aβ load.

Presented by: **Sojkova, Jitka**

45

Amyloid PET Radioligand [18F]MK-3328: Phase I Clinical Trial

Cyrille Sur [1], Aniket Joshi [1], Danna Jennings [2], Rik Vandenberghe [3], Gilles Tamagnan [2], Jan Versijpt [4], Jules Janssens [5], John Palcza [6], Sandra Sanabria-Bohórquez [1], Koen Van Laere [7], Michel Koole [7], Guy Bormans [8], Kim Serdons [7], Jan de Hoon [9], Inge de Lepeleire [10], et al.

[1] Imaging, Merck Research Laboratories, West Point, US
[2] Molecular NeuroImaging, New Haven, US
[3] Department of Neurology, University Hospital Leuven, Belgium
[4] Dept. of Neurology, University Hospital Brussels, Belgium
[5] Dept. of Neurology, Heilig Hart Hospital Leuven, Belgium
[6] Early Development Statistics Merck Research Laboratories, West Point, US
[7] Division of Nuclear Medicine, University Hospital Leuven, Belgium
[8] Laboratory for Radiopharmacy, K.U. Leuven, Belgium
[9] Center for Clinical Pharmacology, University Hospital Leuven, Belgium
[10] Clinical Pharmacology, Merck Sharp & Dohme, Brussels, Belgium

Studies with Alzheimer's Disease (AD) brain tissues and PET studies in Rhesus monkey have supported the clinical investigation of the amyloid PET tracer [^{18}F]MK-3328.

[^{18}F]MK-3328 whole-body scans were conducted in 3 healthy subjects to determine tracer biodistribution and radiation dosimetry. PET studies with arterial blood sampling were performed in 3 healthy elderly (HE) and 3 AD patients to determine optimal scanning parameters and image analysis. The test re-test variability and ability of [^{18}F]MK-3328 to detect amyloid plaque was evaluated in 6 HE and 5 AD patients with 0-90 min dynamic scan post-tracer injection of ~150MBq. A composite cortical Specific Uptake Value Ratio (corSUVR) index for [^{18}F]MK-3328 tracer binding quantification was determined using the cerebellum as reference region and used to differentiate HE from AD patients.

[^{18}F]MK-3328 was well tolerated by subjects with brain uptake reaching a maximum of 4-8 SUV at 3-5 min. Its radiation safety profile was favorable with an Effective Dose of 18.2 microSv/MBq and a 2.7 mSv radiation exposure per injection of tracer (150 MBq) enabling good image quality and quantitative information. Cerebellum was validated as a reference region to quantify [^{18}F]MK-3328 binding and the optimal contrast between cortical areas and white matter was obtained with images in the 60-90 min interval post tracer injection. [^{18}F]MK-3328 exhibited low test re-test variability of SUVR with values of ~5% and ~2% for cortical areas in HE and AD patients, respectively. Visual inspection of [^{18}F]MK-3328 scans from most AD patients revealed the presence of PET signal in many cortical areas as well as hippocampus and striatum. Quantification of the PET signal indicated that [^{18}F]MK-3328 corSUVR values (mean±S.D.) in AD patients (1.56±0.06 SUVR; n=9) were higher than corresponding values in HE (1.30±0.01 SUVR; n=7).

Based on these results, [^{18}F]MK-3328 is being further evaluated in AD and amnestic mild cognitive impairment patients.

Presented by: **Sur, Cyrille**

46

Amyloid Beta 42 Induced MRI Changes in Aged Rabbit Brain Resembles AD Brain

Nicole Michelle Tayler Sucre [1], BN Ramesh [2], KP Raichurkar [3], NM Shamasundar [4], TSS Rao [4], KS Rao [1]

[1] INDICASAT-AIP, Panama
[2] CFTRI, INDIA
[3] Vikram Hospital, India
[4] JSS University, India

Alzheimer's disease is the most common form of dementia and is structurally characterized by brain atrophy and loss of brain volume. Ab is one of the widely accepted causative factors of AD. Ab 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 Ab on brain structure in the aged rabbit brain. Among 20 aged rabbits, one batch (n = 10) rabbits was injected chronically with Ab(1–42) and another batch (n = 10) with saline. The MRI was conducted before Ab(1–42)/saline injection and after 45 days of Ab(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.

Presented by: **Tayler Sucre, Nicole Michelle**

47

The Effect of CR1 on Brain Amyloid Burden during Aging and Its Modification by APOE Genotype

Madhav Thambisetty [1], Yang An [1], Michael Nalls [2], Jitka Sojkova [2], Yun Zhou [3], Andrew Singleton [2], Dean Wong [3], Luigi Ferrucci [2], Susan Resnick [1]

[1] Laboratory of Behavioral Neuroscience, National Institute on Aging, National Institutes of Health
[2] National Institute on Aging, National Institutes of Health
[3] Johns Hopkins University School of Medicine

The rs3818361[A] single nucleotide polymorphism (SNP) in CR1 has been associated with increased risk of Alzheimer's disease (AD). Although this novel risk variant is associated with a small effect size and, by itself, is unlikely to be useful as a predictor of AD risk, it may provide mechanistic insights into AD pathogenesis. We examined the association between the rs3818361[A] SNP in the CR1 gene and brain amyloid deposition in non-demented older individuals. We find that individuals carrying the AD risk allele of the rs3818361[A] SNP in CR1 have significantly lower brain amyloid burden relative to non-carriers. Moreover, we also observed greater variability in brain amyloid deposition in the non-carrier group relative to risk allele carriers, an effect explained partly by APOE genotype. In non-carriers of the CR1 risk allele, APOE ε4 carriers showed significantly higher brain amyloid burden relative to APOE ε4 non-carriers. Our findings suggest that the increased risk for AD associated with polymorphic variation in the CR1 gene is not mediated by increased brain amyloid deposition in cognitively normal older individuals. These findings suggest complex mechanisms underlying the interaction of CR1, APOE and brain amyloid pathways in AD pathogenesis. Our results may also be relevant to recent efforts aimed at targeting brain Aβ deposition and/or clearance in non-demented individuals at increased risk for AD and suggest that clinical outcomes of such treatments are likely to be influenced by complex gene-gene interactions.

Presented by: **Thambisetty, Madhav**

48

Combination of Biomarkers: Amyloid Imaging and Structural MRI in Dementia and MCI

Lennart Thurfjell [1], Roger Lundqvist [1], Jyrki Lötjönen [2], Juha Koikkalainen [2], Victor L. Villemagne [3], Christopher C. Rowe [3]

[1] GE Healthcare, Uppsala, Sweden
[2] VTT Technical Research Centre of Finland
[3] Department of Nuclear Medicine and Centre for PET, Austin Health, Heidelberg, Australia

Background: New NIA-AA diagnostic guidelines for Alzheimer's Disease (AD) incorporate biomarkers in the diagnostic criteria and suggest two categories: Aβ accumulation and neuronal degeneration or injury.

Objective: To compute hippocampus volume from MRI and a neocortical standard uptake value ratio (SUVR) from amyloid PET and investigate the performance of these biomarkers when used individually and when combined.

Methods: All subjects with baseline MR and [^{11}C]PIB scans from the AIBL study, available for download from ADNI, were used. The cohort included 68 healthy volunteers (HV), 83 subjective memory complaints (SMC), 41 mild cognitive impairment (MCI) and 34 AD. The MCI group was divided into stable MCI (sMCI) and progressive MCI (pMCI) based on the clinical status at 18 month follow up. The hippocampus was segmented using an extended multi-atlas segmentation method. Volumes reported were the sum of the left and right hippocampus corrected for total intra-cranial volume. PET data was processed using a fully automated method. The 50-70 min PET sum images were spatially normalized into MNI space and SUVR values for regions corresponding to frontal, lateral temporal and parietal cortices as well as anterior and posterior cingulate/precuneus were computed using a cerebellar cortex reference region. We then computed a composite neocortical SUVR value as an average of the above-mentioned cortical regions.

Results: SMC subjects showed a small non-significant increase in SUVR and decrease in hippocampus volume compared to HV. A larger and significant increase in SUVR and decrease in hippocampus volume was observed in pMCI (n=12) when compared to sMCI (n=22). When both measures were combined, most pMCI subjects clustered in the area with high SUVR and low hippocampus volumes indicating that these subjects were in different stages of neurodegeneration as compared to the sMCI subjects.

Conclusion: Combining amyloid PET with structural MRI in MCI allows more accurate disease characterization.

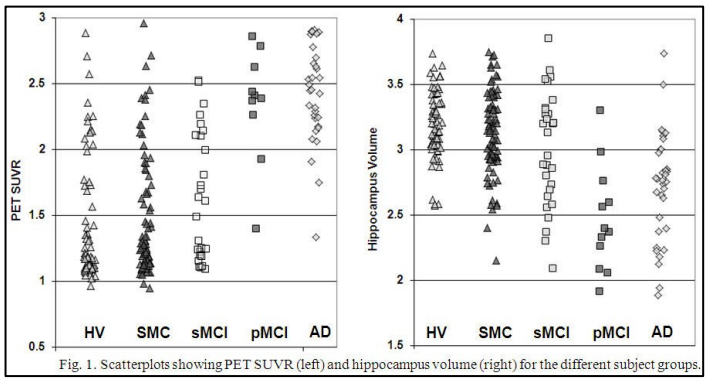

Fig. 1. Scatterplots showing PET SUVR (left) and hippocampus volume (right) for the different subject groups.

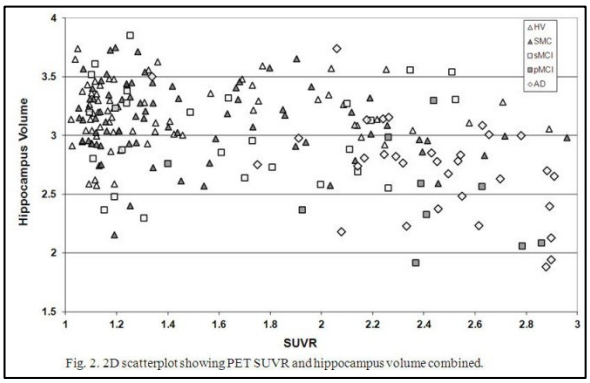

Fig. 2. 2D scatterplot showing PET SUVR and hippocampus volume combined.

Presented by: **Thurfjell, Lennart**

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MR Imaging Signature of Amyloid-Beta Positivity in Individuals with MCI

Duygu Tosun [1], Michael Weiner [1], ADNI Alzheimer's Disease Neuroimaging Initiative [2]

[1] Center for Imaging of Neurodegenerative Diseases Department of Radiology and Biomedical Imaging, University of California, San Francisco
[2] ADNI

The overall goal of this project is to identify brain atrophy patterns(measured by structural-MRI) that best predict the brain amyloid-beta burden(detected by PiB-PET) in individuals with Mild Cognitive Impairment(MCI).Although amyloid-beta has been suggested as the primary cause of synaptic dysfunction in Alzheimer's disease(AD) and there have been various advancements in amyloid-imaging techniques,use of amyloid-imaging in AD-continuum for both diagnostic purposes as well as for evaluating the treatment strategies in the clinical community has been limited due to the technical requirements and cost of available amyloid-imaging techniques.Meanwhile, structural neuroimaging has been shown to be useful in AD diagnosis and has become a part of routine clinical assessment of AD-continuum.To what extend are imaging modalities predict each other has not been examined yet.Applying an unbiased-atlas generation technique(a nonlinear fluid-flow warping) to 58 MCIs (75.22±7.66years;19F) from ADNI, initial deformation momentum capturing the anatomical shape variations(ASVs) at each voxel was computed for each structural-MRI.Using classical partial-least-squares (PLS) regression, we found direction(latent variable (LV)) in the momenta space and direction in the global cortical-PiB-SUVR space that explained their association in the sense of their common variance after accounting for age,sex,education,and APOE4 carrier differences.An increased in mean cortical amyloid-beta burden was associated with ASVs in hippocampus,fornix/stria terminals,caudate,amygdala,and middle temporal,supramarginal,pre-cuneus,inferior parietal,and entorhinal cortices($r=0.61$;$p<10\text{-}6$).In addition,we computed the area under the ROC curve for classification of amyloid-beta positive and negative MCIs based on the established threshold of 1.5.The ASV-derived classifier had accuracy of 78%.This was comparable to 79% accuracy of an APOE4 status-derived classifier($p=0.08$).Classification accuracy of 93% was achieved with a classifier combining ASVs with APOE4 status and accounting for age,sex,and education differences.These results may have high impact on early diagnosis of AD by providing means of predicting amyloid-positivity in MCI(maybe in healthy controls as well) via affordable and widely available structural-MR imaging for routinely performed clinical assessment.

Presented by: **Tosun, Duygu**

50

Relation between Rates of Aβ Deposition, Apoe Genotype and Cognition: Results from 3-5 Year Longitudinal Study

Victor L Villemagne [1], Kathryn A Ellis [2], Gael Chetelat [3], Pierrick Bourgeat [4], Gareth Jones [1], Olivier Salvado [4], Ralph Martins [5], David Ames [6], Colin L Masters [7], Christopher C Rowe [1]

[1] Centre for PET, Austin Health, Melbourne, VIC, Australia
[2] Dept Psychiatry, University of Melbourne, Melbourne, VIC, Australia
[3] Inserm-EPHE, Universite de Caen/Basse-Normandie, Caen, France
[4] ICT, The Australian e-Health Research Centre, CSIRO, Brisbane, QLD, Australia
[5] Edith Cowan University, Perth, WA, Australia
[6] National Ageing Research Institute, Melbourne, VIC, Australia
[7] The Mental Health Research Institute, Melbourne, VIC, Victoria

Background: Longitudinal evaluation of ageing individuals is providing insight into the different factors leading to Alzheimer's disease (AD). In this study, we used longitudinal data from the AIBL cohort, to provide a better understanding of the relationship between Abdeposition and cognition in the development of AD.

Methods: One hundred and nineteen participants -74 elderly healthy controls (HC); 29 Mild Cognitive Impairment (MCI) subjects; and 16 mild AD patients - were evaluated at enrolment and 18 and 36 months later. On each visit, participants underwent neuropsychological examination, a MRI and a ^{11}C-PiB PET scan. Rates of change for Aβ deposition and cognitive decline were derived from the slope of the regression plots over 3-5 years and used in the correlational analysis.

Results: Aβ deposition (0.05±0.04 vs 0.01±0.03 SUVR/yr, $p<0.0001$) and memory decline (-0.17±0.29 vs -0.02±0.22 SD/yr, $p=0.02$) were significantly faster in PiB+ vs PiB- HC. Aβ deposition and memory decline were also faster in PiB+ than in PiB- MCI (0.05±0.01 vs 0.01±0.01 SUVR/yr, $p=0.0004$; and -0.21±0.05 vs -0.04±0.06 SD/yr, $p=0.04$, respectively). Aβ deposition was slightly slower in AD (0.03±0.03 SUVR/yr). Aβ deposition in ApoE e4 carriers was significantly faster only in the MCI group ($R^2=0.39$, $p=0.006$). Cognitive decline was inversely associated with Aβ deposition in all groups: HC ($R^2=0.12$, $p=0.044$), MCI ($R^2=0.23$, $p=0.023$), and AD ($R^2=0.71$, $p=0.033$).

Conclusions: Aβ deposition is associated with cognitive decline even in asymptomatic healthy controls. This supports the theory that Aβ deposition plays a fundamental role in the development of AD and suggests that to be effective, anti-Aβ therapy may need to be given early in the course of the disease, perhaps even before symptoms appear.

Presented by: **Villemagne, Victor L**

51

Amyloid Associated Olfactory Impairment in Normal Elderly

Lauren Wadsworth [1], Mark Albers [1], Natacha Lorius [2], Rebecca Amariglio [3], Dorene Rentz [3], Gad Marshall [3], Scott McGinnis [3], Aaron Schultz [1], Alex Becker [1], Chris Gidiscin [1], Jaqueline Maye [1], Keith Johnson [2], Reisa Sperling [3]

[1] Massachusetts General Hospital
[2] Massachusetts General Hospital, Brigham and Women's Hospital
[3] Brigham and Women's Hospital, Massachusetts General Hospital

Background: Impaired ability to identify specific odors has been reported in a number of neurodegenerative diseases. In particular, performance on a 10-item subset of the University of Pennsylvania Smell Identification Test (UPSIT) has been reported to predict progression from mild cognitive impairment to Alzheimer's disease (AD) dementia. The objective of this study was to investigate the relationship between amyloid deposition on PET using Pittsburgh Compound B (PiB) and performance on the 10-item UPSIT in a sample of clinically normal (CN) older individuals.

Methods: Seventy CN subjects (mean age 73.5 ± 5.9) recruited from the Harvard Aging Brain study underwent odor identification testing using the 10-item UPSIT, and a battery of neuropsychological tests. Amyloid deposition was assessed using PiB PET DVR with an aggregate of cortical regions. Hierarchical linear regression models were used to assess the relationship of the UPSIT to cortical PiB retention, initially on its own; then, covarying for age and cognitive reserve using the American National Adult Reading Test (AMNART) Intelligence Quotient (IQ); finally, covarying for performance on the Boston Naming Test (BNT) and the Free and Cued Selective Reminding Task (FCSRT) to control for naming associated deficits.

Results: We found that worse olfactory identification was associated with greater cortical PiB retention, covarying for age and AMNART IQ (PiB:beta=-1.90, p=0.02). Covarying for measures of naming (BNT), cortical PiB retention was still associated with olfactory identification, but naming was not associated with olfactory identification (R2 =0.19; PiB: beta=-1.88, p=0.03; naming: beta=0.01, p=0.90).

Conclusions: Our findings suggest that olfactory identification impairment is associated with greater amyloid burden among clinically older individuals and may be an early feature of preclinical AD.

Presented by: **Wadsworth, Lauren**

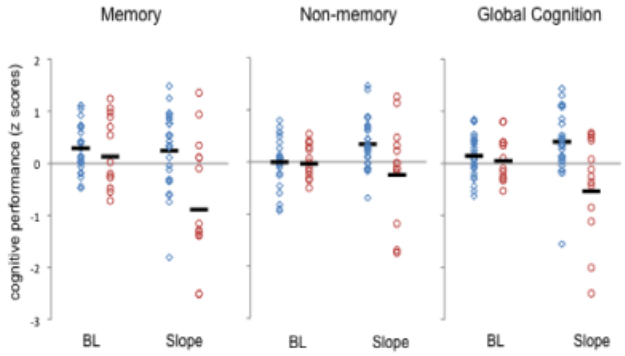
52

A-Beta Deposition in Normal Elderly is related to Longitudinal Cognitive Decline

Cortical Biopsy Histopathology *Wirth, Hwamee Oh, Elizabeth Mormino, Candace Markley, Susan Landau, William Jagust*

Helen Wills Neuroscience Institute

Objective: There is indication that validated Alzheimer's disease biomarkers of beta-amyloid (Abeta) accumulation and neurodegenerative pathology are related to preclinical cognitive decline. The present study therefore contrasted effects of Abeta deposition and posterior cortical metabolism to longitudinal cognitive change in cognitively normal elderly.



Methods: Thirty-eight older people completed at least three consecutive annual neuropsychological examinations. Using Positron Emission Tomography (PET), Abeta-plague burden was traced with [11C] labeled Pittsburgh Compound B and posterior glucose metabolism with [18F] Fluorodeoxyglucose (FDG) PET. In a series of multiple regression analyses, biomarkers were related to cognitive composite trajectories. PIB retention was dichotomized into PIB positive (n=13) and PIB negative (n=25) status using a global PIB uptake cutoff; FDG PET values were treated as continuous variable.

Results: An elevated PIB binding status was associated with concurrent intra-individual decline in memory and global cognition (see figure, category slope, red circles indicate PIB positivity). Non-memory decline was related to low FDG uptake, selectively within PIB positive individuals. There were no main effects of glucose metabolism on cognitive change in the total sample.

Conclusion: Our findings provide evidence that longitudinal cognitive decline is related to Abeta deposition in normal elderly individuals. They further support assumptions that the occurrence of posterior cortical hypometabolism contributes to the early preclinical changes in cognitive trajectories within PIB positive individuals.

Presented by: **Wirth, Miranka**

53

Prospective Evaluation of [18f]-Flutemetamol for Amyloid Detection in the Brain of Living Subjects with Normal Pressure Hydrocephalus

Dean Wong [1], Abhay Moghakar [1], Danielli Rigamonte [1], Juan Troncoso [1], Olivier Rousset [1], Chris Buckley [2], Paul Sherwin [2], William Willis [1], Kim Mansfield [2], Kevin Horgan [2], Igor Grachev [2]

[1] Johns Hopkins University School of Medicine
[2] GE Healthcare

We determined the level of association between brain uptake of [^{18}F]flutemetamol, a radiotracer currently undergoing clinical trials, and quantitative immunohistochemical (IHC) estimates of amyloid levels in biopsy samples in patients with normal pressure hydrocephalus(NPH). The brain uptake of [^{18}F]-flutemetamol (standard uptake value ratios [SUVR]) from the biopsy site were made from positron emission tomography (PET) images. IHC levels of amyloid load were estimated for each biopsy sample using a monoclonal antibody, 4G8, raised against amyloid as the primary standard of truth. Parietal lobe biopsies were obtained from 12 subjects, at least 50 years of age, during shunt placement for NPH. Within 8 weeks after the PET imaging, the shunt procedure and biopsy were performed, followed by a computed tomography scan.

[^{18}F]-flutemetamol was found to be safe and well tolerated. The biopsy site SUVR was significantly correlated with the biopsy specimen amyloid beta level (r=0.8; p=0.0174). Contralateral to biopsy site and composite SUVR values correlated with the percent of biopsy specimen staining for amyloid beta based on 4G8. Blinded visual [^{18}F]-flutemetamol image interpretations showed 100% sensitivity and specificity with pathology staining for amyloid plaque with Bielschowsky and Thioflavin S and overall pathology read. The results of blinded reader agreement for [^{18}F]-flutemetamol PET showed full agreement among 3 readers, with intra-reader reproducibility of 100%. Despite the modest sample size, this study shows 100% sensitivity and specificity of [^{18}F]-flutemetamol PET for detection of fibrillar amyloid beta deposits in the brain of living subjects with NPH.

Presented by: **Wong, Dean**

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