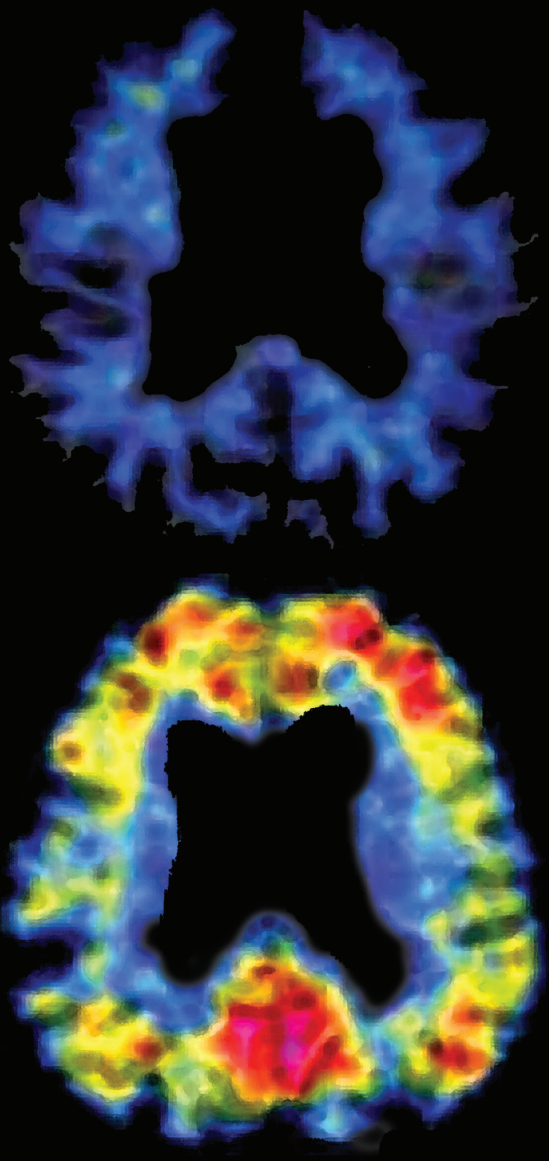

Human Amyloid Imaging

Miami 2011

Friday 14–Saturday 15 January 2011

Miami Beach Resort Hotel

Schedule & Abstract Book

Schedule - Human Amyloid Imaging Meeting

Friday 14–Saturday 15 January 2011

Miami Beach Resort Hotel

FRIDAY	
07:30 – 08:00	**Registration and Continental Breakfast; Posters to be installed for Poster Session 1**
08:00 – 08:15	**Introduction**
08:15 – 09:15	**Session 1: Longitudinal Studies** **Julie Price, Susan Resnick (Chairs)**
08:15 – 08:30	Longitudinal changes in fibrillar amyloid-beta deposition across the cognitive spectrum *AD Cohen, University of Pittsburgh, Pittsburgh, PA, USA*
08:30 – 08:45	Amyloid deposition in non-demented elderly predicts longitudinal cognitive decline *DM Rentz, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
08:45 – 09:00	PET imaging of beta-amyloid deposition in patients with mild cognitive impairment: a two year follow-up study *J Koivunen, Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland*
09:00 – 09:15	Regional expansion of cerebral hypometabolism in AD follows the pattern of amyloid-deposition with temporal delay and is related to a healthy functional connectivity network *S Förster, Department of Nuclear Medicine, Technische Universität München, Munich, Germany*
09:15 – 09:45	**General Discussion (Chairs and Speakers)**
09.45 – 10:00	**Morning Break with Posters**
10:00 – 11:15	**Session 2: Amyloid in Normal Aging** **Susan Landau, Randy Buckner (Chairs)**
10:00 – 10:15	Increased prefrontal activation in amyloid positive cognitively normal individuals during successful episodic memory encoding *EC Mormino, Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA, USA*
10:15 – 10:30	Precuneus beta-amyloid burden is associated with decreased bilateral frontal activation and default network suppression in healthy adults *KM Kennedy, University of Texas at Dallas and University of Texas Southwestern Medical Center, Dallas, TX, USA*
10:30 – 10:45	Precuneus beta-amyloid burden correlates with altered cortical network function in a lifespan sample of healthy adults *MD Devous, Center for Vital Longevity, University of Texas at Dallas and Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX, USA*
10:45 – 11:00	Age and amyloid deposition are associated with functional alterations in posteromedial cortex during encoding and retrieval processes *P Vannini, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
11:00 – 11:15	Functional reorganization of the brain along the Alzheimer's disease continuum *P Vemuri, Mayo Clinic, Rochester, MN, USA*
11:15 – 11:45	**General Discussion (Chairs and Speakers)**

11:45 – 12:30	**Keynote Presentation by Randy Buckner, Harvard University, Cambridge, MA, USA**
12:30 – 14:00	**Lunch and Poster Session 1**
14:00 – 14:45	**Session 3: Genetics/Neuropathology** **Juha Rinne, Gil Rabinovici (Chairs)**
14:00 – 14:15	Biomarkers for following Alzheimer's disease progression – Amyloid ^{11}C-PIB imaging in a multi-tracer paradigm with ^{11}C-d-deprenyl and ^{18}F-FDG studied in preclinial and clinical AD *A Nordberg, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden*
14:15 – 14:30	Influence of APOE genotype on amyloid deposition in Japanese population – Direct comparison of J-ADNI, US-ADNI and AIBL ^{11}C-PiB PET data *K Ishii, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan*
14:30 – 14:45	Early detection of Alzheimer's – ^{11}C-PIB PET in monozygotic and dizygotic twins discordant for cognitive impairment *NM Scheinin, University of Turku, Turku, Finland*
14:45 – 15:00	**General Discussion (Chairs and Speakers)**
15:00 – 15:45	**Keynote Presentation by TBC**
15:45 – 16:45	**Session 4: Pathology** **Clifford Jack, William Klunk (Chairs)**
15:45 – 16:00	PIB versus FDG PET in pathologically verified dementia *GD Rabinovici, University of California San Francisco, University of California Berkeley and Lawrence Berkeley National Laboratory, Berkeley, CA, USA*
16:00 – 16:15	^{18}F-flutemetamol amyloid imaging has strong concordance with cortical biopsy histopathology *DA Wolk, University of Pennsylvania, PA, USA*
16:15 – 16:30	Correspondence between *in vivo* PiB-PET amyloid imaging and post-mortem, regional burden of Aß and Tau lesions *I Driscoll, National Institute on Aging/NIH, Bethesda, MD, USA*
16:30 – 16:45	Microbleeds and amyloid-ß burden in non-demented elderly *KA Johnson, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
16:45 – 17:15	**General Discussion (Chairs and Speakers)**
19:00	**Dinner, Ocean View Room and Pool Side**

Schedule - Human Amyloid Imaging Meeting

Friday 14–Saturday 15 January 2011

Miami Beach Resort Hotel

SATURDAY

07:30 – 08:00	**Continental Breakfast; Posters to be installed for Poster Session 2**
08:00 – 09:15	**Session 5: Technical Emphasis** **Chet Mathis, John Seibyl (Chairs)**
08:00 – 08:15	Methodologic considerations in the acquisition and analysis of amyloid imaging data for pharmaceutical clinical trials *DC Matthews, Abiant Inc., Deerfield, IL, USA*
08:15 – 08:30	Support vector machine analysis of flutemetamol scans *N Nelissen, University Hospitals Leuven, Leuven, Belgium*
08:30 – 08:45	Exploration of the PiB positivity boundary using statistical clustering *W Bi, University of Pittsburgh, Pittsburgh, PA, USA*
08:45 – 09:00	Reliability of longitudinal PIB: How do data processing methods influence detection of change over time? *SM Landau, Helen Wills Neuroscience Institute and Lawrence Berkeley National Laboratory, University of California Berkeley, Berkeley, CA, USA*
09:00 – 09:15	Longitudinal amyloid imaging using [^{11}C]PIB: Choosing the right method *N Tolboom, VU University Medical Center, Amsterdam, The Netherlands*
09:15 – 09:30	**General Discussion**
09:30 – 09:45	**Morning Break with Posters**
09:45 – 10:45	**Session 6: Technical Emphasis: Invited Lectures** **Mark Schmidt, Val Lowe (Chairs)**
09:45 – 10:15	Amyloid PET imaging in large multi-center trials: Technical and practical issues *RA Koeppe, University of Michigan, Ann Arbor, MI, USA*
10:15 – 10:45	TBC *MA Mintun, Washington University, St. Louis, MO and Avid Inc, Philadelphia, PA, USA*
10:45 – 11:00	**General Discussion**
11:00 – 12:15	**Session 7: Metabolism, Age of Onset, F18 Agents** **Sterling Johnson, Bart van Berckel (Chairs)**
11:00 – 11:15	The influence of amyloid burden on cerebral glucose metabolism and cognition in cognitively normal middle-age subjects who have high risk for Alzheimer's disease *G Xu, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA*
11:15 – 11:30	Regional brain metabolism in cognitively normal elder individuals with various levels of cerebral beta-amyloid deposition *AG Vlassenko, Washington University School of Medicine, St. Louis, MO, USA*
11:30 – 11:45	Relationship of amyloid-beta burden with age-at-onset in Alzheimer's disease *D Young Lee, Seoul National University Hospital, Seoul, Korea*

11:45 – 12:00	Multi-level fibrillar amyloid thresholds of florbetapir F18 PET images from five multi-center studies *AS Fleisher, Banner Alzheimer's Institute, Phoenix, AZ and University of California, San Diago, CA, USA*
12:00 – 12:15	[18F]AZD4694 in the symptomatic and presymptomatic study of Alzheimer's disease *JB Langbaum, Banner Alzheimer's Institute, Phoenix, AZ, USA*
12:15 – 12:30	**General Discussion**
12:30 – 14:00	**Lunch and Poster Session 2**
14:00 – 14:05	**Award Presentations** HAI Travel Awards Young Investigator Award (HAI-YIA)
14:05 – 14:45	**Clinical Trials Keynote Panel** **William Jagust, Reisa Sperling (Chairs)**
14:05 – 14:15	*Michael Grundman, Global R&D Partners, San Diego, CA, USA*
14:15 – 14:25	*Howard H. Feldman, Bristol-Myers Squibb, Wallingford, CT, USA*
14:25 – 14:35	*Eric Siemers, Eli Lilly and Company, Indianapolis, IN, USA*
14:35 – 14:45	*Paul Aisen, University of California, San Diego, CA, USA*
14:45 – 15:30	**General Discussion**
15:30	**Meeting Close**

Longitudinal changes in fibrillar amyloid-beta deposition across the cognitive spectrum

AD Cohen, JC Price, CA Mathis, RD Nebes, JA Saxton, BE Snitz, HJ Aizenstein, LA Weissfeld, ST DeKosky, WE Klunk.

University of Pittsburgh (Psychiatry, Neurology and Radiology), Pennsylvania, USA and University of Virginia (Neurology), Virginia, USA.

Background: Studies of Aß show variations in Aß load across cognitive states. It is clear there are time-dependent increases in Aß through progression from amyloid-free to AD-like Aß levels. *In-vivo* amyloid imaging allows an opportunity to follow Aß deposition within individuals over time. Here, we determined changes in Aß over time in normal controls (NC), Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD).

Methods: Longitudinal changes were measured in 55 NC [44% PiB(+)], 27 MCI [74%PiB(+)] and 15 AD [100% PiB(+)] over 1-3yrs and compared to those in six-AD, 7-NC, 9-MCI subjects with two PiB scans (40-60min after tracer injection) within 28d for test-retest variability. Tissue ratios were calculated for cortical regions-of-interest (ROI) and normalized to cerebellum (SUVR). The delta-SUVR [(follow-up)-(baseline)] was calculated.

Results: Test-retest variability was -0.001±0.14 SUVR. Increases above 1.645 standard deviations in any ROI were defined as significant ($p<0.05$). Subjects were divided into three groups: 1) Stable PiB(-); 2) Stable PiB(+) and 3) Converters from PiB(-) to PiB(+) [PiB(-→+)]. Of the Stable PiB(-), 5/32 (16%) NC and 2/8 (25%) MCI showed significant increases in PiB. Of the Stable PiB(+), 10/16 (63%) NC; 11/16 (69%) MCI; and 10/16 (63%) AD showed significant increases. Of the PiB(-→+), 5/8 (63%) NC and 2/4 (50%) MCI showed significant increases. Group analyses showed a fairly linear increase in NC and MCI over 2-3yrs. Additionally, PiB(+) subjects showed larger increases over time than PiB(-), particularly NC.

Conclusions: Progressive accumulation of Aß was detectable with PiB-PET in 58% of PiB(+) and 16% of PiB(-), confirming that Aß increases slowly over time. PiB(-) to PiB(+) conversions occurred in controls and MCI, the latter is surprising because extensive Aß pathology is suspected early in MCI. The frequency and degree of increased PiB retention was similar across diagnoses, suggesting linear increases in Aß across the AD spectrum.

Amyloid deposition in non-demented elderly predicts longitudinal cognitive decline

DM Rentz, RA Betensky, JA Becker, RL England, J Maye, C Gidicsin, RA Sperling, KA Johnson.

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Background: Amyloid-beta (Aß) deposition measured with PiB PET has been observed in a large fraction of non-demented individuals, but it is unknown whether Aß burden means further decline toward Alzheimer's disease (AD) dementia.

Objective: We tested whether PiB retention in non-demented subjects predicts longitudinal decline in neuropsychological (NP) performance and whether cognitive reserve (CR) continues to modify the relationship over time.

Methods: Seventy-four non-demented older subjects (CDR 0 n=47, age 75.2 ± 7y, CDR 0.5 n=27, age 75.8 ± 7y); underwent PiB PET at baseline and neuropsychological assessments at baseline and follow-up (mean duration, 18.6 months). PiB retention was expressed as mean cortical DVR, cerebellar reference, measured in the precuneus/posterior cingulate. Multivariate models related PiB retention at baseline with change in neuropsychological test scores from baseline to follow-up, controlling for CDR 0 versus 0.5, age and cognitive reserve (CR, education as proxy).

Results: Higher PiB retention predicted greater decline in subjects with lower CR, on cued recall (MC30, FCSRT $p<0.01$) and visuospatial perception, while in higher CR subjects, PiB retention predicted decline on retrieval (FRSRT $p<0.01$) and cued recall (MC30 $p<0.01$). In contrast, those with lower PiB retention improved on memory measures in both low and high CR groups, consistent with the practice effect commonly seen in normal aging. Independent of PiB retention, high CR predicted improvement in NP scores while low CR predicted decline, particularly on measures of episodic memory and visuospatial perception. Overall differences between CDR 0 and CDR 0.5 were negligible.

Conclusions: These findings suggest that Aß deposition at baseline in non-demented individuals predicts decline in cognitive domains commonly impaired in AD dementia. High CR contributes to cognitive stability and low CR portends decline with age, regardless of PiB status. Additional longitudinal data is required to determine whether subjects with Aß burden and NP decline will meet criteria for AD dementia.

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

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[1]Turku PET Centre, University of Turku & Turku University Hospital, Turku, Finland; [x]Department of Biostatistics, University of Turku, Turku, Finland.

Background: Patients with amnestic mild cognitive impairment (MCI) have greater risk of conversion to AD. Increased brain amyloid burden in AD and MCI has been demonstrated with PET using [^{11}C]PIB as a tracer.

Objective: To evaluate change in beta-amyloid deposition in with MCI during 2 year follow-up.

Methods: MCI patients and controls were studied with [^{11}C]PIB PET, MRI and neuropsychometry at baseline and these investigations were repeated in MCI patients after follow-up.

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

Conclusions: Hippocampal atrophy and amyloid deposition seem to dissociate during the evolution of MCI, the atrophy increasing clearly and [^{11}C]PIB retention changing modestly when conversion to AD occurs. Longer follow-up is needed to determine whether non-converters would convert to AD later, which would suggest accelerated [^{11}C]PIB retention preceding clinical conversion.

Regional expansion of cerebral hypometabolism in AD follows the pattern of amyloid-deposition with temporal delay and is related to a healthy functional connectivity network

[1,2,5]S Förster, [3]T Grimmer, [1]I Miederer, [1]G Henriksen, [1]BH Yousefi, [4]D Greve, [1]P Graner, [1]H-J Wester, [3]H Förstl, [3]A Kurz, [4]BC Dickerson, [5]P Bartenstein, [1]A Drzezga.

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Background: Hypometabolism and amyloid-deposition in AD show some regional overlap with each other and with the healthy "default-mode" network (DMN) of functional connectivity. This indicates that neurodegeneration may spread within anatomical borders defined by functional connectivity networks (FCN). Aim was to examine longitudinal regional patterns of amyloid-deposition and hypometabolism in the same population of AD patients and to establish their regional relationship to each other and to healthy FCNs.

Methods: Twenty patients with mild AD (67.7 ± 7.9 yrs) underwent baseline (BL) and 2-year follow-up (FU) [18F] FDG- and [11C]PIB-PET. SPM5 voxelwise group comparisons were performed between patients' BL- and FU-data and between patients and 15 elderly controls (64 ± 5 yrs), which had undergone identical imaging procedures. Areas of maximum BL-amyloid-deposits in patients were used as seed regions for calculation of a FCN in a resting-state fMRI dataset from 27 young controls (24 ± 4 yrs). Dice similarity coefficients (DSC) between imaging findings were calculated (significance threshold $p<0.05$ FDR-corrected).

Results: Compared to elderly controls, AD-patients showed typical patterns of BL-hypometabolism- and amyloid-deposition, with a DSC of 40%. At BL amyloid-deposition was more extended than hypometabolism and showed only minor regional expansion, whereas prominent expansion of hypometabolism was observed, primarily within areas already affected by BL-amyloid-deposition; thus, increased DSC (47%) of FU-hypometabolism with BL-amyloid-deposition was found. The FCN calculated in young controls (using BL-amyloid-peaks in AD as seed regions) showed higher similarity with FU-hypometabolism in patients than standard DMN (DSC 45% vs. 26%).

Conclusions: Regional expansion of hypometabolism, as a measure of neuronal dysfunction in AD, appears to follow the anatomical pattern of amyloid deposition with temporal delay. Accurate prediction of FU-hypometabolism was possible by using BL-amyloid-peaks found in AD to seed a healthy FCN, such that amyloid-based disruption of functional networks may contribute to the regional expansion of neuronal dysfunction.

Increased prefrontal activation in amyloid positive cognitively normal individuals during successful episodic memory encoding

[1]EC Mormino, [1]MG Brandel, [1]CM Madison, [1,2]WJ Jagust.

[1]Helen Wills Neuroscience Institute, University of California Berkeley, Berkeley, California, USA; [2]Department of Molecular Imaging and Neuroscience, Lawrence Berkeley National Laboratory, Berkeley, California, USA.

Objective: To compare brain activation during successful memory encoding between young and old subjects, and to investigate relationships between brain activation and Abeta deposition within elderly subjects.

Methods: Twenty-six old subjects were scanned with PIB-PET and fMRI, and 14 young subjects underwent fMRI (mean age: young=23.4[3.4]; old=74.6[6.4]). Distribution volume ratios were extracted using Logan plotting and global PIB index values were used to classify old subjects into PIB+ and PIB- groups. During the fMRI task, 200 outdoor images were presented (4.4s each) and subjects indicated whether water was present. A post-scan recognition task with 100 foils was used to assess performance and sort data into 4 trial types (high confidence hits, low confidence hits, high/low confidence misses, and non-water response trials). Trial types were entered as covariates and contrast images between high confidence hits and misses were used in higher-level random effects models within each age group ($p<0.005$, $k=10$). ROIs were defined in areas showing significant activation in both young and old subjects, and were used to examine effects of age (young versus old) and amyloid (PIB+ versus PIB-).

Results: Significant bilateral activation was present in lateral occipital/parietal, inferior temporal, parahippocampal/fusiform and prefrontal cortices. Young subjects showed greater activation than old subjects across many posterior regions, and trends were present for reduced activation in PIB+ compared to PIB- old subjects. Furthermore, PIB+ subjects showed significantly increased prefrontal cortex (PFC) activation relative to PIB- subjects (young=PIB+ > PIB-).

Conclusions: These data extend previous work in aging by showing relationships between Abeta and brain activation during successful memory encoding. We found that increased PFC activation was specific to elderly subjects with high Abeta deposition, suggesting that preservation of the PFC may be necessary to remain cognitively normal in the presence of Abeta.

Precuneus beta-amyloid burden is associated with decreased bilateral frontal activation and default network suppression in healthy adults

KM Kennedy, KM Rodrigue, AC Hebrank, MD Devous Sr., DC Park.

University of Texas at Dallas, Texas, USA; University of Texas Southwestern Medical Center, Texas, USA.

Limited evidence suggests that increased beta-amyloid deposition even in apparently healthy adults is associated with alterations in functional activity. However, the majority of these findings report on resting-state activity or functional connectivity. Less well understood are the effects of increased beta-amyloid burden on patterns of task-relevant activations. The goal of the current study was to investigate the modifying effects of regional amyloid burden on BOLD-signal activation during the viewing of scenes in a subsequent memory task within a continuous age sample of healthy adults (N=137; 30-89 years old). Participants underwent PET scanning using ^{18}F-AV-45 and a separate fMRI scanning session. Amyloid burden was obtained from the precuneus, a region that shows increasing amyloid load with age. The fMRI task consisted of presentation of 96 outdoor landscape scenes and participants indicated whether or not there was water present in the scene. Out of the scanner, participants were later presented with the same 96 scenes interspersed with 96 matched lures. Encoding trials were backsorted by whether they were remembered with high or low confidence or forgotten. Using SPM, we conducted general linear model analyses on individual-level encoding contrasts with age and precuneus uptake as continuous predictors. We found that during viewing of scenes that were subsequently remembered with high confidence, those individuals with greater precuneus amyloid burden evidenced less activation in bilateral dorsolateral prefrontal cortex and decreased suppression in bilateral lateral temporal and medial frontal cortex regions. Thus increasing amyloid burden exerts negative effects on brain function in both task-active regions routinely recruited as compensatory mechanisms during tasks that pose higher cognitive demands, and in regions comprising the default network.

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.

Precuneus beta-amyloid burden correlates with altered cortical network function in a lifespan sample of healthy adults

MD Devous Sr., KM Kennedy, KM Rodrigue, AC Hebrank, DC Park.

Center for Vital Longevity, University of Texas at Dallas; Department of Radiology, UT Southwestern Medical Center, Texas, USA.

There is evidence that amyloid burden (Aß) alters functional connectivity (FC) in subjects with Alzheimer's Disease and Mild Cognitive Impairment and in elderly controls. We extended these studies by examining the relationship between Aß and FC in a large lifespan sample of healthy controls (Dallas Lifespan Brain Study). BOLD at rest (fcMRI) was measured within a continuous age sample of healthy adults (N = 137; 30-89 years old), and FC was determined as z-score-normalized temporal correlation coefficients based on seeds placed in posterior cingulate to represent the Default Mode Network (DMN) and anterior cingulate to represent the Salience Network (SN). Participants also underwent PET scanning using ^{18}Florbetapir to measure Aß, expressed as standardized uptake value ratios to cerebellum (SUVR), using a precuneus ROI for these analyses. Relationships between Aß and fcMRI in DMN and SN were examined both as continuous variables and by contrasting subjects with high Aß against an age- and gender-matched group of low Aß subjects (N = 25 each). Precuneus Aß across the lifespan was associated with decreased connectivity to the DMN in right precuneus and left orbital frontal cortex and with increased connectivity in left medial temporal lobe, superior middle cingulate, and lateral peri-sylvian temporal lobe. In contrast, reduction in connectivity to the SN (in the resting state) was minimally affected by precuneus Aß, while substantially increased connectivity was seen in bilateral insula, inferior striatum (near nucleus accumbens), hippocampus and dorsolateral prefrontal cortex. Between-group comparisons (high vs. low Aß) revealed significant decreases in frontal connectivity associated with elevated Aß in the DMN, while increased lateral temporal and insular connectivity was seen in the SN – a finding mimicking data in Alzheimer's Disease. Thus increasing amyloid burden exerts negative effects on functional connectivity such that the DMN is less connected with increasing Aß and SN connectivity is inappropriately increased.

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.

Age and amyloid deposition are associated with functional alterations in posteromedial cortex during encoding and retrieval processes

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Cortical ß-amyloid deposition is a major histopathological finding in Alzheimer's disease and a likely contributor to the observed memory impairment. The posteromedial cortices are particularly vulnerable to early amyloid pathology and are thought to play a key role in both memory encoding and retrieval processes. The extent to which aging and amyloid influence modulation of fMRI activity during encoding *vs* retrieval remains an open question. In this study, we used *in vivo* amyloid imaging to investigate the impact of fibrillar amyloid burden on fMRI activity during encoding and retrieval in clinically normal older individuals.

Twenty-six young (M=23.3) and 41 elderly (M=70.9) subjects underwent fMRI scanning while performing a face-name associative encoding and retrieval task. Elderly subjects were imaged with ^{11}-C PiB-PET and each individual's mean cortical PiB retention ratio was calculated. A conjunction analysis of deactivation during encoding and activation during retrieval revealed anatomical overlap in bilateral posteromedial cortices (p=0.001). In this region, a negative correlation (r=-0.43, p=0.02) was observed between the modulation of functional response (Δ change of the functional response elicited during retrieval minus encoding) and age, suggesting that older individuals have a restricted dynamic range in the modulation between deactivation and activation in these regions. Among the older subjects, amyloid deposition was inversely correlated with modulation of functional response (r=-0.55, p<0.001), such that individuals with high amyloid burden showed the least modulation in memory related activity. Across all subjects, a positive correlation was also found between the functional modulation and performance on the task (r=0.28, p=0.04).

Our study supports the hypothesis that the posteromedial cortices represent a critical node in episodic memory function and exhibit a dynamic response to encoding and retrieval processes. As these regions are vulnerable to early amyloid deposition, our findings may serve to elucidate the neural underpinnings of memory dysfunction seen in aging and neurodegenerative disease.

Functional reorganization of the brain along the Alzheimer's disease continuum

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Mayo Clinic, Rochester, Minnesota, USA.

Background: We investigated changes in functional connectivity (FC) in subjects along the Alzheimer's disease (AD) continuum from dementia to cognitively normal (CN) using resting-state fMRI. We assume that amyloid deposition occurs early in the disease process. We used the previous established global cortical PIB threshold of 1.5 to classify subjects as negative or positive and defined the different stages of the AD continuum as: PIB-negative CN (CNN) (n=123), PIB-positive CN (CNP) (n=52); PIB-positive mild cognitive impaired subjects (MCIP) (n=25) and AD (n=48).

Methods and results: Applying graph theory methods on seed-to-seed FC among 2997 nodes placed throughout the cerebral gray matter, we found significant increases in global FC in CNP compared to CNN. This increase in global FC in CNP declined monotonically as subjects moved from CNP to MCIP and AD. In addition, we also performed network level analysis by computing seed-to-seed FC among 143 seeds placed in 27 major networks (these were detected in 341 CN elderly subjects using an ICA analysis). This analysis was done to understand how the FC changes between and within each of the major networks contribute to the observed global FC changes. In CNP, we found only significant between network FC increases but not within network FC changes. In AD, we found significant within network as well as between network FC decreases suggesting a systematic network level decline in FC. Also, we found that the network most affected by disease was the Ventral DMN.

Conclusions: These results suggest significant functional reorganization along the AD continuum. Increased FC in CNP is consistent with functional reorganization in CN subjects with a significant amyloid load who are able to compensate. Progressive loss of FC in MCIP and AD subjects suggests that these subjects are no longer able to compensate for the effects of progressively more severe disease.

Biomarkers for following Alzheimer's disease progression—Amyloid ^{11}C-PIB imaging in a multi-tracer paradigm with ^{11}C-d-deprenyl and ^{18}F-FDG studied in preclinial and clinical AD

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[1]Karolinska Institutet, Stockholm, Sweden; [2]Karolinska University Hospital Huddinge, Stockholm, Sweden; [3]Uppsala Academical Hospital, Uppsala, Sweden; [4]Uppsala University, Uppsala, Sweden.

Recent progress in molecular imaging provides new knowledge for the understanding of the time course of early pathological disease processes in Alzheimer's disease (AD). We have observed that ^{11}C-PIB PET can detect increasing accumulation of fibrillar Aß in the brains of MCI patients at follow up while more stable levels of fibrillar Aß are measured at clinical AD. For understanding of the pathological impact of different forms of Aß in brain there is a need for development of PET ligands detecting smaller forms of Aß, oligomeric forms in brain but also to understand how synaptic activity and inflammatory processes are related to Aß pathology. PET fibrillar Aß imaging together with CSF biomarkers are promising biomarkers for early recognition of subjects at risk for AD. In a current longitudinal study, we are enrolling both presymptomatic and symptomatic members of different Swedish families harboring mutations in the *PS1* gene and the 'Swedish' and the 'Arctic' APP gene mutations. We use the PET tracers ^{11}C-PIB for measuring fibrillar Aß load, ^{18}F-FDG to investigate cerebral glucose metabolism, and ^{11}C-d-Deprenyl to visualize astrocytosis as a component of neuroinflammatory processes. The subjects also undergo neuropsychological testing, MRI scan and assays of CSF biomarkers. Cohorts of AD and MCI patients are studied with the same protocol. Data are analyzed with use of principle component analysis method. Data so far obtained indicate that increases in Aß deposition as well as astrocytosis occur early in brain at presymptomatic stages of AD but the time course of changes as well as brain regions afflicted differ between PET tracers reflecting the complexity of AD pathology. These studies are important for future drug trials in presymptomatic AD.

References: Nordberg *et al*. *Nature Reviews Neurology* 2010; Kadir *et al. Neurobiol Aging* 2010; Schöll *et al*. 2009; Kadir, Nordberg. *J Nucl Med* 2010; **51**: 1418-1430; Kadir Marutle *et al. Brain* in press.

Influence of APOE genotype on amyloid deposition in Japanese population – Direct comparison of J-ADNI, US-ADNI and AIBL ^{11}C-PiB PET data

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It has not been established whether the association between Alzheimer's disease (AD), apolipoprotein E (APOE) ε4 allele, and amyloid deposition is similar in different between ethnic groups. In this study, we evaluated the influence of APOE ε4 on the cortical accumulation of ^{11}C-Pittsburgh compound B (PiB) in three multi-center imaging studies of Alzheimer's disease; Alzheimer's Disease Neuroimaging Initiative (US-ADNI), Australian Imaging Biomarker and Lifestyle Flagship Study of Aging (AIBL), and Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI).

We analyzed the initial ^{11}C-PiB scan data from US-ADNI: 19 cognitively normals (NL) (78.3 ± 5.3 year old, mean ± SD), 64 mild cognitive impairment (MCI) subjects (75.5 ± 7.9), and 19 AD patients (73.4 ± 8.7), AIBL: 119 NL (73.1 ± 7.3), 41 MCI (76.0 ± 7.2), 27 AD (73.1 ± 8.8), and J-ADNI: 46 NL (66.3 ± 4.6), 32 MCI (69.4 ± 12.2), and 21 AD (74.3 ± 6.0). The ^{11}C-PiB PET images were acquired 50-70 min post-injection in US-, and J-ADNI, whereas 40-70 min in AIBL. The PET images were coregistered to individual MRI data, and mean cortical standardized uptake value ratio (mcSUVR) in reference to cerebellar cortex was measured with the same platform of data analysis using DARTEL template, standard set of regions of interest, and cerebrospinal fluid volume correction. The cut-off mcSUVR value for PiB-positivity was set at 1.5 for all the studies.

The PiB-positive rate (%) in each group with or without ε4 allele (ε4+/ε4-) were; NL (80/57), MCI (83/52), AD (100/88) in US-ADNI; NL (56/23), MCI (88/31), AD (100/100) in AIBL; and NL (59/7), MCI (100/44), AD (100/80) in J-ADNI. The averaged mcSUVR of PiB-positive subjects in each group by the number of ε4 allele (0, 1, 2) were; NL (1.9, 2.1, -), MCI (2.2, 2.3, 2.6), AD (2.2, 2.2, 2.6) in US-ADNI; NL (1.9, 2.1, 2.3), MCI (1.9, 2.3, 2.5), AD (2.4, 2.4, 2.5) in AIBL; and NL (1.8, 2.0, 2.1), MCI (2.1, 2.3, 2.4), AD (2.2, 2.3, 2.3) in J-ADNI. Positive influence of APOE ε4 allele on amyloid deposition with gene dose effect was observed in Japanese population similarly as observed in US-ADNI and AIBL studies.

We conclude that the effect of APOE ε4 allele on amyloid deposition is similar in Japanese population to those in caucasians, despite the lower ε4 allele frequency in the Japanese population.

Early detection of Alzheimer's – ^{11}C-PIB PET in monozygotic and dizygotic twins discordant for cognitive impairment

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Background: The relative impacts of genetic and environmental factors are still unknown for sporadic, late-onset Alzheimer's disease. The importance of genetic factors with regard to beta-amyloid (Aß) accumulation in the brain is therefore of great interest. Knowledge of Aß accumulation in cognitively healthy individuals could improve our understanding of the pathology of Alzheimer's disease and allow its early detection. Carbon-11 labeled 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole i.e. ^{11}C-PIB is a PET imaging agent applicable for *in vivo* Aß plaque detection, and it was used as a marker of Aß accumulation also in this study.

Subjects and methods: We performed a ^{11}C-PIB PET study on 9 monozygotic and 8 dizygotic twin pairs discordant for cognitive impairment as well as on 9 healthy elderly control subjects. ^{11}C-PIB uptake was analyzed with Statistical Parametric Mapping (SPM) and with region-of-interest (ROI) analysis with the region-to-cerebellum ratio as a measure of tracer uptake.

Results: Cognitively preserved monozygotic co-twins of cognitively impaired probands had increased cortical ^{11}C-PIB uptake (117-121% of control mean) in their temporal and parietal cortices and the posterior cingulate. Cognitively preserved dizygotic subjects did not differ from the controls (uptake 96-103% of control mean). Further, the cognitively preserved monozygotic subjects showed similar ^{11}C-PIB uptake patterns as their cognitively impaired co-twins. The cognitively impaired subjects (monozygotic and dizygotic individuals combined) showed typical Alzheimer-like patterns of ^{11}C-PIB uptake.

Conclusions: Genetic factors appear to influence the development of Alzheimer-like Aß plaque pathology. Alzheimer's disease may be detectable in high-risk individuals in its presymptomatic stage with ^{11}C-PIB PET, but clinical follow-up will be needed to confirm this. This would have important consequences for future diagnostics and research on disease-modifying treatments.

Keywords: Alzheimer's disease, early detection, PIB, PET, twin.

PIB versus FDG PET in pathologically verified dementia

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Objective: To compare PIB and FDG PET to histopathology in a heterogeneous dementia population.

Design/Methods: Thirteen dementia patients (mean age 67.8±10.0, MMSE 19.3±7.5) underwent [11C]PIB and [18F]FDG PET. Clinical diagnoses included Alzheimer's disease (AD, N=3) and the frontotemporal lobar degeneration (FTLD) syndromes frontotemporal dementia (N=4), semantic dementia (N=3) and corticobasal syndrome (CBS, N=3). PIB DVR images (cerebellar reference) were visually rated by two investigators blinded to clinical diagnosis as PIB-positive or negative. FDG scans (pons-normalized) were visually rated as consistent with AD or FTLD. Histopathology was determined by autopsy (N=11, 2.3±1.4 years after PET), biopsy (N=1) or presence of a pathogenic mutation (N=1).

Results: Pathologic diagnoses included high-likelihood AD (N=3), mixed AD/dementia with Lewy bodies (AD/DLB, N=1), FTLD-TDP (N=5), Pick's disease (N=2) and corticobasal degeneration (CBD, N=2). PIB Index (mean DVR in frontal, parietal, lateral temporal and cingulate cortex) was higher in patients with AD pathology (1.43±0.38) than in pathologically-confirmed FTLD (1.01±0.08, $p<0.05$). PIB visual reads correctly classified 100% of cases compared to histopathology (PIB-positive AD or PIB-negative FTLD), while FDG reads misclassified 21% of cases. Both PIB and FDG correctly predicted AD in a patient with clinical CBS (pathologically AD/DLB). One AD patient who was visually PIB-positive but had low DVR values (PIB Index=1.22) was found to have amyloid angiopathy in the cerebellar reference region. Two patients with primary FTLD-TDP were PIB-negative on visual reads despite the presence of early amyloid pathology (moderate diffuse plaques in one, PIB Index=0.99; frequent diffuse and moderate neuritic plaques in the other, PIB Index=1.13).

Conclusions: Visual reads of PIB outperformed FDG in predicting histopathology in this small series. PIB visual reads did not detect early amyloid pathology co-morbid with FTLD, which in this case enhanced specificity for primary AD. Amyloid PET is likely to improve *in vivo* prediction of histopathology in dementia.

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^{18}F-flutemetamol amyloid imaging has strong concordance with cortical biopsy histopathology

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Objective: To determine the correspondence of *in vivo* quantitative estimates of brain uptake of ^{18}F-flutemetamol with immunohistochemical estimates of amyloid levels in previously biopsied patients.

Background: The development of molecular imaging techniques to 'visualize' amyloid *in vivo* represents a major achievement in the study of Alzheimer's disease (AD). In addition to a potential role in early diagnosis, molecular imaging is likely to play a critical role in drug development. ^{11}C-Pittsburgh Compound B (^{11}C-PIB) is the most well-studied PET amyloid imaging tracer, but its widespread use is limited by the short half-life of carbon-11 requiring on-site production. ^{18}F-flutemetamol is similar to ^{11}C-PIB, except for the presence of fluorine-18, a radionuclide with a longer half-life. Preliminary work suggests ^{18}F-flutemetamol may have similar imaging properties to ^{11}C-PIB.

Methods: We recruited patients for ^{18}F-flutemetamol PET scanning who previously had undergone venticulo-peritoneal shunting for presumed Normal Pressure Hydrocephalus. A right frontal cortical biopsy was obtained routinely at the site of shunt insertion. Quantitative measures of ^{18}F-flutemetamol uptake were made at a location contralateral to the biopsy site and compared to estimates of amyloid load based on immunohistochemical and histological staining.

Results: Seven patients underwent PET scans obtained ~3 to 45 months after biopsy. A regression model, including time from biopsy as a covariate, demonstrated a significant relationship ($p=0.011$) between ^{18}F-flutemetamol uptake and percent area of amyloid measured by a monoclonal antibody raised against amyloid (NAB228). Similar results were found with the amyloid specific monoclonal antibody 4G8 and Thioflavin S. Blinded visual reads demonstrated a sensitivity ($n=4$) and specificity ($n=3$) of 100% with the pathologic specimens.

Conclusions: This data is the first to demonstrate the strong concordance of ^{18}F-flutemetamol PET imaging with histopathology, supporting its sensitivity to detect amyloid. As a fluorine-18 based compound, this tracer has great potential for widespread clinical and research use.

Correspondence between *in vivo* PiB-PET amyloid imaging and post-mortem, regional burden of Aß and Tau lesions

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The definitive diagnosis of AD requires *post-mortem* confirmation of neuropathological hallmarks – amyloid-ß plaques (Aß) and neurofibrillary tangles. The advent of radiotracers for amyloid imaging presents an opportunity to investigate amyloid deposition *in vivo.* The Pittsburgh Compound-B (PiB) PET ligand remains the most widely studied to date; however, the extent of agreement with neuropathological assessment has not been thoroughly investigated. We examined the correspondence among quantitative immunohistological assessments of Aß and phosphorylated Tau in *post-mortem* tissues, and regional PiB load (PET) and brain volume (MRI) in 6 older Baltimore Longitudinal Study of Aging participants who came to autopsy. Based on consensus clinical diagnosis, five were nondemented and one demented. All individuals underwent PiB-PET and MRI assessments with imaging-autopsy intervals ranging between 1.1 to 2.4 years. We used unbiased stereology (fractional area) to estimate the burden of Aß (6E10) and Tau (PHF1) immunoreactivities in 5 random, systematically-selected paraffin sections from each of the following regions: hippocampus, orbito-frontal cortex, anterior and posterior cingulate gyri, precuneus and cerebellum. The cerebellum served as a reference region for *in vivo* quantification of Aß and was negative for both Aß and Tau immunoreactivity. In general, there was agreement between the regional measures of Aß obtained stereologically and via imaging, with significant associations observed for anterior ($r=0.83$; $p=0.04$) and posterior ($r=0.94$; $p=0.005$) cingulate gyri, and the precuneus ($r=0.94$; $p=0.005$). No significant associations were observed between PiB load and Tau immunoreactivity ($p's>0.2$). Moreover, neither Aß or Tau immunoreactivity were associated with regional brain volumes ($p's>0.05$). Methodological differences notwithstanding, we report an agreement between amyloid imaging and *post-mortem* assessment of Aß deposition. The strong correlation of *in vivo* PiB retention with region-matched, quantitative analyses of Aß in *post-mortem* tissue offers support for the validity of PiB-PET imaging as a method for evaluation of Aß burden *in vivo.*

Microbleeds and amyloid-ß burden in non-demented elderly

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Background: Lobar microbleeds (LMB) are associated with cerebral amyloid-ß angiopathy (CAA) and are frequently observed in Alzheimer's disease (AD) dementia.

Objective: Here we examined the relationship of LMB to *in vivo* amyloid burden measured with amyloid PET in non-demented elderly.

Methods: We evaluated 92 non-demented subjects with neuropsychological tests, susceptibility weighted MR imaging (SWI) and PiB-PET. There were 68 CDR0 subjects, mean age 74 ± 7y, mean CDR Sum of Boxes (SB) = 0.02, and 24 CDR0.5, mean age 74 ± 8y, mean CDR SB = 1.57 (range 0.5 - 3.5). Two readers (K.J. and M.L.) independently inspected SWI data and identified each microbleed as lobar or non-lobar. Amyloid burden was evaluated as a dichotomous (non-partial volume corrected mean cortical PiB DVR (mcPiB) cutpoint = 1.15) and a continuous variable.

Results: In the CDR0 group, 51% were classified as PiB positive and 16% had one or more LMB (range 1 - 3). In the CDR0.5 group, 54% were PiB positive and 13% had one or more LMB (range 1 - 5). Adjusting for age, mcPiB was associated with number of LMB in both groups ($p<0.01$), and this association remained significant when APOEe4 carrier status ($p<0.02$) was included in the model. Regional PiB analysis did not show an association of relative occipital PiB retention with CDR group, LMB or APOEe4 status. Neither presence nor number of LMB was significantly correlated with cognitive test scores.

Conclusions: These data suggest that LMB, frequently observed in non-demented elderly, are related to amyloid-ß burden measured with PET and are a feature of preclinical AD. These findings may have implications for amyloid-lowering treatment trials at earlier stages of the disease.

Methodologic considerations in the acquisition and analysis of amyloid imaging data for pharmaceutical clinical trials

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The availability of amyloid imaging agents for use with Positron Emission Tomography has provided a valuable biomarker to measure amyloid burden as an indicator of Alzheimer's disease, and may be used to evaluate the potential of anti-amyloid therapeutic candidates to modify disease progression. To date, much research has focused upon the application of these agents to discriminate between diseased and normal subjects, and to study the temporal progression of disease pathology as it relates to clinical progression. However, application to drug development studies significantly raises the threshold for the degree of sensitivity, reproducibility, and power required to predict clinical outcomes. Sources of variability that impact results and power must therefore be understood, identified, and controlled to the extent possible. Our work has focused upon the analysis of the many sources of variability in amyloid imaging data collected using [11C]PIB and [18F]AV45 and provided through ADNI, and upon development of methods of quality control and analysis to optimize study power. Sources of variance include image acquisition parameters, instrument and image reconstruction characteristics, subject artifact, image pre-processing choices, and analysis methods. Specific factors include anatomical inclusion, noise at the edge of the scanner, field of view, subject motion, image acquisition time window, image alignment, and selection of reference and target regions of interest. To evaluate the potential contributions of these factors, we selected a set of [11C]PIB dynamic scans. Scans were evaluated with regard to image quality and completeness, movement, impact of different acquisition time windows, use of different ROI definitions, impact of reference region variance, and use of voxel-based methods, and results were compared. The results of this survey identify the relative impact of sources of amyloid image data variability and may lead to practical actions that can support the reliability of imaging endpoints in both patient selection and drug evaluation.

* 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).

Support vector machine analysis of flutemetamol scans

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Background: Support vector machines (SVM), a supervised learning approach, can perform a strictly automated pattern classification into one of two categories based on whole-brain images. In a purely data-driven manner, the feature weights defined by the classifier provide information on which image components are most discriminative. Clinically, a classifier may be useful in case of uncertainty about image interpretation.

Methods: 27 early-stage AD subjects (25 with raised uptake, 'flut-pos AD'), 15 elderly controls (14 with normal uptake, 'flut-neg HV'), 10 young controls and 20 mild cognitive impairment (MCI) patients participated in the 18F-flutemetamol phase 2 study (Vandenberghe *et al. Ann Neurol* 2010). First, we used a leave-one-out procedure to evaluate the diagnostic performance of an SVM with a linear kernel on the spatially normalised flut-pos AD and flut-neg HV scans and also determined the distribution of the feature weights. The absolute distance of a subject to the separating hyperplane normalised to unit vector ('d') gives an indication of the classification's robustness Second, we evaluated performance of the algorithm in the 2 flut-neg AD subjects, 1 flut-pos HV and MCI. For comparison, we determined how a structural MRI-based SVM (grey matter segmentation maps) categorized scans from the 25 flut-pos AD and the 24 flut-neg HV.

Results: SVM classified all scans from flut-pos AD and from flut-neg HV correctly, with the highest absolute feature weights in precuneus and striatum (d median 87.5, range 59.7-212.0). Automatized SVM classification of the flut-neg AD, the flut-pos HV and the MCI was fully concordant with the visual reads. MRI-based classification had a sensitivity and specificity of 84% and 70.8% for categorizing scans from the 25 flut-pos AD and the 24 flut-neg HV.

Conclusions: Flutemetamol scans can be reliably categorized in a strictly automated manner using an SVM.

Exploration of the PiB positivity boundary using statistical clustering

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Objectives: Statistical clustering of PiB retention measures was performed to study retention characteristics in subjects at the PiB+/- boundary.

Methods: PiB PET (SUVR 40-60 min) was performed for 62 control subjects (NC). Region definition and CSF correction were MR-based. Cortical (e.g., anterior cingulate (ACG); precuneus (PRC); frontal (FRC); parietal (PAR); lateral temporal (LTC)) and subcortical (e.g., anterior ventral striatum (AVS), thalamus, and pons) regions were evaluated. Basic (Basic_kM) and sparse (Sparse_kM) k-means clustering were performed. Basic_kM treats all regions with equal importance. Sparse_kM assigns regional weights that reflect regional importance in the grouping. Two or three clusters explored PiB-, PiB intermediate (PiBint), and PiB+ groupings. Clustering results were compared to groupings determined by a boxplot iterative outlier (IO) cut-off.

Results: Two clusters yielded 13 PiB+ NC by both methods, relative to 16 PiB+ by IO. For three clusters, Basic_kM identified 13 PiB+, while Sparse_kM placed 4 of these in the PiBint group. A 2.5% boundary about the IO cut-off defined 5 PiBint. Sparse_kM weights indicated 6 key regions, similar for 2 and 3 clusters: ACG, PRC: 0.21 >FRC: 0.13 >PAR: 0.11 >LTC: 0.10 >AVS: 0.09, with other regions <0.05. Always PiB+ NCs (n=9) had an average cortical SUVR (Global5) >1.72 that was <1.41 for always PiB- NCs (n=42). Of the remaining 11 (Global5:1.42-1.72), six showed substantial retention in anterior regions only, two in posterior regions only, and 3 exhibited low retention in at least 1 of the 6 regions.

Conclusions: Statistical clustering showed objective evidence of differences in the magnitude and distribution of Aß in presymptomatic controls at the PiB+/- boundary, relative to the very PiB+ or PiB-, and may prove useful as a tool to better identify early Aß deposition.

Reliability of longitudinal PIB: How do data processing methods influence detection of change over time?

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The ability to accurately measure amyloid longitudinally is critical for making inferences about how amyloid changes relate to clinical progression or response to amyloid-modifying drugs. Furthermore, these changes are likely to be small, so distinguishing them from processing-related artifacts is particularly challenging. Recent Pittsburgh Compound B (PiB) PET studies have reported test-retest variability of 1-6% for normal older controls and 3-10% for Alzheimer's patients (Tolboom *et al* 2009; Aalto *et al* 2009), indicating that "real" amyloid changes of around 5-10% may be difficult to distinguish from artifacts of image processing methods, such as smoothing, intensity scaling, and spatial normalization.

We investigated the influence of imaging processing methods on detection of longitudinal amyloid changes by comparing the results of two processing streams: (Method 1) defining ROIs and a cerebellar reference region by spatially normalizing each PIB scan to an MCI template, and (Method 2) defining ROIs and a cerebellar reference region in native space using regional parcellation with Freesurfer software. Both processing streams were fully automated, and no partial volume correction was applied. PIB-PET imaging data was acquired longitudinally through the Alzheimer's Disease Neuroimaging Initiative (ADNI). 103 subjects (20% normal controls, 20% Alzheimer's patients, 60% MCI patients) had baseline PiB scans, 80% had 1-year follow-up scans, and 40% had 2-year follow-up scans.

Annual change in the non-scaled cerebellum was similar for Alzheimer's, MCI, and Normals, and averaged +/- 2.8% (SD: 2.3) using Method 1 and +/- 2.5% (SD: 3.8) using Method 2. Of participants with at least 1-year follow-up data, 22% of Alzheimer's patients, 55% of MCI patients, and 67% of normals had a greater than +/-5% cortical PIB change as shown by at least one of the two processing methods. For this subset of participants, the estimates of the amount of 1-year PIB change between processing Method 1 and Method 2 differed by 4.7% (SD: 2.9), although neither processing method showed a consistently greater magnitude of change. Different image processing techniques introduce variability in longitudinal PiB estimates, likely due to differences in the measurement of cortical regions rather than the cerebellum, but the overall directionality of these changes are generally consistent.

Longitudinal amyloid imaging using [^{11}C]PIB: Choosing the right method

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Objective: To assess the effects of different analytical methods on observed changes in [^{11}C]PIB binding over time.

Methods: Data from repeat (i.e. baseline and follow-up (FU)) dynamic 90 minutes [^{11}C]PIB PET scans of 7 Alzheimer's disease (AD) patients, 11 patients with Mild Cognitive Impairment (MCI) and 11 healthy controls were used (mean FU: 30±5 months). PET scanning was performed as previously described.[1] Global cortical binding values were derived using standardised uptake values for the interval 60-90 min after injection (SUV_r), reference Logan[2] and RPM2[3] (basis function implementation of the simplified reference tissue model). RPM2 provides non-displaceable binding potential (BP_{ND}). For the present comparison, however, results were expressed as BP_{ND}+1, as this corresponds to the outcome using reference Logan (DVR; distribution volume ratio) and SUV_r. For each method percentage change between baseline and FU was calculated.

Results: SUV_r values at baseline and FU were on average 12% higher than values obtained with RPM2 and 19% higher than values obtained with reference Logan. Percentage change between baseline and FU differed substantially between methods, especially in AD patients where SUV_r (mean±SD) changed with -4±8%, while RPM2 and reference Logan values were relatively stable (0±6 and -1±5%, respectively). Differences were less pronounced in controls and MCI patients (SUV_r: 3±4, 8±9%; RPM2: 2±3, 6±7%; reference Logan: 2±3, 5±6%. respectively for controls and MCI).

Conclusion: These data emphasize that for longitudinal imaging, data analysis using quantitative methods such as RPM2 and reference Logan, and thus 90 minutes dynamic scanning, is essential. The decrease at FU in SUV_r values for AD patients suggests that this method is biased by factors associated with progression of disease, possibly heterogeneous flow effects. This has important implications, especially for the evaluation of efficacy of novel drugs aimed to lower amyloid load in the brain.

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Amyloid PET imaging in large multi-center trials: Technical and practical issues

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Large multi-center trials involving PET have been performed in the field of oncology for the past decade or so. More recently, multi-center trials involving brain imaging have becoming increasingly common, including studies funded by NIH or sponsored and coordinated by industry. The Alzheimer's Disease NeuroImaging Initiative (ADNI), a ~60 site, ~800 subject project funded jointly by NIH and the pharmaceutical industry, and begun in 2004, is one of the largest of these. Longitudinal PET scans using [^{18}F]FDG and [^{11}C]PiB were performed in a subset of these subjects, which included the diagnostic groups of MCI, early AD, and normal elderly control. Continuation of ADNI (ADNI-GO and ADNI 2) has recently started, with subjects in these projects getting both [^{18}F]FDG and now [^{18}F]AV-45 amyloid scans instead of [^{11}C]PiB.

The talk will focus on both technical and practical issues of amyloid PET imaging specific to multi-center trials. Topics will cover issues related to the following areas: 1) scanner differences across sites, including both hardware and software-related differences between vendors and scanner models, which make analysis and interpretation of results more challenging than for studies performed at a single site. 2) dynamic vs static imaging and the scan duration used for each approach, which will affect the quantitative results. 3) Use of a bolus versus a partial-bolus plus constant infusion administration of tracer. 4) Effect of the choice of reference tissue on the precision amyloid measure. 5) Differences between [^{11}C]PiB and [^{18}F]AV-45. 6) Practical issues and lessons learned from ADNI and ADNI-GO.

Results from the ADNI and ADNI-GO projects will be used to illustrate the effects that these issues have on our ability to extract accurate and precise data from amyloid imaging studies using PET, and hence our ability to draw meaningful and reliable conclusions from the results of these important multi-center trials.

The influence of amyloid burden on cerebral glucose metabolism and cognition in cognitively normal middle-age subjects who have high risk for Alzheimer's disease

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Background & objective: There is growing evidence that healthy middle-aged adults at risk for Alzheimer's Disease (AD) experience preclinical brain changes, but the relationship between fibrillar amyoid burden, glucose metabolism, and cognitive status in pre-disease states is not yet well understood. Here we present initial baseline results from an ongoing longitudinal multimodal imaging study in people at risk for AD.

Method: A total of 60 subjects (age 51-75) participated including 7 MCI and 53 subjects from a unique registry of adult children of AD affected individuals known as WRAP (Wisconsin Registry for Alzheimer's Prevention). All subjects underwent imaging scans of [18F]FDG PET, [11C]PiB PET, MRI and neuropsychological battery tests including the Rey auditory verbal learning test (RAVLT). All subjects' PIB distribution volume ratio (DVR) and FDG SUVR images were coregistered and normalized to the MNI standard template for the voxel-based analyses. An amyloid burden index (ABI) was measured by averaging the DVR values from the posterior cingluate cortex (PCC), precuneus, superior parietal lobules (SPL), and frontal cortex. A multiple linear regression model was used to estimate the relationship between cerebral glucose metabolism and cognitive function and whether the ABI influenced that relationship.

Results: With or without adjusting for their brain amyloid burden, these subject's cognitive memory function (RAVLT score) was found both tightly and positively correlated to the brain metabolism at bilateral parietal lobules, PCC, anterior cingulate cortex and frontal lobes. A significant PiB-RAVLT by group interaction was also observed (MCI *vs* preMCI-decliner and control), such that the relationship was more negative in the MCIs than people at risk and preMCI stage. Additionally, across all subjects, the ABI was negatively correlated to glucose metabolism in the bilateral mesial temporal lobe and this relationship influenced memory.

Discussion & conclusion: These are early baseline results from a longitudinal multi-model neuroimaging project that represents a unique opportunity to comprehensively study high-risk patients from cognitively normal to pre-MCI, and eventually to MCI and AD. Two conclusions are drawn thus far: 1) glucose metabolism tracks better with cognitive function in preclinical and early AD; 2) the influence of amyloid on the metabolism-cognition relationship was region specific (it was observed in the MTL region but not the medial and lateral parietal regions). Collection of a larger sample and longitudinal imaging is underway to better elucidate the temporal relationships between amyloid burden, glucose metabolism and cognition in people at risk for AD.

Regional brain metabolism in cognitively normal elder individuals with various levels of cerebral beta-amyloid deposition

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The concept of preclinical Alzheimer's disease (AD) implies that beta-amyloid (Aß) deposits may accumulate in the brain years prior to the clinical manifestations of AD. In this study, we analyzed whether clinically asymptomatic Aß deposition is associated with regional changes in the metabolic state of the brain. Twenty one cognitively normal individuals (mean age 74 years old) underwent [^{18}F] fluorodeoxyglucose PET scan to measure the relative cerebral metabolic rate of glucose and ^{15}O-labeled CO, OO, and H_2O scans to measure the relative metabolic rate of oxygen. An image of aerobic glycolysis, expressed as glycolytic index (GI), was created using linear regression between cerebral metabolic rates of oxygen and glucose. All individuals also underwent [^{11}C]PIB PET scans and binding potentials were evaluated in MRI-defined brain regions. Mean cortical binding potential (MCBP) was calculated from four representative regions and used as a global measure of brain Aß deposition (with 0.18 as a threshold level). Aß deposition was low (MCBP <0.18) in 11 individuals, moderately elevated (MCBP ranged from 0.19 to 0.34, mean 0.24) in 4 individuals; and high (MCBP ranged from 0.41 to 0.73, mean 0.59) in 6 individuals. The cerebral metabolic rate of glucose and GI were significantly higher in posterior cingulate, precuneus and ventromedial prefrontal cortex in individuals with moderate Aß deposition compared to individuals with low or high MCBP. Our findings indicate that regional metabolism may be temporarily increased at some point in the preclinical stage, perhaps when Aß accumulation approaches a critical level. We suggest that main metabolic events associated with pathological increase in Aß deposition occur at the very initial stage of preclinical AD, but they may disappear long before clinical manifestation of AD and even before maximal Aß load is achieved.

Relationship of amyloid-beta burden with age-at-onset in Alzheimer's disease

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Objectives: To investigate the relationship between *in vivo* brain amyloid-beta (Aß) burden, measured by ^{11}C-labeled Pittsburgh Compound B (^{11}C-PiB) retention, and age-at-onset in Alzheimer's disease (AD) patients.

Design: Cross-sectional study. **Setting:** University Dementia Clinic. **Participants:** Twenty-two AD patients including 11 early-onset AD (EOAD: onset <65 years) and 11 late-onset AD (LOAD: onset ≥ 65 years) cases with matched dementia severity, duration of illness, and apolipoprotein E ε4 allele number.

Intervention: ^{11}C-PiB PET scans. **Measurements:** Both region of interest and voxel-based analyses were performed to compare ^{11}C-PiB retention between EOAD and LOAD group, and to test linear relationship between age-at-onset and ^{11}C-PiB retention.

Results: Both ROI- and voxel-based analyses revealed that EOAD patients had significantly higher ^{11}C-PIB retentions than LOAD patients in diffuse brain regions including frontal, lateral parietal, lateral temporal and occipital cortex, and basal ganglia. Subgroup analyses showed that negative correlation between age-at-onset and ^{11}C-PiB retention was significant in LOAD, but not in EOAD.

Conclusion: Our finding of a heavier Aß burden in the brain of living EOAD patients than LOAD patients is in agreement with those from postmortem studies. The inverse relationship between age-at-onset and Aß burden is possibly associated with aging-related decrease of brain or cognitive reserve, and with aging-related increase of brain vulnerability.

Multi-level fibrillar amyloid thresholds of florbetapir F18 PET images from five multi-center studies

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Objectives: To characterize quantitative and visual florbetapir F18 positron emission tomography (PET) measurements of fibrillar amyloid-ß (Aß) burden in a large clinical cohort of probable Alzheimer's disease (pAD), mild cognitive impairment (MCI), and older healthy controls (oHC); and to assess percent positivity of those meeting empirically predetermined florbetapir PET criteria associated with an intermediate-to-high likelihood of pathologic AD (pathAD) or having "any Aß" pathology above that typically seen in young-low-risk individuals.

Materials and Methods: PET scans and clinical evaluations were analyzed for 210 participants from 5 multi-center studies. Cerebral-to-whole-cerebellar florbetapir standard-uptake-value ratios (SUVRs) were computed in 68 pAD, 60 MCI, and 82 oHCs (≥55 years old). A threshold of SUVRs ≥1.17 was used to reflect pathAD based on separate antemortem PET and postmortem neuropathology data from 19 end-of-life patients; Similarly a threshold of SUVRs >1.08 was used to signify "any Aß" as this was the upper limit from a separate set of 46 18-40 year-old APOE4 noncarriers.

Results: The pAD, MCI, and oHC participants differed significantly in mean cortical florbetapir SUVRs (1.39±0.24>1.17±0.27>1.05±0.16; p<1.0e-7), in percentage meeting pathAD levels of florbetapir by SUVR criteria (80.9>40.0>20.7%, p<1.0e-7), and in percentage meeting SUVR criteria for "any Aß" pathology (85.3>46.6>28.1%, p<1.0e-7). Among oHCs, percent florbetapir positivity increased linearly by age decile (p=0.05). For the 54 oHCs with available APOE genotypes (13 APOE4 carriers; 41 non-carriers; 28 not genotyped), APOE4 carriers had higher mean cortical SUVRs than noncarriers (1.14±0.2>1.03±0.16, p=0.048).

Conclusions: This analysis supports the ability of florbetapir PET SUVRs to characterize Aß levels in clinical pAD, MCI, and oHC groups, and in oHC APOE4 carriers and noncarriers, using continuous and dichotomous measures of fibrillar Aß burden. It introduces criteria to determine whether an image is associated with Aß of intermediate-to-high likelihood of pathologic AD or with "any Aß" levels.

[18F]AZD4694 in the symptomatic and presymptomatic study of Alzheimer's disease

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

Methods: 90min dynamic PET scans were acquired following the administration of [18F]AZD4694 10 mCi IV in 6 patients with probable mild AD (2 apolipoprotein E (*APOE*) ε4 carriers, 4 non-carriers), 9 healthy elderly adults (5 *APOE* ε4 carriers, 4 non-carriers), and 5 healthy younger *APOE* ε4 non-carriers. Fibrillar Aß burden was alternatively quantified using cerebral-to-cerebellar standard uptake value ratios (SUVRs) versus distribution volume ratios (DVRs), data from the 27-39min versus 0-90min frames, blind visual ratings, and gray matter, white matter, and cerebellar time-activity curves (TACs).

Results: Our findings provide additional support of the following observations: 1) [18F]AZD4694 reaches equilibrium relatively quickly (about 27min following radiotracer administration). 2) There is a high specific binding in AD cerebral cortex, relatively low non-specific binding in white matter, intermediate (higher than background) binding in pons, and easy assessment of fibrillar Aß burden using visual ratings. 3) 21-33min SUVR images are roughly similar to 21-33min DVR, 0-90min SUVR, and 0-90min DVR images in their ability to distinguish fibrillar Aß from background uptake and to distinguish between subjects in the probable AD, healthy elderly *APOE* ε4 carrier, and healthy elderly and younger ε4 non-carrier groups.

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

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

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 1

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In Alzheimer's disease (AD) there is strong evidence that brain amyloid deposition precedes the emergence of dementia by many years. In addition, a greater accumulation of amyloid in the postmortem brain has been demonstrated in people who carry the major genetic risk factor for AD—*APOE*-e4. 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 50-69 with a first-degree family history for AD were genetically screened to select three groups: *APOE* genotype e4e4 (n=14), e3e4 (n=14), and e3e3 (n=14), matched for age and sex. Subjects were then studied with ([^{11}C]PiB) PET, MRI, and neuropsychological testing. PET and MR images were co-registered for application of an ROI template (AAL for SPM2) to generate regional time-activity curves with cerebellum as reference region. Parametric BP_{ND} images were then generated using SRTM2 such that BP_{ND}=0 reflected no specific binding. BP_{ND} 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 BP_{ND} (0.17±0.19) in comparison to non-carriers (0.04±0.09; F=6.35, p=0.016, ANCOVA controlling for age and sex), with no dosage effect between e4e4 (0.19±0.13) and e3e4 (0.15±0.23) groups. There was no significant effect of *APOE* genotype on neuropsychological test performance. There were also no significant associations between mean cortical [^{11}C]PiB BP_{ND} and neuropsychological test performance in the overall sample, although some tendency was observed for an association with performance on the Boston Naming Test (r=-0.34, p=0.03).

Conclusions: These results corroborate and extend observations by Reiman *et al* (2009) but with a somewhat reduced *APOE*-e4 effect in a younger sample (mean age 59 *vs* 65). Neuropsychological test results confirm the full cognitive "normality" of many at risk subjects with considerable fibrillar amyloid burden.

Instrumental activities of daily living impairment is associated with increased amyloid burden

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 2

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Background: Impairment in instrumental activities of daily living (IADL) greatly increases caregiver burden and is a hallmark of Alzheimer's disease (AD). IADL impairment in AD has been associated with frontal and posterior hypometabolism *in vivo* and with global amyloid deposition in post-mortem studies. With the advent of Pittsburgh Compound B (PIB) PET imaging, it is now possible to visualize amyloid deposition *in vivo* much earlier in the disease process.

Objective: We sought to determine whether IADL impairment is associated with increased cortical PIB retention in normal older control (NC) and mild cognitive impairment (MCI) subjects.

Methods: Fifty-six subjects (19 NC and 37 MCI) participating in ADNI or an investigator-initiated ADNI ancillary study underwent clinical assessments and dynamic PIB PET imaging. Cortical PIB retention was evaluated using the distribution volume ratio (DVR, cerebellar reference). Global PIB retention and then precuneus and superior and middle frontal PIB retention were correlated with IADL using the Functional Activities Questionnaire (FAQ). Linear multiple regression analyses were conducted with FAQ as the dependent variable and PIB retention, age, education, AMNART IQ, and memory performance as predictors.

Results: Mean age was 74.6±7.2 years, 63% male, education 16.6±2.8 years, AMNART IQ 120.8±10.4, RAVLT delayed recall 5.5±4.5, MMSE 28.4±1.6, and FAQ 2.4±3.7. In the linear regression model including all subjects, greater IADL impairment was associated with greater global (R^2=0.30, p=0.003 for model; partial ß=4.9, p=0.002), precuneus (R^2=0.33, p=0.001 for model; partial ß=4.6, p=0.001), and middle and superior frontal PIB retention (R^2=0.28, p=0.004 for model; partial ß=3.9, p=0.004). When looking at MCI subjects only, these associations remained significant.

Conclusions: These results suggest that daily functional impairment is related to greater amyloid burden within the spectrum of MCI. Future longitudinal studies will help determine whether early amyloid deposition will predict rapid functional decline and progression to dementia.

PiB retention and neuropsychological test performance among cognitively normal men

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 3

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Retention of the amyloid ligand, Pittsburgh Compound B (PiB) occurs in cognitively normal, elderly individuals. What is less clear is the extent to which there is a relationship between the extent of PiB retention and performance on neuropsychological tests among cognitively normal individuals who are, on average, younger than 65 years. We report here the results of the analysis of PiB data from a group of 22 young (age = 61.5 years) cognitively normal men (mean education = 15.9 years) who are participating in a study of amyloid deposition and cardiovascular risk factors.

PiB data were reconstructed and corrected for attenuation, scatter, and decay. Regions-of-interest were applied to obtain regional time-activity data and analyzed to obtain measures of the standardized uptake value. The SUV measure was normalized to the cerebellum.

The scores from the neuropsychological test battery were reduced to T-scores adjusting for age, education, sex and race. The T-scores were then converted into domain and global impairment scores using standard methods. 16/22 of the subjects (73%) had global impairment ratings in the normal range; the remainder scored in the Borderline range.

The performance of the subjects on measures of cognitive speed were significantly associated with amyloid deposition in the Anterior Cingulate (rho = 0.45), Frontal Cortex (rho = 0.40) and Lateral Temporal Cortex (rho = 0.39). The highest level of PiB retention was found in the subjects classified as performing in the Borderline range. There was no association between performance in the Speed Domain and overall classification of PiB “positive”.

The results of this initial analysis demonstrate that it is possible to find links between the relative amount of PiB retention, and performance on measures of cognitive function. The findings are consistent with prior work that reported early amyloid deposition in anterior cortical regions.

Predicting cognitive decline in MCI subjects using Fusion ICA Toolbox to combine multimodality biomarker data

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 4

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The aim of this study was to combine a variety of biomarkers (such as structural MRI and CSF measures) in subjects with mild cognitive impairment (MCI) using a novel multimodality fusion tool in order to extract non-redundant information that is useful in predicting future cognitive decline. Alzheimer's Disease Neuroimaging Initiative (ADNI) screening MRI and baseline CSF markers for 97 subjects with MCI (mean [sd] age 75 years [7.1], 54% ApoE4+, 35% FH+) were used. The CSF biomarkers included were tau, p-tau_{181P}, and $A\beta_{1-42}$. 43 MCI subjects converted to AD and 54 did not (as of October 19, 2010). Converters did not differ from non-converters in mean age, gender ratio, education, and tau level but had lower baseline delayed recall memory scores ($p<0.05$), higher ADAS-Cog ($p<0.05$) and lower function ($p<0.06$). P-tau_{181P} tended to be higher ($p=0.066$) and $A\beta_{1-42}$ tended to be lower ($p<0.06$) in converters than non-converters. From the MR images we extracted whole brain gray matter probabilities using FSL-VBM technique. These biomarkers were then combined with Fusion ICA Toolbox (FIT Version 2.0b, 2009) software that uses parallel ICA to isolate unique features from each of the biomarkers of interest. The primary aim is to contrast and differentiate MCI-converters compared to the MCI-non-converters. The results will identify any regions of the brain or specific tests that contribute unique information about the risk of conversion from MCI to AD, some of which may not have been identified in other region-of-interest based studies. The analyses are in progress and final results will be presented at the meeting.

Acknowledgment: Data used in 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. A complete listing of ADNI investigators can be found at:
http://loni.ucla.edu//ADNI//Collaboration//ADNI_Authorship_list.pdf

Beta-amyloid in healthy aging: regional distribution and cognitive consequences

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 5

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Beta-amyloid deposition has been detected *in vivo* in a significant portion of non-demented older adults, but the time course, regional distribution and cognitive consequences of this deposition is unclear. To address these questions, we prospectively examined beta-amyloid across a lifespan sample of healthy adults and assessed its impact on cognition. Participants (N=137, aged 30-89) were scanned by PET using ^{18}Florbetapir and were administered a range of cognitive tests. Cognitive construct composites with two or more measures each were calculated for speed of processing, working memory, reasoning, and crystallized intelligence. Standardized uptake value ratios (SUVRs) were obtained from *a priori* masked regions of interest including anterior and posterior cingulate, precuneus, lateral temporal, dorsolateral and orbital frontal, parietal, and occipital cortices. Our results revealed a differential pattern of amyloid distribution across region and age. Some regions showed small, but significant increases with aging, such as prefrontal and parietal cortices, whereas other regions displayed steeper increases with age and greater variability in amyloid deposition in adults age 60 and over (e.g., anterior and posterior cingulate, precuneus). These age-associated increases in amyloid burden were correlated with differences in behavior. Specifically, across the entire sample increases in mean cortical amyloid burden were associated with decreases in processing speed. Subanalysis of the group of older participants with the highest amyloid burden showed stronger amyloid-cognitive associations. In the high-amyloid individuals, a dose-response effect was observed where higher amyloid burden predicted poorer processing speed, working memory and fluid abilities. Thus, beta-amyloid burden appears to first exert an effect on the most basic of cognitive measures (processing speed), whereas higher-order cognitive operations such as working memory and fluid reasoning are only affected in those with markedly elevated amyloid. Cognitive abilities which rely upon expertise, such as verbal abilities or crystallized intelligence, are impervious to the effects of Aß deposition, at least in healthy adults.

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Predicting amyloid deposition using multiple neuropsychological measures

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 6

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Objective: Many traditional neuropsychological measures cannot detect subtle cognitive changes at presumed preclinical stages of Alzheimer's disease characterized by PiB positivity. We administered FNAME, a challenging face-name memory association test, along with traditional neuropsychological measures, to investigate which tests showed the strongest ability to predict PiB retention in cognitively normal individuals.

Method: We studied 109 normal subjects (mean age = 73.5±8.1, education = 16.2±2.8; AMNART IQ = 122.6±9.3) with CDR scores = 0 and MMSE ≥28. PiB retention (DVR, cerebellar reference) was expressed as a dichotomous variable (PiB mean cortical DVR cutoff = 1.15). We transformed individual neuropsychological scores into z-scores (SRT, FCSRT, Trails A&B, FAS, 3 Categories, BNT), as well as subscores of the FNAME (e.g. face-name recall, face-occupation recall). Logistic regression was used to generate ROC curves, and the AUCs were used to compare the predictive accuracy for PiB positivity of FNAME alone *vs* FNAME with traditional neuropsychological measures. Both models included age and AMNART as independent variables.

Results: For the predictive equation generated by the first model, (FNAME immediate and delayed recall for names retained) the AUC was 0.73 (95% confidence interval [CI] = 0.61-0.85). For the predictive equation generated by the second model (model 1 variables plus Trails A and age retained), the AUC was 0.81 (95% CI = 0.71-0.91). No other cognitive measures were retained in the model.

Conclusions: The FNAME is a highly sensitive memory measure that has strong predictive accuracy for the presence of amyloid deposition alone. Moreover, the predictive ability of the FNAME was enhanced by a measure of processing speed (Trails A) and age when entered into a second model predicting PiB deposition. Taken together, results suggest that specific neuropsychological measures may help to identify the subset of clinically normal individuals who are amyloid positive.

Cognitive activity is associated with amyloid deposition in normal older individuals

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 7

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Participation in cognitively stimulating activities throughout life is associated with a decreased risk of Alzheimer's disease (AD), but the mechanism underlying this association is unknown. AD is characterized by accumulation of beta-amyloid (Aß) in areas that overlap with the default mode network, a group of brain regions active at rest and inactive during performance of many externally-driven cognitive tasks. Lifetime cognitive stimulation may affect the risk of AD through its association with these features. To investigate this question, we examined the relationship between self-reported frequency of cognitively stimulating activities across the lifespan, Aß deposition measured using PET imaging, and default mode network function measured using functional MRI imaging in normal older participants. Linear and whole-brain regression models revealed that less cognitive stimulation was associated with greater Aß deposition, and this relationship was localized within brain regions that overlapped considerably with the default mode network. Furthermore, increased lifetime cognitive activity was related to better default mode network function, and this association was driven by individuals with the most Aß pathology. These findings suggest that lifelong cognitive engagement may influence the development of Alzheimer's pathology and dysfunction in the DMN, prior to the onset of any cognitive decline. Cognitive activity appears to prevent or slow deposition of Aß and also plays a protective role in supporting the connectivity of brain networks influenced by Aß deposition.

Antidepressants are associated with lower brain amyloid in transgenic mice and cognitively normal humans

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 8

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We recently conducted *in vivo* microdialysis studies in mouse models of AD and found that acute citalopram and fluoxetine, both selective serotonin reuptake inhibitor (SSRI) antidepressants, acutely reduced soluble brain levels by 25%. Direct infusion of serotonin also reduced Aß levels by 30%, suggesting that serotonin signaling can alter Aß generation. Studies are now underway to determine if chronic administration of citalopram, compared to vehicle, reduces Aß plaque formation in Tg PS1APP$^{+/-}$ mice when initiated 1 month before typical age of plaque onset. Preliminary results are positive with visibly lower plaque burden in citalopram treated mice (n = 3 treated *vs* 3 vehicle). To explore the association of antidepressant use and Aß plaques in humans, we retrospectively compared the levels of Aß plaques using positron emission tomography (PET) imaging with Pittsburgh Compound B (PIB) in cognitively normal elderly participants who had been exposed to antidepressants within the past 5 years (n = 36) to matched participants who had not (n = 46). Antidepressant-treated participants had significantly lower Aß as quantified by the Mean Cortical Binding Potential (MCBP) (0.02; SD 0.10) than untreated participants (0.13; SD 0.20; Wilcoxon rank sum test p = 0.01) and significantly lower rates of having a positive amyloid scan (2/36 *vs* 11/46; X^2 =5.10, p = 0.02). Also, cumulative amount of antidepressant use within the 5-year period preceding the PET Aß scan negatively correlated with MCBP (rho = -0.298, p = 0.006), indicating that the greater the time exposed to antidepressants, the lower the risk for Aß plaque deposition. While the human data is limited by being a sample of convenience, given the established safety profile of SSRIs and the accumulating evidence it may be reasonable to explore this drug class as a therapeutic strategy to inhibit Aß production and block plaque formation.

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Voxel degree as a measure of functional connectivity changes in Alzheimer's disease

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 9

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The causes underlying the pattern of amyloid deposition in the Alzheimer's brain are not well understood. It has been shown that amyloid distribution in Alzheimer's disease (AD) overlaps that of major brain network hubs in healthy individuals, implying a relationship between the brain's underlying network architecture and the pattern of amyloid deposition. It remains unclear how the brain's hub architecture evolves over the progression of AD as amyloid deposition ensues. In this study, we examine the brain's functional network architecture using fcMRI to determine its evolution over the progression of AD. 13 patients with mild AD, 11 patients with prodromal AD (pAD), 23 patients with stable mild cognitive impairment (sMCI), and 28 elderly controls (ONS) underwent functional MR imaging during a face-name associative encoding task. Images were normalized to a standardized brain template (Montreal Neurologic Institute) using statistical parametric mapping software (SPM 5) and masked to include only grey matter. Pair-wise correlations were calculated and summed for every remaining voxel to obtain an estimate of that voxel's weighted degree. These 'degree maps' were normalized to z-scores in each individual. To assess group differences, a 'disease rank' of 1-4 was assigned for patients in, respectively, AD, pAD, sMCI, and ONS. This rank was then used in a voxel-wise correlation with the weighted connectivity to identify areas which showed functional disruption along with the progression of AD. A cluster in the right inferior gyrus showed significant functional disruption along with disease. Mean values of connectivity (z-scored) were found to be 0.75 (ONS), 0.60 (sMCI), 0.27 (pAD), and 0.04 (AD). As tissue classification schemes improve, it may be possible to extend these methods to measures of nonlinear connectivity which may then give us deeper insight into the pathological changes that parallel disease.

Hubs of atrophy and amyloid-ß in AD and normal aging

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 10

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Background: Neurodegenerative diseases such as Alzheimer's disease (AD) are thought to affect large systems in the brain where pathology spreads along particular networks rather than randomly appearing in unrelated regions. Although critical advances have been made in order to understand dementia neuropathology, networks and mechanisms of pathologic spread remain largely unknown.

Methods: We used structural MRI and PET-PIB imaging to characterize hubs of atrophy and amyloid in elderly (PIB-, N=25; and PIB+, N=25) and AD dementia (N=25). We first obtained the specific networks for each modality and clinical condition using the group volume or PIB intensity variability, applying degree centrality to quantify the number of links or edges connected to each node. Correlation coefficients were computed in the ith row and jth column of adjacency matrices to obtain the links of the final graphs. Additionally, we used a seed-based approach and diffusion of information algorithms to isolate sub-networks and analyze diffusion patterns of atrophy and amyloid across the brain.

Results: We identified four top hub regions in both neuroimaging modalities: hippocampus/parahipocampus formation (HPHF), posterior cingulate (PCC), prefrontal midline and lateral prefrontal. Seed placement in the medial temporal lobe revealed three main pathways: (1) one anterior path, from HPHF to orbitofrontal regions, (2) one posterior path, from HPHF to PCC and (3) one lateral path, from HPHF to temporolateral regions. At later stages of information diffusion, there are another three important pathways: (1) from PCC to prefrontal midline, (2) from PCC to temporolateral regions and (3) from PCC to lateral prefrontal regions. Finally, at latest stages, we detected covariance in atrophy and amyloid in the lateral prefrontal subnetworks.

Conclusions: These results suggest that AD is a network "community" disease engaging well-defined systems of interconnected neurons at the short and large-scale and that amyloid deposition is associated with atrophy across specific brain networks.

Amyloid deposition disrupts local coupling of intrinsic brain activity in cognitively normal elderly

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 11

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Background: Amyloid-ß deposition has been associated with disruption of large-scale intrinsic functional connectivity in cognitively normal older individuals.

Objective: To determine whether local coherence within nodes of the default network is related to amyloid-ß deposition and disruption in long-range connectivity.

Methods: Forty-two cognitively normal older participants were scanned with resting-state functional magnetic resonance imaging (fMRI), and ^{11}C Pittsburgh Compound B (PiB) PET. Amyloid burden was estimated by calculating mean cortical PiB retention, and was analyzed as both continuous and dichotomous variable (PiB+ = DVR > 1.15). Local coherence was measured by computing Kendall's coefficient of concordance between fMRI time course of a given voxel and time courses of that voxel's nearest neighboring voxels (number of neighboring voxels = 26), reflecting the internal homogeneity of regional intrinsic activity. Local coherence was assessed at the voxel-wise map level and in *a priori* regions-of-interest (ROIs), including posterior cingulate cortex (PCC), inferior parietal lobules (IPL), medial prefrontal cortex (MPFC) and hippocampus. Long-range connectivity was estimated with a summary measure of the inter-regional correlation between the same set of ROIs as above.

Results: Map level analyses revealed that increasing amyloid burden was related to decreased local coherence in the PCC, MPFC, and IPL. This finding remained significant when analyses were restricted to grey matter voxels within cortical ribbon to account for potential effects of atrophy. ROI analyses revealed that high amyloid burden disrupted both local coherence in the PCC and long-range connectivity across the default network nodes. Furthermore, 36% of variance in long-range default network connectivity was explained by the PCC local coherence.

Conclusions: These findings suggest that amyloid-related disruption of local coherence, particularly in the PCC, may prove to be a sensitive indicator of early regional dysfunction, and may account for much of the observed abnormality in long-range default network connectivity among amyloid-positive cognitively normal elderly.

Effect of APOE on rate of change of PIB retention across the cognitive continuum

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 12

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Objective: To study the effect of APOE ε4 status on the annual change in brain Aß amyloid load as measured by PIB-PET in cognitively normal (CN), amnestic mild cognitive impairment (aMCI) and Alzheimer's disease (AD).

Methods: We included all 147 subjects (67 CN, 59 aMCI, 21 AD) from the Alzheimer's disease Neuroimaging Initiative and the Mayo Clinic Study of Aging with a baseline PIB scan and at least one follow-up PIB scan. We used linear mixed-effects models with a random subject-specific intercept and slope to estimate the longitudinal change in mean PIB ratio. We fit two models, the first with years since baseline PIB scan, clinical diagnosis, and their interaction. The second model additionally included APOE genotype and all interactions.

Results: We found that the annual change in PIB ratio significantly increased in CN and MCI ($p<0.001$) and not in AD ($p=0.178$). In the first mixed-effect model, we found that the annual change in PIB ratio did not differ by clinical group when APOE ε4 carriers and non-carriers were combined together. When APOE genotype was included in the model, we found that there was a trend for greater annual change in PIB ratio in APOE ε4 carriers aMCIs when compared to annual change in APOE ε4 non-carriers aMCIs ($p=0.07$).

Discussion: In this study we found evidence that the annual change in PIB ratio does not differ by clinical group but may differ by APOE ε4 status especially in aMCIs. Additionally, APOE ε4 aMCIs tended to be younger that non-carriers aMCIs at the same level of cognitive performance suggesting that APOE ε4 status not only lowers the onset of AD but also increases the rate of disease progression in aMCIs.

Evaluation of longitudinal PiB data using linear mixed models

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 13

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Objectives: This work applies linear mixed modeling (LMM) to analyze longitudinal amyloid (Aß) imaging data acquired at baseline (BL) and annual follow-up over 2 years. LMM accounts for correlation among repeated measures, includes all data and subject groups and assesses effects of time and group.

Methods: [C-11]PiB PET imaging was performed (i.e., SUVR40-60 outcome, cerebellum reference). Manual region delineation and CSF correction was based on each subject's MRI. Thirteen regions were examined that included primary cortical areas, as well as anterior ventral striatum and pons. Data were acquired in normal control [NC, 72±9 yrs at BL N=81 (23 PiB+); Yr1 N=23 (11 PiB+); Yr2 N=44 (14 PiB+)], mild cognitive impairment [MCI, 69±9 yrs at BL N=48 (30 PiB+); Yr1 N=25 (16 PiB+); Yr2 N=10 (6 PiB+)] and Alzheimer's disease [AD, all PiB+, 71±11 yrs at BL N=41; Yr1 N=15; Yr2 N=5] subjects. Statistical analyses were performed (SAS software) for each ROI with 5 subject groups: PiB- NC, PiB+ NC, PiB- MCI, PiB+ MCI, AD (PiB+).

Results: All PiB+ groups (NC, MCI or AD) showed evidence of PiB retention increases in cortical areas within the 2-year follow-up that was most notable for PiB+ MCI subjects. The PiB+ MCI annual increases, for several regions, were greater than those for PiB+ NC and AD (albeit small Yr2 sample). SUVR interval differences as large as 0.29-0.30 SUVR units were observed in precuneus and anterior cingulate for PiB+ MCI subjects.

Conclusions: The LMM analysis provides further evidence of detectable *in vivo* Aß plaque accumulation in NC, MCI and AD, within a 2-year follow-up period. This work demonstrates the power of LMM to enable further understanding of early and sustained amyloid deposition in human brain through utilization of all data, i.e., very PiB+ and PiB-, to assess time and group effects.

Time course of specific [^{11}C]PIB and [^{18}F]FDDNP binding: paired studies in patients with Alzheimer's disease, mild cognitive impairment and healthy controls

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 14

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Disclosure: all authors report no conflicts of interest.

Background: [^{11}C]PIB and [^{18}F]FDDNP are PET tracers for *in vivo* assessment of neuropathological characteristics underlying Alzheimer's disease (AD). It has been shown that [^{11}C]PIB has high diagnostic sensitivity for detecting AD. Follow-up studies, however, have shown inconsistent results with either no or only modest changes of [^{11}C]PIB binding over time. [^{18}F]FDDNP also discriminates between AD and healthy controls, but has a 9-fold lower specific signal compared with [^{11}C]PIB. It has been suggested, however, that [^{18}F]FDDNP reflects presence of neurofibrillary tangles, which are strongly related to cognition and disease progression. In the present longitudinal study, changes in both [^{11}C]PIB and [^{18}F]FDDNP were investigated in patients with AD and mild cognitive impairment (MCI), and in healthy controls (HC).

Methods: Repeated, paired, dynamic 90 minute, [^{11}C]PIB and [^{18}F]FDDNP PET scans were performed in 11 controls, 12 MCI patients and 7 AD patients. The mean interval between baseline and follow-up scans was 2.5 years (range: 2.0-4.0 years). For both tracers, parametric images of binding potential (BP_{ND}) were generated using a basis function implementation of the simplified reference tissue model. Changes in global cortical BP_{ND} were evaluated using paired t-tests.

Results: A significant increase (m±sd baseline: 0.404±0.412, follow-up: 0.440±0.408) in global [^{11}C]PIB BP_{ND} ($t(28)=2.104$, p=0.044) was found. This increase was most prominent in healthy controls (m±sd baseline: 0.123±0.272, follow-up: 0.148±0.288, $t(10)=2.242$, $p=0.049$) and MCI patients (m±sd baseline: 0.389±0.393, follow-up: 0.462±0.391, $t(10)=2.165$, $p=0.056$). No change was found for AD patients (m±sd baseline: 0.868±0.095, follow-up: 0.863±0.129, $t(6)=-0.961$, $p=0.906$). For [^{18}F]FDDNP, no longitudinal changes in global BP_{ND} were found (m±sd baseline: 0.058±0.034, follow-up: 0.060±0.035, $t(29)=0.303$, $p=0.764$).

Conclusions: A significant increase in [^{11}C]PIB binding over time was observed, especially in controls and MCI patients. These results suggest that amyloid deposition predominantly occurs during preclinical stages of AD, and reaches a plateau once progression to AD is clinically established.

Brain [^{11}C]-PiB uptake reflects beta-amyloid burden detected by immunohistochemistry in frontal cortex biopsy specimens

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 15

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Objective: To compare Carbon 11–labeled Pittsburgh Compound B ([11C]PiB) positron emission tomography (PET) findings in patients with and without Alzheimer's disease lesions in frontal cortical biopsy specimens.

Patients: 21 patients (14 women, 14 men; mean age; SD 72.7; 4.6 years, range 62–83 years) who had undergone intraventricular pressure monitoring with a right frontal cortical biopsy for suspected normal-pressure hydrocephalus participated in the study.

Methods: A dynamic 90 min [11C]PiB PET scan was performed. The data was quantified as a region-to-cerebellar cortex ratio from 60-90 min after injection by using an automated region-of interest analysis. Ventricular cerebrospinal fluid (CSF) Aß-, tau- and phophotau-levels were measured. The number of Aß aggregates in the frontal cortical biopsy specimen was evaluated by immunohistochemistry.

Results: In patients with Aß aggregates in the frontal cortical biopsy specimen, PET imaging revealed significantly higher [11C]PiB uptake in the right frontal cortex and in the composite neocortical score (an average of uptake in frontal, parietal, lateral temporal, occipital and posterior cingulate cortices). There was a clear association between the number of Aß aggregates in the frontal cortical biopsy specimen and both [11C]PiB uptake in the right frontal cortex ($r=0.91$, $p<0.001$) and the composite neocortical [11C]PiB uptake score ($r=0.89$, $p<0.001$). The ventricular CSF Aß-, but not tau and phosphotau levels were associated with both frontal cortical [11C]PiB uptake and the number of Aß aggregates in the biopsy specimen.

Conclusions: Our study supports the use of noninvasive [11C]PiB PET in the assessment of Aß deposition in the brain by showing a clear association between *in vivo* [11C]PiB uptake and the number of Aß aggregates in frontal cortical biopsy specimen.

Pharmacological characterization of a novel fluorinated PET tracer for the detection of amyloid-ß plaques

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 16

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Background: Amyloid-ß (Aß) plaques have been successfully visualized in the brain of Alzheimer's disease (AD) patients with PET tracers such as [^{11}C]PIB. Yet, the short $t_{1/2}$ of carbon-11 (20min) limits its use to clinical facilities close to a cyclotron. In order to support multicenter clinical trials for novel AD therapies, the present work aimed at developing a fluorine-18 ($t_{1/2}$ 110min) Aß PET tracer.

Methods: *In vitro* binding studies were performed on cortical homogenates from AD and aged-matched controls with [^{3}H]MK-3328, [^{3}H]PIB and [^{3}H]lazabemide. Autoradiographic mapping of [^{3}H]MK-3328 binding site expression was performed on AD brain sections and compared to the distribution of Aß plaques and astrocytes.

Results: [^{3}H]MK-3328 binds to cortical Aß plaques with a Kd of 17±4 nM (n=5) and a Bmax of 1600±419 nM (n=5). Screening against a diverse set of enzymes and receptors unexpectedly revealed an interaction between MK-3328 and monoamine oxidase B (MAO-B). [^{3}H]MK-3328 binds purified MAO-B with a Kd of 6±3 nM (n=3). Specific [^{3}H]MK-3328 binding was also observed in non-AD human cortical membrane preparations and fully displaced by MAO-B inhibitor lazabemide. Saturation studies in AD cortex demonstrated that MAO-B levels accounted for only 17±3% (n=5) of Aß levels measured by [^{3}H]PIB. [^{3}H]MK-3328 autoradiography revealed a punctated expression pattern in AD cortical areas comparable to [^{3}H]PIB that was not blocked by lazabemide. Immunocytochemistry on adjacent sections supported a close association between [^{3}H]MK-3328 positive areas, Aß plaques labeled with 6E10 antibody and astrocytes stained with GFAP antibody.

Conclusions: Despite unanticipated MAO-B binding, these results indicate that MK-3328 has an *in vitro* pharmacological profile supporting its development as a fluorine-18 PET tracer for the detection of Aß deposits in AD patients. On going clinical studies will establish the value of this novel imaging agent for the detection of Aß plaques in AD patients.

Florbetapir F 18 and ^{11}C-PIB PET imaging provide concordant measures of underlying brain amyloid pathology

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 17

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Background: ^{11}C-PIB was the first and to date most thoroughly studied amyloid imaging agent. Emerging ^{18}F-labeled ligands such as florbetapir will expand availability of PET amyloid imaging. The transition from ^{11}C-PIB to florbetapir F 18 PET amyloid imaging in the ADNI protocol provides an opportunity to compare performance of the two ligands.

Methods: Florbetapir F 18 imaging results (qualitative visual read (Aß+/Aß-) and cortical to cerebellum SUVR) were compared to the most recent ^{11}C-PIB imaging results for the first 9 subjects (7 MCI and 2 cognitively normal controls) with data available for both ligands in the ADNI database. Mean time between the florbetapir-PET scan and the most recent ^{11}C-PIB scan was 1.5 years.

Results: Qualitative visual reads of the florbetapir F 18 and ^{11}C-PIB scans yielded identical results. The same 3 subjects were rated Aß+, with the remaining 6 subjects rated Aß-. The correlation between florbetapir F 18 and ^{11}C-PIB mean cortical to cerebellar SUVR was statistically significant ($r=0.98$, $p<0.0001$), and comparable in magnitude to the correlation between two consecutive ^{11}C-PIB scans in the same subjects (2007-2008: $r=0.99$; 2008-2009, $r=0.94$). The dynamic range for ^{11}C-PIB SUVR appeared greater than that for florbetapir F 18. Although mean SUVR for ^{11}C-PIB and florbetapir F 18 were comparable for visually negative subjects, ^{11}C-PIB SUVR tended to be higher than florbetapir SUVR for visually positive subjects (Table). However, because the between subject variance was also greater for ^{11}C-PIB than for florbetapir F 18, the effect size (Cohen's d, SUVR for visually positive *vs* visually negative subjects) was comparable for the two ligands.

Conclusions: These preliminary results suggest that Florbetapir F 18 and ^{11}C-PIB PET scans provide concordant estimates of brain amyloid burden. Additional studies, with Florbetapir F 18 and ^{11}C-PIB PET scans conducted in closer temporal proximity, are required to confirm the limits of concordance between these tracers.

	Mean SUVR (Standard Deviation)		Cohen's d
	Aß+	Aß-	
Florbetapir F 18	1.64 (0.110)	0.95 (0.077)	7.25
^{11}C PIB	2.06 (0.188)	0.99 (0.070)	7.58

Comparison of [H-3]Flutemetamol and [H-3]PiB binding to cortical amyloid in brains from Alzheimer's disease and control subjects

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 18

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Background: Flutemetamol is a 3'-fluoro analog of Pittsburgh Compound-B (3'-F-PiB) and is a new promising imaging agent for *in vivo* detection of ß-amyloid deposits in Alzheimer's disease (AD). PET imaging shows that compared to [C-11]PiB, [F-18]flutemetamol has similar retention characteristics although higher non-specific retention in white matter. Whether the two tracers have comparable binding in AD and control brain tissue homogenates and bind to cortical Aß deposits in a similar fashion in tissue sections is unknown.

Methods: [H-3]flutemetamol and [H-3]PiB binding were quantified *in vitro* in fresh frozen homogenates of frontal, temporal, and occipital cortex from AD (n=14) and cognitively normal control (n=5) subjects. Serial paraffin sections of frontal, temporal and occipital cortex were processed using highly fluorescent derivatives of flutemetamol (6-CN-flutemetamol) and PiB (6-CN-PiB), as well as for Aß immunohistochemistry (clone 4G8 mab) and the Bielschowsky silver method, to examine the pattern of flutemetamol and PiB plaque labeling and the extent of their overlap with Aß-immunoreactive and Bielschowsky positive plaques.

Results: We observed a strong direct correlation between [H-3]flutemetamol and [H-3]PiB binding across brain regions in AD and control subjects (r=0.99). There was also a one-to-one match of 6-CN-flutemetamol and 6-CN-PiB labeling of Aß plaques and cerebral vascular Aß deposits. No labeling of neurofibrillary tangles was detected with either compound. In Aß-immunoreactive plaques, the fluorescence was more intense in compact/cored deposits, while diffuse Aß plaques were less intensely labeled. Bielschowsky positive neuritic plaques were prominently labeled with 6-CN-flutemetamol and 6-CN-PiB.

Conclusions: Our results demonstrate that 6-CN-flutemetamol and 6-CN-PiB have comparable patterns of binding in brain tissue homogenates and comparable labeling of Aß plaque and vascular Aß deposits in postmortem neocortical tissue sections. These data suggest that *in vivo* PET retention of [F-18]flutemetamol in AD brains reflects neocortical Aß plaque load in a manner similar to PiB.

[^{18}F]flutemetamol PET imaging and medial temporal atrophy measures in distinguishing aMCI and AD from elderly normals

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 19

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Objective: To evaluate the individual and combined contributions of [^{18}F]flutemetamol-labeled amyloid PET and volumetrically-acquired MRI measures for diagnostic classification.

Methods: We studied 10 young normals (yo-NCI) (38.9 yr), 15 elderly normals (el-NCI) (70.8 yr), 20 amnestic MCI (aMCI) (72.1 yr) and 27 AD (71.1 yr) subjects. A mean cortical SUVR of 1.56+ was used to classify subjects as Amyloid positive (Am+ve). Hippocampal (HP) volumes and a visual rating system (VRS) were used to rate HP and entorhinal cortex atrophy on MRI scans, using a mean VRS score of 1.75+ to classify subjects as MRI positive (MRI+ve).

Results: VRS and HP volumes were equivalent for classifying aMCI and AD. The rates of MRI+ve scans among yo-NCI, el-NCI, aMCI and AD subjects was: 0%, 7%, 70% and 75%, respectively. The rates of Am+ve scans for these same groups of subjects was: 0%, 7%, 50% and 93%, respectively. The rates of either Am+ve or MRI+ve scan for these subject groups was: 0%, 13%, 85% and 96%, respectively. Among all MRI+ve subjects, 83% were Am+ve, but among all Am+ve subjects, 43% were MRI-ve, suggesting that amyloid deposition leads structural changes. Only 2/27 AD subjects were Am-ve, one of which was MRI+ve. However, 10/20 aMCI were Am+ve, of which 7/10 were MRI+ve and 7/10 Am-ve aMCI subjects were also MRI+ve. By logistic regression this represented a significant added value of MRI in combination with flutemetamol-PET in the classification of aMCI versus el-NCI.

Conclusions: [^{18}F]flutemetamol PET and structural MRI provided additive information in the diagnostic classification of cognitvely impaired subjects. This was most evident among Am-ve aMCI subjects, 70% of whom were MRI+ve, suggesting a substantitive non-AD neurodegenerative etiology among aMCI subjects in this sample.

Head-to-head comparison of amyloid-specific PET radioligands [^{18}F]AZD4694 and [^{11}C]AZD2184

POSTER ABSTRACT (Session 1: Friday)

Poster Board No. 20

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[^{11}C]AZD2184 and [^{18}F]AZD4694 are two compounds that have been evaluated in preclinical and clinical studies and showed suitability for imaging and quantification of ß-amyloid in brain. They have appeal for use in research programs and [^{18}F]AZD4694 has also potential to be used in multi-center studies involving PET facilities without cyclotron. The present study is a small-scale, direct comparison of the two radioligands aiming at facilitation of translatability of results between studies employing one or the other of the tracers.

Two cognitively normal elderly control subjects (age 50 and 54 years) and four probable Alzheimer's disease patients (age 57±4 years) were involved in the comparison. The subjects were first examined after injection of [^{11}C]AZD2184 (384±79 MBq), and at least 150 minutes later, after injection of [^{18}F]AZD4694 (206±7 MBq). Individual MR images were obtained for segmentation and region of interest delineation. Qualitative image inspection, descriptive assessments of kinetics, and the results of reference region-based kinetic analyses were used to compare the two radioligands.

Visual inspection of normalized images, showed that the distribution and contrast of binding in grey matter areas was similar between the two radioligands. There was negligible white matter binding for [^{11}C]AZD2184 whereas some was observed for [^{18}F]AZD4694 albeit less than half of that seen in cortical areas in AD patients. While kinetics of both radioligands was rapid, the brain uptake, washout and specific binding of [^{11}C]AZD2184 was even faster than for [^{18}F]AZD4694. Regression analysis of regional specific binding ([^{11}C]AZD2184 *vs* [^{18}F]AZD4694) showed that there was close agreement (slope>0.95) and high degree of correlation (R^2>0.85) between results of the radioligands.

In conclusion, these preliminary findings support that visual readings and quantitative results obtained using either radioligand may be translatable to the other one thereby providing opportunities to compare or pool results obtained from different studies.

Design and synthesis of potential retinoid based PET imaging agents to study Alzheimer's disease biology

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 1

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The pathological hallmarks of Alzheimer's disease (AD) are the presence of senile plaques containing amyloid-beta (Ab) peptide and the formation of neuronal tangles in the cerebral cortex. Several radiolabeled PET compounds were reported as AD biomarkers, the most tested are PIB and AV45. Here we present a novel biomarker approach for AD imaging. Retinoid signaling pathway is involved in mAD genetic linkages. This pathway is mediated by retinoic acid (RA) receptors (RARs) and retinoid X receptors (RXRs), both of which have three types, α, ß and γ, and various isoforms. RA is derived from vitamin A. Deficiency of this vitamin in rats leads to Ab brain vasculature deposits and neuronal cell death. These were correlated with the lack of RARα signaling, as this receptor is down regulated in vitamin A deficient rats. Similar RARα deficit was found in the cortices in pathology samples of AD patients. Recent work has also shown that all-trans RA (atRA) applied intra peritoneally in a mouse model of AD results in a decrease in Ab production, and the neuronal cell death associated with Ab can be prevented by RARα signaling, and an RARα agonist can cross the blood-brain barrier (BBB). We synthesized a small library of novel retinoic acid analogues and tested their activity by evaluating phenotypic changes caused in developing zebrafish embryos. We showed that several compounds showed receptor activity and specificity and significantly affect development. Our reporter assays determined that BT10, interacts with RAR-α receptor sub-types and had no activity for RXR receptors at the tested concentrations. We will report on the 18F labeled BT10 as PET tracer for animal imaging to measure the concentration of RAR-alpha in normal neural cell and pathological AD neural cells. Our approach may lead to an early indicator for predicting amyloid-beta production leading to AD. We are planning to modify and our lead BT10 to improve receptor activity and specificity for *in-vivo* RAR receptor activity to study AD biology.

Quantitative measurement of B amyloid plaques with C-11 PIB positron emission tomography of hypogonadal men with type 2 diabetes

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 2

HA Nabi, M Sajjad, S Dhindsa, D Erb, D Wack, A Chaudhuri, S Dubey, S Wisniewski, P Dandona.

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Introduction: Type 2 diabetes (DM) and hypogonadism in males are both known to increase the risk of Alzheimer's disease (AD) markedly. We have recently shown that 33% of DM men have hypogonatrophic hypogonadism (HH) with low free testosterone (FT) concentrations, elevated C-reactive protein and an increased fat mass. Since the pathogenesis of AD is dependent upon oxidative and inflammatory stress, patients with HH and DM would be expected to have enhanced risk of AD. Consistent with this, we have now discovered that DM men with low FT have increased expression of amyloid precursor protein (APP) in their peripheral blood mononuclear cells, as well as an increased expression of APP and tau protein in adipose tissue when compared to normal subjects. Treatment of these patients with testosterone suppresses APP.

We hypothesize that hypogonadal DM men will show more expression of PIB in the brain than healthy men. The relationship between the cellular and molecular indices and the uptake patterns of PIB on PET scans will also be assessed.

Methods: Dynamic C-11 PIB images of the brain were acquired from three subjects (2 with HH and DM, one age-matched control, ages 42, 59, 59, respectively) following the iv administration of a mean of 8.3mCi (322mBq). A noise reduction algorithm was applied and the intensity values of C-11 PIB (25 minutes post-injection) with cerebellum reference were calculated for frontal, parietal, temporal, occipital, and insula regions.

Results: The two subjects with DM and HH showed more PIB retention than the normal subject, with prominent differences in the temporal lobe (0.9563 vs 0.9009), and insula (0.9759 vs 0.9025). Occipital lobe values were similar.

Conclusion: These preliminary results support our hypothesis that patients with type 2 DM and HH express more amyloid in their brains as measured by C-11 PIB than a normal subject.

Multi-modality fusion of neuroimaging and genetic data in predicting abnormal cognitive decline in aging

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 3

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Recently, a novel data fusion method developed by Calhoun *et al* (2009) using parallel Independent Component Analysis (Fusion ICA Toolbox, FIT Version 2.0b) has shown potential in discovering disease-contributing characteristics by encompassing whole-brain image analysis and incorporating multiple data types into a single model. To examine characteristics that may predict a decline from normal aging to MCI, we obtained data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and used the Fusion ICA Toolbox to analyze the MRI, FDG-PET, and SNP genetic data of 103 normal study participants (M/F: 63/40, mean (sd), age: 75.8 (4.73), baseline ADAS-Cog: 10.4 (4.24), baseline MMSE: 29.0 (1.12)). CSF abeta and tau data are available only in a subset, but APOE4 genotyping, available in all subjects, will be used as a surrogate for abeta levels. 27 of these patients showed cognitive decline based on the CDR sum of boxes score at either 36- or 48-month follow-up visits. Data analysis is ongoing and the multi-modality data will be fused to create a model for determining potential clinically relevant characteristics. By comparing the imaging and genetic data of normal controls to those who experienced cognitive decline, we anticipate developing sensitivity and specificity measures for using the above modalities together in predicting progression from normal aging to pathologic impairment. This method may aid in the early detection of preclinical stages of MCI and AD, and may enable the most effective use of disease-modifying therapeutics designed to stop or slow the progression of the disease. The results of our work in progress will be presented at the meeting.

ß-Amyloid deposition, ^{1}H MRS metabolites and cognitive function in a population-based cohort of cognitively normal elderly

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 4

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Background: Understanding the relationship between imaging markers and cognitive function in the cognitively normal elderly population may be useful in identifying the imaging markers of preclinical Alzheimer's disease (AD) pathology.

Objective: To determine the relationship between ß-amyloid (Aß) deposition on PET and proton MR spectroscopy (^{1}H MRS) metabolites as potential preclinical markers of AD pathology.

Methods: We studied 311 cognitively normal older adults (median age=80; range=70-90) who participated in the population-based Mayo Clinic Study of Aging (MCSA) from January 2009 through September 2010. The participants underwent amyloid imaging with [^{11}C]-Pittsburgh Compound B (PiB), single voxel ^{1}H MRS from the posterior cingulate gyrus and neuropsychometric testing. Associations between cognitive function, ^{1}H MRS metabolites and PiB retention were investigated. We adjusted for age, sex and education level in all analyses.

Results: Global cortical PiB retention ratio was associated with higher glial marker myoinositol/creatine (mI/Cr) (r=0.17; p=0.003) and membrane integrity marker choline (Cho)/Cr (r=0.13; p=0.022) after adjusting for age, sex and education. Higher PiB retention was associated with lower performance on the Trail Making Test Part B (r=0.13; p=0.03), WAIS-R Digit Symbol (r=-0.12; p<0.01) and Boston Naming (r=-0.14; p=0.01) tests. Higher Cho/Cr was associated with lower performance on Trail Making Test Part B (r=0.12; p=0.04), AVLT delayed recall (r=-0.12; p=0.04), WAIS-R Digit Symbol (r=-0.18; p<0.01), and WAIS-R Block Design (r=-0.12; p=0.03) tests.

Conclusion: ^{1}H MRS metabolite markers of AD are associated with Aß deposition in cognitively normal elderly. Whereas higher global PiB retention was associated with lower performance in naming, attention/executive function measures, higher Cho/Cr ratio was associated with lower performance on memory, attention/executive function and visual-spatial processing measures in cognitively normal elderly. These associations between ^{1}H MRS metabolite markers, PiB retention and cognition suggest that ^{1}H MRS metabolites are related to the preclinical pathological processes in the amyloid cascade influencing cognitive function.

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

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 5

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One of the pathological features of Alzheimer's disease (AD) is the conversion of a normal soluble protein, amyloid beta (Ab) into aggregates of its monomeric form. Contemporary science holds that Ab oligomers and larger aggregates, believed to contribute to neurocognitive deficits, may precede AD plaque burden by many years providing a window in which to diagnose AD earlier and monitor progression prior to advanced and irreparable neurocognitive decline. This premise is dependent on means to identify Ab cascade elements earlier than advanced plaques, such as Ab oligomers/aggregates. Adlyfe has been developing unique peptides, Pronucleon™, that preferentially recognize Ab oligomers and aggregates by specifically binding to epitopes unique to misfolded, beta-sheet docking sites. The Pronucleon™ peptide undergoes a sequence-specific conformational change in the presence of the amyloid beta aggregates which results in intense fluorescence as a result of the association of N-and C-terminal pyrene additives. Using Pronucleon™ peptides, we have demonstrated *ex vivo* plaque specific staining of brain sections obtained from hAPP over-expressing mice bearing the Swedish/London genetic mutations (APP_{SL}) that cause excessive plaque formation in the brain along with neurological deficits commensurate with human AD. These, *ex vivo*, fluorescent bodies are plaque like in morphology and correlate well with ThioflavinS staining (positive control). In addition, Pronucleon™ peptides were administered *in vivo* via peripheral administration to APP_{SL} mice that develop extensive plaque pathology and quantitatively visualized. The Pronucleon™ peptide labeled plaques in the hippocampus and cortex of these transgenic mice. Furthermore, *ex vivo* labeling of post mortem human AD brain tissue sections demonstrated that Ab amyloid structures were labeled and co-stained with either ThioflavinS or anti-Ab 6E10. Taken together, Adlyfe Pronucleon™ technology holds the promise of providing a new imaging tool for Ab cascade elements that precede advanced plaque and fibril formation thereby providing early diagnosis and treatment opportunities.

The relation of serotonin 5-HT_{1A} receptors and amyloid load in prodromal AD

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 6

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Objective: The goal of this study is to identify a neural system that reveals a measurable response prior to the development of AD. The serotonin (5-HT_{1A}) system was examined under conditions of increasing amyloid burden in prodromal AD subjects.

Methods: A total of 15 subjects have undergone multimodality imaging and neuropsychological testing (RAVLT and CDR), consisting of 11 controls, with 4 of the subjects classified as "decliners" based upon repeated RAVLT tests, and 4 with *amnestic MCI*. Dynamic PET scans using [C-11]PIB (amyloid binding) and [C-11]WAY100635 (5-HT_{1A} receptor binding) and T1- and T2- weighted MRI scans were acquired. Parametric images of specific binding (DVR) were created from the PET data and spatially transformed into normalized space for ROI and voxel-based analysis. Partial volume correction was used for the ROI based data and mean cortical values were used as an index for PIB binding.

Results: A positive correlation was found between PIB binding and 5-HT_{1A} binding in the hippocampus (Hi) **(R=0.72, p=0.003)** and the posterior cingulate gyrus (PCG) **(R=0.63, p=0.015)**. There was a significant difference in median values between CDR_SOB=0 and CDR_SOB>0 for PIB binding, 5-HT_{1A} Hi and PCG (p=0.004, 0.039, 0.005, respectively). Voxel-based analyses revealed a negative correlation between the global PIB and 5-HT_{1A} binding in the raphe nuclei (p=0.005, uncorrected).

Conclusion: These data suggest there is an upregulation of 5-HT_{1A} cortical postsynaptic receptors with increasing amyloid burden and a downregulation of 5-HT_{1A} binding to the autoreceptors of the raphe nuclei. The serotonin 5-HT_{1A} system may provide an early indication of neural changes prior to the onset of AD.

Investigating astrocytosis with ^{11}C-deuterium Deprenyl in mild cognitive impairment and mild Alzheimer's – a multi-tracer PET paradigm

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 7

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Background: High amounts of astrocytes co-localise with fibrillar Aß-plaques in post-mortem AD brains. It is therefore of great interest to develop a PET tracer for visualising reactive astrocytes in Alzheimer's disease's earliest stages and study the regional distribution in brain in comparison to fibrillar Aß. Monoamine oxidase-B (MAO-B) is found primarily in astrocytes. ^{11}C-L-deterium-deprenyl (DED) is a PET tracer with high affinity and specificity for MAO-B. In the current investigation we performed DED-, PIB- and FDG-PET in a group of MCI and AD patients to evaluate the inter-relationship between the three tracers.

Methods: DED-PET was performed in MCI (n=8; age=62.6 ± 7.5; MMSE=27.5 ± 2.1) and AD patients (n=7; age=65.1 ± 6.3; MMSE=24.4 ± 5.7) and in healthy age matched controls (n=14; age=64.7 ± 3.6), A modified reference-Patlak model, with cerebellar grey matter as reference, was chosen for kinetic analysis of the DED data. Individual DED data from 20-60 minutes was analysed using a digital brain atlas. Mean regional glucose metabolism and PIB uptake ratios were calculated for each patient with cerebellum grey matter as reference.

Results: ANOVA on the regional DED binding data revealed a significant group effect in the bilateral frontal and bilateral parietal cortices. Increased DED binding in most cortical and sub-cortical regions was observed in the MCI patients relative to the controls and AD patients. All patients, except three MCI, were PIB+. Limited regional correlations were found between the three PET tracers particularly between DED and PIB.

Conclusions: Increased DED binding throughout the brain of the MCI patients might suggest that astrocytosis is an early phenomenon in AD development. DED-PET did not correlate with FDG or PIB in most brain regions. To better understand the lack of a strong relationship between the tracers, particularly DED and PIB, requires further investigation with parallel neuroimaging and post-mortem studies.

Increased ß-amyloid deposition is related to regional cerebral blood flow in nondemented older adults

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 8

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Approximately 30% of nondemented older adults have elevated fibrillar ß-amyloid (Aß) in the brain. Whether these individuals have changes in brain function that are associated with Aß has not been extensively studied. We hypothesize that Aß accumulation is related to regional cerebral blood flow (rCBF) even in nondemented elderly.

Methods: Fifty-five nondemented participants (78.5±6.3 years, 24 females, 6 CDR=0.5) in the Baltimore Longitudinal Study of Aging underwent [^{15}O]-water PET and dynamic [^{11}C]PiB PET. A simplified reference tissue model with linear regression and spatial constraint (Zhou *et al* 2007) was applied to 15 regions of interest (ROI) drawn on co-registered MRIs to quantify distribution volume ratio (DVR) using cerebellum as reference region. Regressions of mean cortical DVR (mcDVR), representing an average of 8 cortical regions, and individual regional DVRs on [^{15}O]-water PET scans were performed in SPM5, adjusting for age and sex.

Results: Increased mcDVR was associated with decreased grey matter rCBF in parahippocampal and inferior frontal regions and at the junction of the planum temporale and insula (p=0.005, spatial extent k=50). When search was restricted to CBF in cortical ROIs, regional DVRs negatively correlated with rCBF in the same region (p=0.05, k=50).

Conclusion: Elevated Aß is associated with alterations in brain function in nondemented older individuals. rCBF decreases in medial temporal and inferior frontal regions correlate with higher global Aß. Inverse associations between rCBF and regional Aß load are also seen. These findings suggest that increased Aß adversely affects brain function in nondemented older adults.

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

Relationship of neuropathological markers of white matter burden and amyloid accumulation to attentional control during aging

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 9

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Apparently healthy older adults often harbor various neuropathologies, including white matter burden and amyloid-beta accumulation. White matter abnormalities have been previously associated with declines in executive function, whereas amyloid accumulation has been associated with disruption of memory-related systems. We investigated disruption of executive function operationally defined as failures to dynamically allocate attention across levels of task difficulty during a functional magnetic resonance imaging (fMRI) task. The task involved parametric manipulations of task demand in a global-local paradigm by varying the invocation of inhibition and shifting requirements. Fifty-one younger (aged 18-27) and 62 older adults (aged 60-87) participated in the global-local task paradigm while undergoing fMRI scanning. All older adults were cognitively normal individuals with a Clinical Dementia Rating of 0. Older adults displayed a pattern of greater activation than younger adults in frontal and parietal regions associated with attentional control. However, older adults who exhibited a pattern of increasing activation as task demand increased also exhibited better performance than did older adults who exhibited a failure to dynamically modulate activation across task difficulty levels. Among older adults with high white matter burden measured from hyperintensities in fluid attenuation inversion recovery (FLAIR) images, there was a significant correlation between white matter burden and the tendency to exhibit failures to dynamically allocate attention. In contrast, an individual's level of amyloid accumulation as measured with Pittsburgh Compound B using positron emission tomography (PET) was not related to dynamic allocation of attention. Among this cognitively normal sample of older adults, there was little co-occurrence of white matter burden and amyloid accumulation, further suggesting that these two neuropathological markers have distinct etiologies and effects on neural function.

Comparison of cerebral metabolism using the PALZ tool in clinically unimpaired elderly and MCI subjects with and without amyloid deposition

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 10

AD Cohen, JC Price, M Rudolph, Z Jones, BL Rosario, LA Weissfeld, RD Nebes, JA Saxton, BE Snitz, CA Mathis, WE Klunk.

Background: Lowered cerebral metabolism, using [18F]fluoro-2-deoxy-D-glucose (FDG), has long been associated with AD pathogenesis. One method for identification of "AD-like" FDG scans is the PALZ tool. Using Pittsburgh Compound-B (PiB), several have reported ~25% of clinically unimpaired, elderly controls (NC) and ~60% of Mild Cognitive Impairment (MCI) subjects display increased PiB. The present studies compared cerebral metabolism in MCI and NC with and without amyloid deposition.

Methods: Subjects underwent PiB and FDG PET imaging. Tissue ratios were calculated for cortical regions-of-interest (ROI) and normalized to cerebellum (SUVR). The FDG PET data were analyzed using the PALZ tool, which implements automatic Alzheimer discrimination methods developed by Herholz *et al.* A t-sum >11,090 is considered AD-like, but values over 6,000 may be associated with more subtle abnormalities.

Results: Among both MCI and NC subjects, those identified as PiB(+) at baseline displayed significantly higher (i.e. more abnormal) PALZ score ($p<0.05$) than those identified as PiB(-). Of 35 MCI, 19 were PiB(+), of these, 7 had an AD-like PALZ score and 6 had an elevated PALZ score (>6,000). Of the 16 PiB(-) MCI, 1 had an AD-like PALZ score and 4 had an elevated PALZ score (>6,000). Of 75 NC, 21 were PiB(+), of these, 4 had an AD-like PALZ score and 4 had an elevated PALZ score (>6,000). Of the 54 PiB(-) NC, 2 had an AD-like PALZ score and all others had PALZ scores under 6,000. A Fisher exact test revealed in both MCI and NC a significant difference between the proportion of PiB(+) and PiB(-) with abnormal PALZ scores ($p>0.05$).

Conclusions: Among both MCI and NC subjects, it appears that increased PiB is associated with cortical hypometabolism, measured by PALZ. It will be of great interest to follow the four categories of subjects: PiB(+)/PALZ(+), PiB(-)/PALZ(-), PiB(+)/PALZ(-) and PiB(-)/PALZ(+) to determine the eventual clinical outcome.

FDG metabolism, amyloid deposition and APOE status in cognitively normal elderly subjects

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 11

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Background: APOE-ε4 carrier status in normal individuals has been associated with both altered glucose metabolism and higher levels of amyloid deposition.

Objective: To relate cortical FDG metabolism, PiB retention and APOE-ε4 carrier status in cognitively normal (CN) older individuals.

Methods: Fifty-six CN subjects mean age ± sd = 74.7 ± 7.7 (43 ε4 non-carriers, mean age = 76.1 ± 7.0, and 13 carriers, mean age = 70.3 ± 8.5) underwent PiB (DVR, cerebellar reference region) and FDG (SUV, covariance adjusted for cerebellar SUV) PET, and MR imaging. Analyses performed at each cortical vertex (Freesurfer) included linear regressions (in carriers and non-carriers separately) of FDG metabolism on PiB retention covarying local cortical thickness and age, and ANCOVA of PiB retention and FDG metabolism by ε4 status with the same covariates. Local cortical thickness was included to control for partial volume error.

Results: Compared to non-carriers, ε4 carriers had higher PiB retention in precuneus/posterior cingulate, inferior parietal lobule (IPL), and lateral and inferior temporal regions ($p<0.001$). ε4 carriers had lower FDG metabolism in precuneus but higher metabolism in frontal regions ($p<0.001$). Among ε4 carriers, FDG metabolism was inversely related to PiB retention in precuneus and IPL ($p<0.001$), but in non-carriers was positively correlated with PiB in prefrontal regions.

Conclusions: These results suggest that ε4 carrier status modulates the relationship of FDG metabolism and PiB retention differentially across the cortex, with carriers exhibiting significant decline in metabolism with increasing amyloid burden. They confirm previously reported increased amyloid burden in CN carriers compared to non-carriers, but suggest that there may be regions of FDG hypermetabolism in CN ε4 carriers relative to non-carriers.

Early ^{11}C-PIB frames and ^{18}F-FDG measures are comparable

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 12

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Despite the availability of amyloid imaging, physiological information in the form of perfusion and metabolism may still be useful in dementia evaluations. In this study we investigated whether early ^{11}C-PIB PET frames (perfusion, pPIB) can provide information equivalent to blood flow and metabolism by assessing the similarity of pPIB and ^{18}F-FDG PET images in patients with AD and FTLD.

Methods: To identify the ^{11}C-PIB frames best representing perfusion, an iterative algorithm was run on the test cohort with various diagnoses (N=10) that created pPIB images across multiple frame ranges and calculated Pearson R values for these frame ranges in comparison to FDG images. Once this perfusion frame range was determined on the test cohort, it was validated on an extended cohort of AD patients (N=42) and FTLD patients (N=31). pPIB diagnosis was then compared to ^{18}F-FDG diagnosis by performing a logistic regression of regional tracer measures (pPIB or ^{18}F-FDG) versus diagnosis.

Results: Minutes 1-8 produced the highest voxel-wise correlation between ^{18}F-FDG and pPIB (R=0.78±0.05). This pPIB frame range was further validated on the extended AD and FTLD cohort across 12 ROIs (R=0.91±0.09). A logistic model using pPIB was able to classify 90.5% of the AD and 83.9% of the FTLD patients correctly. Using ^{18}F-FDG, 88.1% of AD and 83.9% of FTLD patients were classified correctly. The temporal pole and the temporal neocortex were significant discriminators ($p<0.05$) in both models, whereas in the model with pPIB the frontal region was also significant. Regional pPIB and FDG values also showed similar correlations with dementia severity in both groups.

Conclusions: Early PIB frames and ^{18}F-FDG provide similar diagnostic information and are similarly associated with dementia severity. This could be a useful approach, obviating the need for ^{18}F-FDG scans when longer-lived amyloid imaging agents become available.

Consideration of pons normalizing region for [^{11}C]PIB PET scans

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 13

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Introduction: Negligible levels of cerebellar (CER) fibrillar Aß deposits in sporadic Alzheimer's disease (AD) supports the use of CER as reference for normalizing regional [^{11}C]PiB retention measures. A CER reference, however, may not be ideal for all groups, particularly eoFAD or Down's subjects, where significant CER Aß deposition is a common autopsy finding. For this reason, we examined the suitability of pons (PON) as reference region for [^{11}C] PiB studies.

Methods: [^{11}C]PiB PET was performed in 188 subjects (92 Con, 50 MCI, 46 AD) and 47 of these (21 Con, 14 MCI, 11 AD) underwent fully quantitative imaging involving 90 min dynamic scanning, arterial input function determination, and estimation of Logan DVR outcomes (ART90). Regional SUVR 50-70 retention measures were determined for all using CER ($SUVR_{CER}$) and PON ($SUVR_{PON}$) as reference. For the quantitative subjects, results of the SUVR methods were compared to ART90.

Results: CER:plasma ratios reached a plateau of ~6 at 30 min, while PON:plasma plateau was slower and more transient, peaking at ~12 at 50 min. Across cortical areas, $SUVR_{CER}$ was less biased and more highly correlated with ART90 than $SUVR_{PON}$. However, both provided similar Cohen's effect sizes for the distinction of AD and PIB negative Con groups (63/92 Con subjects classed as PiB- using iterative outlier method). This is attributable to lower variance in $SUVR_{PON}$ outcomes despite a compressed dynamic range. PiB positivity cutoffs for $SUVR_{PON}$ identified significantly more PIB+ Cons than $SUVR_{CER}$ cutoffs (40% vs 28%) and included some misclassification.

Conclusion: $SUVR_{PON}$ effectively discriminates amyloid negative controls from AD subjects and may be useful when cerebellar data is unavailable or contraindicated. However, the transient kinetics underlying $SUVR_{PON}$ may lead to less reliable subject classification at the PiB +/- interface, relative to $SUVR_{CER}$.

Complex singular value decomposition improves the image quality of C11-PIB PET images

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 14

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Introduction: C11-PIB PET imaging typically uses multiple frames, which enables the tracer to be followed in time. However, individual frames of PET data become increasing noisy as the duration decreases. Our method, based on the Hilbert transform and Singular Value Decomposition (SVD), expresses the entire dynamic PET study in terms of a few basis components. This provides a dramatic improvement in the appearance of each frame, a reduction in noise, and should improve parameter estimation. Unlike conventional SVD approaches, our approach has complex valued components (magnitude and phase). We refer to our approach as complex SVD (CSVD).

Methods: Dynamic PIB PET brain scans were acquired from three participants. Data from each scan were converted to a 2-dimensional m x n matrix with m representing the number of voxels and n the number of frames. This matrix was used as input to a Hilbert transform, with the result used in SVD. A noise reduced version of the PET image is created by constructing the PET image from only the first 4 components from the SVD process. Evidence of noise reduction was measured as a decrease in the standard deviation (SD) of an ROI placed in the cerebellum.

Results: The average SD of the cerebellum reference ROI was 16% and 10% of the mean values for the unprocessed and CSVD processed frames, respectively. Mean value differences were within 4%. Notably, the second phase component image had strong similarities to a grey/white matter image segmentation.

Discussion: Reduction in measured SD implies a reduction in image noise was achieved by our method. Unlike smoothing, each frame showed dramatic improvement in the definition of structures.

Dynamic PET imaging, typically, requires a tradeoff between image quality and temporal resolution. Our approach allows an improved temporal resolution, while actually improving image quality of each frame.

Automated image quantification methods of PET beta-amyloid scans

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 15

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Background: Automated, objective image processing of PET scans is of potential value when 18F PET amyloid tracers become available for clinical use. We have developed and tested PC executable code as a stand-alone software application which automatically places regions of interest (ROIs) onto human PET brain scans and extracts regional SUVr values for evaluating beta-amyloid levels.

Methods: Over 200 PET scans were analyzed, representing a combined group of healthy controls and subjects with probable Alzheimer's disease (AD). The Alzheimer's Disease Evaluation of Radiotracers software package (ADER): 1) reads the reconstructed images, 2) registers, in 3D, the subject's brain volume to a beta-amyloid PET template, 3) overlays the regions defined in the Automated Anatomical Labeled (AAL) template, 4) identifies areas of white and gray matter, and 5) uses predetermined ROIs from the AAL template to extract regional SUVr values for the 116 VOIs in the AAL template. These same PET scans were analyzed using a gold-standard rigorous manual technique in which MRI scans are co-registered to the PET scans for extracting gray matter counts for SUVr evaluation of amyloid burden.

Results: Compared to the gold-standard analysis, ADER provides similar regional and composite brain SUVr values. The R-values comparing the two methods exceeded 0.8 in all areas commonly evaluated for disease onset, with no statistically significant group differences. Individual scan processing time for ADER is 5% that required for the gold standard.

Conclusions: ADER, a fully automated and objective brain analysis software package: a) decreases processing time to evaluate beta-amyloid concentrations in human brains, b) potentially permits an objective method for comparing clinical results across imaging centers, and c) provides a method for testing currently available radiotracers targeting beta-amyloid and may serve as an adjunct to visual interpretation when these tracers are incorporated into the clinic.

Amyloid deposits in the cerebral cortex of patients with Alzheimer's disease align with cytoarchitectonic properties

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 16

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Background: According to Braak and Braak stage, the amyloid deposits in the post-mortem AD brains are not distributed at random but show a characteristic pattern. They differ in both topographical and neuroanatomical perspectives reaching from basal portions of the isocortex through all isocortical association areas to primary sensory and motor cortices. Of particular a predilection of laminar preference for amyloid deposits is also noticeable. The above characterizations of amyloid distributions are purely derived from mapping on the post-mortem human tissues. Today the introduction of *in vivo* visualizing the amyloid deposits using ^{11}C-PIB in PET technique has made it possible to gain further insight into the neuropathological characterization of AD in their living brains. However (1) a comprehensive mapping of amyloid deposits regarding the cytoarchitecture of the cerebral cortex, and (2) whether the pathological consequences of amyloid deposits within particular type of cerebral cortex appear more indicative of mental decline remain unanswered.

Methods: To address such questions, a cytoarchitectonic probabilistic map whose cytoarchitectonic borders are scientifically testable by an observer- independent approach was for the first time used to quantitatively measuring amyloid deposits across cortical types in AD, MCI PIB+, MCI PIB-, and control subjects. Six cortical types including granular, dysgranular, agranular, allocortex, periallocortex, and corticoid are classified.

Results: Our findings demonstrated a marked variability between AD and MCI PIB- group, and control group for the amount of amyloid deposits for most cortical types, except in allocortex and corticoid, which were nearly invariant between AD and control groups. The amyloid deposits in MCI PIB+ group was significantly greater than those who were PIB- in all cytoarchitectures, with the exception of corticoid.

Conclusions: The amount of amyloid deposits in selective cytoarchitecture differed among groups, suggesting possible disruption of neural transmission involving a large scale of cerebral cortex link the severity of the disease.

A software application for automated analysis of [^{18}F] flutemetamol amyloid imaging data

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 17

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Background: Although visual read can be readily used to categorize amyloid imaging scans into raised or normal uptake levels, image quantification can help in equivocal cases and will also be necessary for longitudinal comparisons. For use in routine clinical practice, a fully automated quantification method will be beneficial to aid in image analysis and reporting.

Methods: The application for quantification of [^{18}F]flutemetamol data takes the patient's PET and MR scan as input and the following processing steps are applied: 1) the MR is co-registered to the PET; 2) the PET is spatially normalized to MNI space and the transformation is applied to the co-registered MR; 3) counts in a reference region (cerebellum or pons) are extracted and an SUVR image is computed; 4) a VOI atlas is applied and SUVR values within cortical regions defined by the atlas are computed; 5) cortical surface projections are computed; and 6) the results are compared to a normals database and z-scores are computed. Result views include VOI SUVR values and z-scores, voxel-based z-scores projected on the subject's MR as well as SUVR and z-score surface projections. The MR is optional and if not available, an MR template (ICBM-152) is used for display purposes.

27 patients with early-stage AD, 20 with MCI and 25 healthy volunteers (HV) from the [^{18}F]flutemetamol Phase II study was used to evaluate the application. The HV data was used to build a normals database. All scans were analyzed and were categorized into raised or normal levels of amyloid based on the z-score value of a composite cortical VOI using a threshold of 2.0. The results were compared to a blinded visual read using five trained readers.

Results: The categorization of scans made by the automated application showed concordance with the visual read results in all the AD and HV scans and in 19 of 20 MCI scans. The results were identical for both reference region methods.

Conclusion: [^{18}F]flutemetamol scans can be reliably categorized using a fully automated software intended for clinical use.

Optimized ROI measures of FDG PET improve characterization of early cognitive impairment and are comparable to PIB PET

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 18

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Objective: PiB or FDG PET may be most helpful when characterizing early cognitive impairment. Improvements in FDG PET data analysis as compared to PiB may be possible by using selective, strategic ROI measurements as hypometabolism occurs selectively early in dementia. We attempted to optimize FDG PET performance as compared to PiB PET and utilize it to discriminate amnestic (aMCI), non amnestic MCI (naMCI) and AD.

Statistical methods: For FDG PET of 96 ADNI subjects with AD and 104 subjects who were cognitively normal (CN), we fit a penalized logistic regression model with AD as the event and the pons-normalized uptake values for 46 bilateral ROIs as the predictors. We selected the model using cross-validation of the area under the ROC curve (AUROC). We used the resulting model to calculate an estimated probability of aMCI, naMCI, or AD by FDG as compared to PiB PET for subjects in our Mayo Clinic cohort that consisted of CN (340), aMCI (91), naMCI (21) and AD (31) subjects.

Results: FDG ROIs that contributed most, and with regression coefficients that were approximately equal in magnitude, were posterior cingulum (PC), angular, and the postcentral gyrus (PG). Reduced uptake in the PC and angular ROIs was associated with increased odds of AD while *increased* uptake in the PG was associated with increased odds of AD, after holding all other ROIs constant. These ROIs were then used as an “optimized” FDG measure. The AUROC (95% CI) for PiB, global FDG and optimized FDG PET for CN vs. aMCI was 0.72 (0.66, 0.78), 0.61 (0.54, 0.67), and 0.71 (0.65, 0.77). PiB and optimized FDG performed significantly better than global FDG. For aMCI vs. naMCI, the values were: 0.73 (0.59, 0.83), 0.53 (0.40, 0.66), and 0.66 (0.52, 0.77) with PiB and optimized FDG both performing better than global FDG. Similar discriminative performance of the PET models was seen when AD was the comparative group.

Conclusion: Our regression model identified an optimized FDG PET analysis method that can help better discriminate between CN, aMCI, and naMCI with discrimination comparable to that of PiB PET. This analysis method may improve the characterization of early cognitive impairment.

Species-dependent metabolism of [C-11]PiB

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 19

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Objectives: Recent studies have found that estrogen sulfotranferase metabolizes [C-11]PiB in rat brain (Cole *et al. PNAS* 2010; **107**: 6222). We sought to determine if this occurs to a significant degree in human brain tissue.

Methods: The radiolabeled metabolite of [C-11]PiB found in rat brain was identified and injected i.v. in mice, rats, and baboons to determine brain uptake. Incubations of [H-3]PiB with mouse, rat, and human brain homogenates were conducted to assess the production of the radiolabeled metabolite in brain tissues.

Results: Spectroscopic and chromatographic properties of chemically synthesized 6-sulfato-PiB were identical to those of the metabolite extracted from rat liver and rat brain. Uptake studies indicated that [C-11]6-sulfato-PiB did not enter mice, rat, or baboon brain to a significant extent following i.v. injection (brain concentrations <0.004 %ID-kg/g). [C-11]6-sulfato-PiB was found to be a major metabolite in extracted rat tissues following i.v. injection of [C-11]PiB while this metabolite was absent in extracted mouse brain, indicating significant species differences in metabolite production *in vivo* in brain. Incubation of [H-3]PiB with fresh and previously frozen mouse brain homogenates did not produce the radiolabeled metabolite, but incubations with fresh and previously frozen rat brain homogenates produced the radiolabeled metabolite. Incubation of [H-3]PiB with human brain homogenates did not produce the radiolabeled metabolite.

Conclusions: The radiolabeled metabolite of PiB found in rat brain is 6-sulfato-PiB. The metabolite is produced peripherally in mice, rats, baboons, and humans, but does not cross the blood-brain barrier to a significant extent. 6-Sulfato-PiB is produced in rat brain, but is not produced to a significant degree in mouse or human brain tissues. As in mice, radioactivity in the brain of human subjects following the i.v. injection of [C-11]PiB is likely comprised of unmetabolized [C-11]PiB.

Profiling of hepatic clearance pathways of PIB with cytochrome P450 phenotyping

POSTER ABSTRACT (Session 2: Saturday)

Poster Board No. 20

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Introduction: The clearance of ^{11}C-PIB from plasma during PET studies has been well described. ^{11}C-PIB is rapidly cleared from blood with 10-20% of unmetabolized tracer remaining 30 minutes after injection. We conducted cytochrome P450 phenotyping to evaluate their contributions to the metabolism of ^{11}C-PIB and profiled liver microsomal incubations for metabolites. We wished to explore whether peripheral clearance could be susceptible to cytochrome P450 inhibition or induction, as may occur over the course of progression studies or treatment trials.

Methods: PIB was incubated up to 1 hour in 5 recombinant human CYPs (rhCYPs, 1A2, 2D6, 2C9, 2C19 and 3A4), and in human liver microsomes (HLM) in the presence/absence of isoform-specific chemical inhibitors. The amount of parent remaining in each sample was quantitated by LC/ToF-MS, and incubates were profiled for phase 1 metabolites using Metabolynx. The relative contribution of each CYP to metabolism was evaluated on the basis of turnover in recombinant systems, and reduction in turnover in the presence of inhibitors.

Results: In rhCYPs, all isoforms turn the compound over to some degree (1A2>2D6>2C19>3A4>2C9). The only observed metabolite was the demethylation product, and appearance of metabolite is related to turnover. LC/UV data suggested that mass balance was not completely covered by the formation of the desmethyl metabolite. In HLM, reductions in turnover were only significant for inhibitors of 1A2 and 3A4. In the absence of inhibitors, there is less desmethyl metabolite at 60 minutes than at 15, suggesting a pathway downstream of demethylation. Inhibition of 3A4 appears to affect the second step, as does 1A2.

Discussion: Based on these experiments, the data suggest polyzymic metabolism, and clearance of PIB is unlikely to be significantly altered by introduction of discontinuation of CYP inhibitors or promoters over the course of serial examinations. *In vivo* experiments can more fully characterise metabolism of PIB.

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