IC-P-024　　BIN1 AND CR1 VARIANTS AFFECT COGNITIVE
PERFORMANCE, NEURODEGENERATION, AND
BRAIN AMYLOIDOSIS IN ADNI SUBJECTS

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**Background:** Genome-wide association studies (GWAS) have identified
many risk genes for Alzheimer's disease (AD). The precise mechanism
through which many of these genes exert their effect on AD remains un-
known. **Methods:** We downloaded the top 10 AD gene single nucleotide
polymorphism, baseline clinical and MR volumetric data (hippocampal,
ventricular, fusiform and entorhinal volumes) of 33 ADNI-2/GO cognitively
normal and 126 mild cognitive impairment subjects. The corresponding
AV45 images were downloaded and processed with the FDA-approved
AmyQ software. For each individual AmyQ derived the mean SUVR in
46 ROIs across the brain with whole cerebellum as a reference. We em-
ployed ANOVA with Bonferroni correction for multiple comparisons to
investigate the effect of minor allele dosage on cognitive and functional per-
formance, neurodegeneration and brain amyloidosis. **Results:** CR1
rs6691117 and BIN1 rs749008 had significant effects on multiple measures.
The minor allele of CR1 rs6691117 showed significant association with
functional decline at 6, 12 and 24 months as measured with the Functional
Activity Questionnaire (FAQ). The minor allele of CR1 rs6691117 also
associated with lower entorhinal and fusiform volumes as well as with
greater brain amyloidosis in the lateral temporal, parietal and occipital asso-
ciation cortices at baseline. The minor allele of BIN1 showed a negative as-
sociation with ventricular size and amyloid load in the frontal association,
sensorimotor, posterior cingulate, medial temporal cortices, the pons, the
midbrain and the lentiform nuclei. **Conclusions:** Both CR1 rs6691117
and BIN1 rs749008 demonstrate significant associations with brain
amyloidosis and neurodegeneration providing further support for the rele-
vance of these two genes to AD pathophysiology. The minor allele of
CR1 rs6691117 appears to have a disease-promoting effect while the minor
allele of BIN1 rs749008 seems to convey a disease-protective effect. The as-
sociations differed significantly in terms of localization in the brain.

IC-P-025　　AGE IS A SIGNIFICANT FACTOR IN
DETERMINING PATHOLOGICAL POSITIVITY
MEASURED WITH [18F]FLORBETAPIR PET

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**Background:** The effect of age on amyloid burden in Alzheimer's Disease
patients and in the discriminative power of amyloid imaging needs to be
determined. **Methods:** 246 Healthy Control (HC), 342 Mild Cognitive
Impairment (MCI) and 138 AD with raw [18F]Florbetapir- and [18F]
FDG-PET data were downloaded from the Alzheimer's Disease Neuroimag-
ing Initiative (ADNI) database. Florbetapir data were analysed using a Flor-
betapir-PET population template and atlas. Two age groups were created;
mean = 70.9 ± 3.5 (young) and 80.9 ± 3.9 (old) years, matched for gender
and disease severity (MMSE). A Receiver Operating Characteristic Anal-
ysis derived a composite neocortex ratio (cctxr) cut-off of 1.34. The AD pa-
tients with Amyloid negative scans had their Florbetapir and FDG scan read
visually. **Results:** The Florbetapir cut-off displayed lower sensitivity and
specificity in the old ADNI group in comparison to the young one (87/87
vs 73/74). The young HC displayed significant lower amyloid in the Poste-
rior Cingulate (1.16 vs 1.24) and the Putamen (1.18 vs 1.25) in comparison
to the older HC. The cctxr values of the old AD patients (oAD) were
bimodal in mixture model analysis whereas the values of the younger AD

(yAD) patients followed a normal distribution. The yAD patients, whether
analysed dichotomously or continuously, displayed significantly higher
values in all ROI examined in comparison to the oAD, except in Putamen
and Occipital lobe. The neocortical FDG pattern of amyloid negative AD
patients (n=27; 10 yAD vs 17 oAD) were all consistent with AD; whereas
10 of the same individuals had negative Florbetapir scans when read visu-
ally. In agreement with the PET template analysis the amyloid negative
oAD had a greater number of Florbetapir scans read as negative (n=8) in
comparison to the yAD (n=2). **Conclusions:** The Florbetapir cut-off, as
well as the visual read of the Florbetapir scans, displayed a diminished
discriminative ability in the old ADNI group in comparison to the younger
patients. The oAD patients showed less prominent amyloid burden and
different distribution of their values in comparison to the yAD group. This
might have important implications for the clinical diagnostic use of
Florbetapir imaging in the oldest patients.

IC-P-026　　HIGH BLOOD PRESSURE, BUT NOT CEREBRAL
AMYLOIDOSIS, IS ASSOCIATED WITH LATE-LIFE
ONSET DEPRESSION IN NON-DEMENTED
ELDERLY

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**Background:** Previous researches on the late-life onset depression (LLOD)
have revealed its association with vascular risk factors, which supported
vascular depression hypothesis. However, several recent studies raised the
possibility of the role of cerebral amyloidosis in LLOD. We aimed to inves-
tigate the independent association of vascular risk factors and cerebral
amyloidosis with the experience of LLOD. **Methods:** Twenty eight non-
demented subjects who first experienced major depressive episode after
age of 60 years were recruited as LLOD patients. Twenty seven non-
demented elderly individuals who had no experience of major depressive
episode were also included as normal control (NC) subjects. All participants
received comprehensive clinical assessment including vascular risk evalua-
tion, 11 C labeled Pittsburgh Compound B (PiB) positron emission tomog-
raphy (PET), and magnetic resonance imaging (MRI). **Results:** There were
no group differences in age, education level but the frequency of female par-
ticipants was significantly higher in LLOD patients compared to NC sub-
jects. Univariate group comparison demonstrated that LLOD subjects had
significantly higher systolic blood pressure than NC. In contrast, no signif-
icant between-group differences were found in regard of mean cortical PiB
retention, and the frequency of PiB-positive and ApoE e4 carriers. Multiple
logistic regression analysis including diagnostic group (LLOD vs. NC) as a
dependent variable showed that systolic blood pressure was significantly
associated with LLOD diagnostic state after controlling age, education,
gender, and mean cortical PiB retention as covariates. Mean cortical PiB
retention did not show any significant association with LLOD state in the
same regression model. **Conclusions:** The results suggest that while
vascular risk, hypertension in particular, is closely related to LLOD as indi-
cated by vascular depression hypothesis, cerebral amyloidosis per se is
probably not a major contributor to LLOD.

IC-P-027　　VALUE OF AMYLOID IMAGING FOR PREDICTING
CONVERSION TO DEMENTIA IN MCI SUBJECTS
WITH INITIALLY INDETERMINATE FDG-PET
SCANS

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**Background:** Amyloid and FDG-PET have been previously independently tested for their abilities to predict future cognitive and functional decline. A subset of subjects who undergo FDG-PET have scans that are ambiguous for predicting subsequent cognitive course. We recently reported that for most of such subjects, this ambiguity could be resolved by repeating FDG-PET one year later (JNM 2013; 54:142). In the present analyses, we tested an alternate strategy: namely, analyzing amyloid PET data obtained contemporaneously with the initial FDG-PET scan. **Methods:** A total of 108 subjects with mild cognitive impairment (MCI) (98 early MCI, 10 late MCI) from the Alzheimer's Disease Neuroimaging Initiative undergoing amyloid and FDG-PET within one month of each other and who had at least 2yrs of clinical follow-up were assessed. Conversion was defined by clinical dementia rating increasing from 0.5 to $\geq$ 1 within 2yrs. Using commercially available software FDA-cleared for clinical use, both a metabolic dementia prognosis index(DPI), optimized for FDG predictive value, and an amyloid tracer retention index(TRI), based on recently published literature and optimized for amyloid imaging diagnostic value, were automatically calculated and used to assess accuracies of predicting conversion to dementia. FDG criteria defined in an independent ADNI-1 data set were applied to classify ADNI-2 subjects as having high, low, or statistically indeterminate risk of progression to dementia. **Results:** Of 108 subjects, 6 (6%) converted to dementia, 12 (11%) reverted to normal cognition, and 90 (83%) remained cognitively stable. By baseline metabolic DPI, 11 (10%) were predicted to show imminent cognitive progression, 71 (66%) had low risk for progression, and 26 (24%) were in the indeterminate range. Repeating FDG for ambiguous scans one year later had yielded a prognostic accuracy of 78%. By amyloid TRI, 19/26(73%) were correctly classified, while applying the DPI to baseline amyloid scans yielded correct classifications in 81% of cases. **Conclusions:** A strategy of following up an indeterminate FDG-PET scan with an amyloid scan obtained within a month had comparable prognostic value for predicting likelihood of conversion of MCI patients to dementia as did repeating FDG-PET scans in such patients one year after the initial FDG-PET.

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IC-P-028

## ASSOCIATION BETWEEN SERUM LIPIDS AND CEREBRAL AMYLOIDOSIS IN COGNITIVELY NORMAL ELDERLY

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**Background:** Cerebral amyloid-beta protein (A$\beta$) deposition has been considered as a key initiating step in Alzheimer's disease (AD) process. Although many preclinical studies have suggested the possible linkage between dyslipidemia and cerebral amyloidogenesis or amyloid deposition, the association between serum lipids and cerebral A$\beta$ deposition in human brain is still poorly known. We aimed to investigate such association in cognitively normal (CN) elderly individuals. **Methods:** Sixty two CN elderly individuals were included. All participants received comprehensive clinical and neuropsychological assessment based on the CERAD protocol, 11 C labeled Pittsburgh Compound B (PiB) positron emission tomography volumetric MRI, and quantification for serum lipid components including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) with apolipoprotein A1 (APOA1) and B (APOB). **Results:** Global cerebral A$\beta$ deposition was defined as mean cortical PiB retention of the cortical regions including frontal, lateral temporal, lateral parietal and precuneus/posterior cingulate cortices. Univariate analyses showed significant positive association of mean cortical PiB retention with the levels of serum TG and APOB, and negative association with HDL-C and APOA1 levels. Multivariate statistical models that controlled age, education, gender, apolipoprotein E ε4 genotype revealed independent associations between the levels of TG and mean

cortical 11 C-PiB retention. Higher serum TG level was associated with heavier cortical 11 C-PiB retention. No association was found between both total cholesterol and LDL-C, and cortical 11 C-PiB retention. **Conclusions:** Our findings strongly support the association between lipid profiles in serum, especially TG level, and the degree of cerebral amyloidosis in cognitively normal elderly people.The findings also suggest that the mechanisms through which serum lipid or lipoproteins affect cerebral A$\beta$ could provide novel targets of AD therapeutics. More specifically, various approaches known to reduce blood TG level, such as moderate exercise and omega-3 fatty acid intake, might be helpful for slowing A$\beta$ deposition and reducing AD occurrence.

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IC-P-029

## ENHANCED BRAIN UPTAKE OF C11-PIB IN MOUSE MODEL OF ALZHEIMER'S DISEASE VIA A SYNTHETIC PEPTIDE CARRIER

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**Background:** Uptake of amyloid imaging agents by specifically binding to amyloid protein in the human brain is compromised by a relatively weak target to background ratio in the range of 3 to 1. Blood brain permeability may be a limitation to improved target to background signal. We tested the ability of a novel blood-brain permeability peptide, termed K16ApoE, to enhance uptake of C11 (Pittsburgh Compound B) PiB in animal models of Alzheimer's disease (AD). **Methods:** AD mice (APP/PS1) (n= 12) and wild type (WT) mice (N=13) were imaged with C11 PiB PET dynamically with K16ApoE and without. Quantitation using SUV measurements of PET uptake in brain, liver and heart was performed. Mice were then sacrificed and autoradiography of brain tissue was performed to assess the quantitative uptake measured in digital light units (DLU). Analysis was performed to compare brain-uptake of PiB on PET and on autoradiography with and without K16ApoE. **Results:** Brain uptake of C11 PiB on PET was enhanced 3 fold in AD mice when delivered with K16APoE at early perfusion phase and 6 fold at 40 minutes (Figure 1; p = 0.01). The degree of enhancement in AD mice on PET was similar to that seen in WT. No enhancement of PiB uptake was seen in heart or liver on PET. Autoradiography confirmed a 20-fold increase in specific brain retention of PiB in amyloid carrying mice when delivered with K16APoE. **Conclusions:** Enhancement of C11 PiB uptake in AD mice on PET imaging occurs by using blood brain barrier permeability enhancement with a novel blood-brain permeability peptide. This model could allow for more sensitive imaging of human brain amyloid in the future.
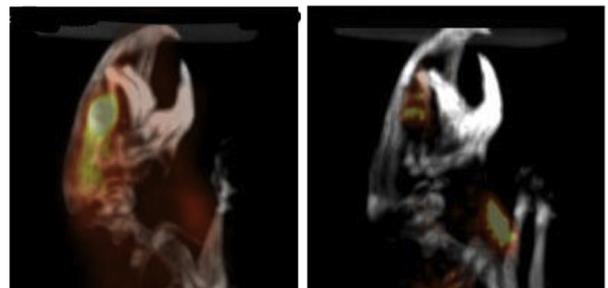


Figure 1. C-11 PiB PET image of an AD mouse performed with (left) and without (right) the blood-brain permeability peptide. Greater brain uptake is seen when the permeability peptide is used.

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IC-P-030

## CLINICAL AND NEUROIMAGING BIOMARKERS OF ALZHEIMER'S DISEASE PRESENTING WITH PROGRESSIVE APHASIA

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