Background: Alzheimer's disease (AD) affects an increasing number of individuals in our societies. It is characterized by accumulation of fibrillary amyloid plaques in the brain. Recently, several studies have emphasized the role of positron emission tomography (PET) using amyloid biomarkers which allow *in vivo* visualization of plaques to distinguish AD pathology from other forms of protein accumulations leading to dementia. However, very few studies have investigated the role of amyloid imaging in the differential diagnosis of atypical/unclear cases, that is complex dementia syndromes where even a comprehensive investigation yields no clear diagnosis. Moreover, no studies have investigated the impact of a correct diagnosis on caregivers and their perception of the process. **Methods:** Using a novel amyloid tracer (NAV4694), we scanned 20 patients with an atypical/unclear dementia syndrome as determined by an experienced behavioral neurologist from a tertiary care center. All patients had a full work-up (i.e., clinical, blood tests, neuropsychological evaluation, structural and functional imaging) yet no certain diagnosis. Amyloid-PETs were either positive or negative based on qualitative and quantitative reads by two independent readers. A questionnaire was given to the treating neurologist to determine whether amyloid imaging allowed a more accurate diagnosis and changed treatment plans. Caregivers were met one month after the revelation of the diagnosis and completed a questionnaire followed by a standardized interview designed to assess its impact. **Results:** A statistically significant increase in confidence levels amongst physicians who ordered amyloid imaging in such cases was found. Revelation of diagnosis to caregivers was associated with better acceptance of the disease as well as a clearer view of future challenges. **Conclusions:** This study suggests that amyloid imaging is useful in the differential diagnosis of atypical/unclear dementias, and has a positive impact on caregivers. Amyloid-PET is indicated in the investigation of complex, atypical/unclear dementing disorders.

IC-P-008 ANXIETY IS ASSOCIATED WITH BRAIN AMYLOIDOSIS IN COGNITIVELY NORMAL AND MILD COGNITIVE IMPAIRMENT SUBJECTS: A [^{18}F]FLUTEMETAMOL PET STUDY

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Background: Neuropsychiatric behaviors are prominent features of Alzheimer's disease (AD) and mild cognitive impairment (MCI). Their association with brain amyloidosis is poorly understood. **Methods:** 65 subjects (27 NC and 38 MCI) who provided yearly neuropsychiatric inventory (NPI) data received [^{18}F]Flutemetamol PET scan 4.6 ($\pm$1.0) year into the study. In our analyses neuropsychiatric symptoms were coded as present if present at one or more visits and absent if never reported by the caregiver. Mean standard uptake volume ratios (SUVR) using the whole cerebellum as the reference were calculated. Brain amyloidosis was defined as mean SUVR$\geq$1.27. We used Chi-square statistics to compare neuropsychiatric symptom prevalence between the amyloid positive and amyloid negative groups. Next we examined the association between amyloid status and neuropsychiatric symptoms using logistic regression with fixed effects for baseline diagnosis, amyloid status, their interaction and cognitive decline (defined as transition from NC to MCI or dementia and transition to MCI to dementia in follow up). **Results:** There were no significant differences in baseline diagnosis, age, sex, education, follow-up duration or time to PET scan between the amyloid positive and amyloid negative groups. Amyloid positive individuals had significantly higher rates of pre-existing anxiety (46 vs. 10%, p=0.0009) and apathy (42 vs. 20%, p=0.05) relative to amyloid negative subjects. Presence of anxiety remained significantly associated with brain amyloidosis after adjusting for baseline diagnosis and longitudinal decline (β=2.5, p=0.05). NC who tested amyloid positive in follow-up were 12 times more likely to develop anxiety compared to amyloid negative NC. MCI who tested amyloid positive in follow-up were 4 times more likely to develop anxiety compared to amyloid negative MCI. **Conclusions:** We found a strong association between amyloid pathology and pre-existing anxiety in both our cognitively normal and MCI subjects. Our analyses suggest that NC subjects develop anxiety at a minimum at the time of but potentially even prior to reaching the threshold for amyloid positivity and suggest that anxiety might be one of the first clinical correlates of brain amyloidosis.

IC-P-009 LONGITUDINAL FOLLOW UP OF MCI PATIENTS WITH NEGATIVE PIB

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Background: The likelihood of progression from MCI to any form of dementia has been suggested to occur at a rate 3 to 5 times higher than those with normal cognition with an annual rate of progression of 12-20%. MCI patients with negative AD biomarkers are supposed to have a lower risk of dementia related to AD. However they still could suffer from other non-AD etiologies and convert to dementia. The aim is to assess the risk of progression to dementia of Mild Cognitive Impairment (MCI) patients with negative PET PIB for Alzheimer's Disease (AD). **Methods:** Thirty-two patients diagnosed with MCI and with negative PET PIB were selected. These patients underwent a complete Neuropsychological battery; brain MRI, PET FDG. Patients were classified into amnestic MCI, multiple domains MCI or non-amnestic MCI. They have been followed up with new neuropsychological testing after AD biomarkers were performed. We considered worsening of MCI status when patients presented worsening of global CDR (conversion to dementia), declination on neuropsychological testing or need to increase anti-dementia medication. **Results:** Fourteen patients were diagnosed with amnestic MCI, 6 with multiple domains MCI and 12 with non-amnestic MCI. All of them had negative PIB scan and were followed up for 1.6 years. The average age was 68 years old and the average educational level was 16 years. Eight of the 32 patients have worsened their clinical status and seven of them (21.8%) have converted to dementia (CDR 1). Only one of the patients that has converted to dementia was diagnosed with Dementia of Alzheimer type, this one had also PET FDG typical of AD. The rest who have converted to dementia were diagnosed with non-AD dementia (2 Frontotemporal Dementia, 2 vascular dementia, 1 suspected of encephalitis and 1 with psychiatric symptoms). **Conclusions:** We found in our MCI with negative PIB cohort the same conversion rate to dementia previously documented in MCI patients alone (12-20%). However, those patients who converted to dementia seemed to be due to non-AD dementia. Therefore,

we conclude that specialists must be concerned even when PIB scan is negative since patients could have dementia due to other causes.

IC-P-010 COMBINATORIAL BIOMARKER ENRICHMENT STRATEGIES FOR MCI CLINICAL TRIAL DESIGN

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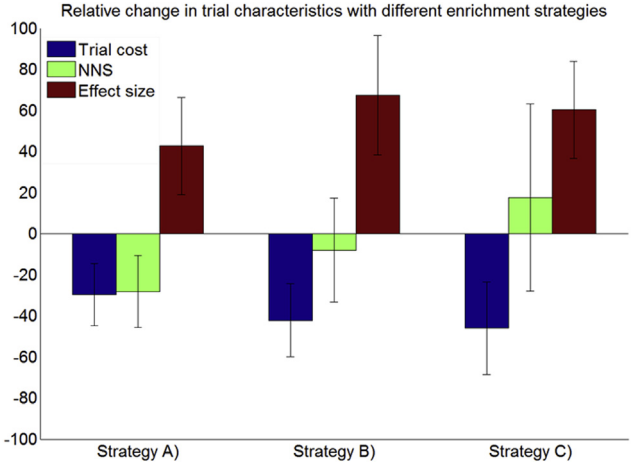
Background: Brain amyloid is part of the definition of Alzheimer's disease (AD) and increasingly used in clinical trial screening. ApoE genotype is associated with presence of brain Amyloid. Biomarkers of neurodegeneration reflect disease progression and can yield theoretical power advantages in mild cognitive impairment (MCI) trials. Whether and how these different markers can be combined, and the implications for trial design, remain open questions. **Methods:** We propose different strategies for patient selection in trial design: A): Screen out amyloid negative (AM-) subjects. B): Screen out subjects with no neurodegeneration. Then further screen out AM- subjects. C): Screen out subjects with no ApoE risk factor. Then further screen out subjects with no neurodegeneration. Strategy A) is the implementation of the Amyloid hypothesis into trial design. Strategy B) follows the hypothesis that amyloid positive (AM+) MCI subjects with neurodegeneration are closer to clinical onset of AD and can have operational advantages over A). Strategy C) hypothesizes that MCI subjects at genetic risk and with neurodegeneration are closer to clinical onset of AD. We hypothesize that Strategy C) is similar with Strategy A) with lower costs. All strategies were assessed on 152 ADNI I and 112 ADNI II subjects with an amyloid marker and clinical follow-up over 24 months. AM+ was defined using established criteria. Neurodegeneration was defined as hippocampal volume below the 15th percentile of healthy subjects. All subjects carrying at least one ε4 allele were defined as being at genetic risk of AD. Trial cost, the number of subjects needed to screen (NNS) and effect size were calculated for both studies and three clinical endpoints, MMSE, CDR-SB and ADAS-Cog 13. **Results:** All three enrichment strategies increased effect size and reduced trial cost in both ADNI studies (Figure 1). Strategy C) resulted in a trial population with 96% AM+ subjects. **Conclusions:** Additional or alternative biomarkers can have operational advantages over using amyloid markers alone for patient selection: Strategy B) helps further reduces costs and screens out slowly progressing AM+ subjects; Strategy C) screens out most AM- subjects without actually measuring amyloid marker.



IC-P-011 COMPARISON OF GLOBAL AND VOXEL-BASED DIAGNOSTIC CLASSIFICATION USING [^{18}F]FLORBETAPIR ROC ESTIMATES

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Background: Accurate diagnosis of Alzheimer's disease and its prodromal state is of paramount importance for effective intervention. Recent studies have shown that imaging biomarkers provides excellent knowledge for classification but failed to account to a compelling classifier due to usage of consolidated information (global SUVR measurements). We hypothesize that using voxel-based information we would be able to better classify Alzheimer's individuals from cognitively normal individuals. **Methods:** [^{18}F]Florbetapir PET images were acquired from 83 subjects (65 Cognitively Normal [CN], 18 Alzheimer's Disease [AD]) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The respective standardized uptake value ratio (SUVR) maps were subsequently generated using cerebellar grey-matter as reference region. Corresponding cortical uptake values (vertex based) were extracted using an average mid-surface structure generated using the study subjects and vertex based Receiver Operating Characteristic (ROC) analysis was carried out to identify the brain regions that best discriminates patients from cognitively normal individuals. ROC analysis based on the consolidated measurements was also carried out as a comparison study. **Results:** Based on the Area Under the Curve (AUC) values, brain regions including precuneus, posterior cingulate cortex, medial orbitofrontal cortex and temporal lobe showed the best separation between patients and normal individuals with an AUC value of over 0.8. The same regions show sensitivity values of over 0.7 and specificity values of over 0.8 (Figure 1). In the study done using consolidated measures, the best separation resulted in AUC of 0.6872 with a specificity of 0.8 and sensitivity of 0.722. **Conclusions:** ROC estimate of regional concentrations of brain [^{18}F]Florbetapir may contribute to the identification of pathological patterns of amyloidosis in predementia population and will enable accurate and effective classification in to the disease stages. The preliminary data reported here support the hypothesis that regional amyloidosis might contribute to a better discrimination between AD patients and cognitively normal individuals when compared with a global measurement, and the regions that allows best separation need to be used to generate a better consolidated measurement.