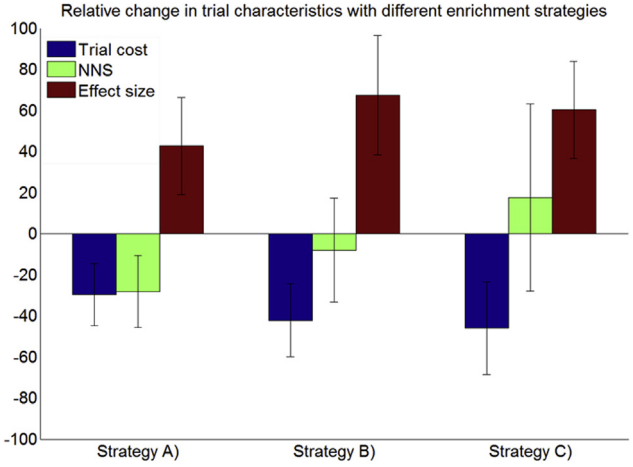
we conclude that specialists must be concerned even when PIB scan is negative since patients could have dementia due to other causes.

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

Robin Wolz[1,2], Adam J. Schwarz[3], Peng Yu[3], Katherine R. Gray[1,2], Derek L. Hill[2], *[1]Imperial College London, London, United Kingdom; [2]IXICO, London, United Kingdom; [3]Eli Lilly and Company, Indianapolis, IN, USA. Contact e-mail: rwolz@ixico.com*

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

Sulantha S. Mathotaarachchi[1], Sara Mohades[2], Monica Shin[2], Thomas Beaudry[2], Andrea Lessa Benedet[2], Tharick Ali Pascoal[1], Seqian Wang[2], Sarinporn Manitsirikul[3,4], Maxime J. Parent[5], Min Su Kang[6], Vladimir Fonov[7], Chang Oh Chung, Sr.,[2], Serge Gauthier[2], Pedro Rosa-Neto[2,8,9,10], *[1]McGill University, Montreal, QC, Canada; [2]McGill Centre for Studies in Aging, Montreal, QC, Canada; [3]McGill Centre for Studies in Aging/Translational Neuroimaging Laboratory, Montreal, QC, Canada; [4]Bangkok General Hospital, Payathai, Thailand; [5]McGill Centre for Studies in Aging, Verdun, QC, Canada; [6]McGill University Centre for Studies in Aging, Verdun, QC, Canada; [7]Image Processing Laboratory, Montreal Neurological Institute, McGill University, Montreal, QC, Canada; [8]Centre for Studies on Prevention of Alzheimer's Disease (StoP-AD Centre), Douglas Mental Health Institute, Montreal, QC, Canada; [9]Douglas Hospital Research Centre, Montreal, QC, Canada; [10]Translational Imaging Laboratory, Montreal, QC, Canada. Contact e-mail: sulantha.s@gmail.com*

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.

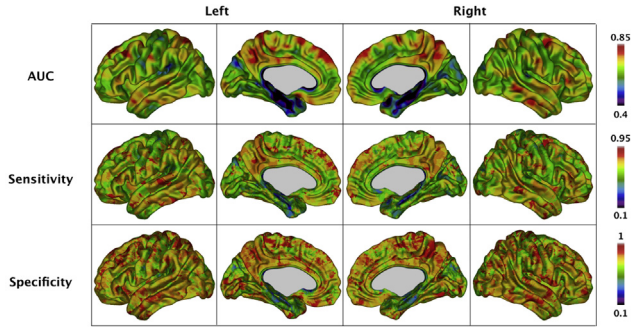


Figure 1. Image shows Area Under the Curve (AUC), sensitivity and specificity of the regional ROC analysis. Regions including the precuneus, posterior cingulate cortex, medial orbitofrontal cortex and temporal lobe showed the highest AUC value indicating the best separation between AD patients and CN individuals. These regions also show a high sensitivity and specificity.

IC-P-012 SHOULD A GLOBAL OR A REGIONAL MEASURE OF AMYLOIDOSIS BE USED IN A LONGITUDINAL STUDY?

Sulantha S. Mathotaarachchi[1], Sara Mohades[2], Monica Shin[2], Thomas Beaudry[2], Andrea Lessa Benedet[2], Tharick Ali Pascoal[1], Seqian Wang[2], Sarinporn Manitsirikul[3], Maxime J. Parent[4], Min Su Kang[5], Vladimir Fonov[6], Chang Oh Chung, Sr.[2], Serge Gauthier[2], Pedro Rosa-Neto[2,7,8,9], *[1]McGill University, Montreal, QC, Canada; [2]McGill Centre for Studies in Aging, Montreal, QC, Canada; [3]McGill Centre for Studies in Aging/Translational Neuroimaging Laboratory, Montreal, QC, Canada; [4]McGill Centre for Studies in Aging, Verdun, QC, Canada; [5]McGill University Centre for Studies in Aging, Verdun, QC, Canada; [6]Image Processing Laboratory, Montreal Neurological Institute, McGill University, Montreal, QC, Canada; [7]Centre for Studies on Prevention of Alzheimer's Disease (StoP-AD Centre), Douglas Mental Health Institute, Montreal, QC, Canada; [8]Douglas Hospital Research Centre, Montreal, QC, Canada; [9]Translational Imaging Laboratory, Montreal, QC, Canada. Contact e-mail: sulantha.s@gmail.com*

Background: Global amyloid burden is widely used as measurement to assess the brain amyloidosis in many studies, but its reliability in a longitudinal study is yet to be fully understood. In this study we developed a surface based technique to assess the relationship between amyloidosis and neurodegeneration measured by hypo-metabolism across diagnosis stages of Alzheimer's disease. We hypothesize that the regional effects of amyloid retention on the rate of hypo-metabolism depend on the diagnosis stage. We will further investigate whether a consolidated measure of amyloidosis (global SUVR) can capture the effects shown in the regional analysis. **Methods:** The study included 213 subjects (65 Cognitively Normal [CN], 111 Early Cognitive Impairment [EMCI], 19 Late Cognitive Impairment [LMCI], 18 Alzheimer's Disease [AD]) taken from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Their [^{18}F]Florbetapir and [^{18}F]FDG PET images were acquired 24 months apart and the SUVR maps were subsequently generated using cerebellar grey/white matter and pons as reference regions for [^{18}F]Florbetapir and [^{18}F]FDG PET images, respectively. The effects of [^{18}F]Florbetapir on yearly rate of metabolism were computed using vertex-based regression models including the baseline glucose metabolism, age, gender and APOE genotype as covariates. **Results:** During the 24-month observation period, for the subjects in CN and EMCI stages, the regional rates of hypo-metabolism did not show a linear relationship to the localized amyloid burden. However, at LMCI and AD stages, regional amyloid load shows a linear relationship to the rate of metabolic decline in precuneus and temporo-parietal areas (Figure 1). In contrast, the global measure of amyloid burden showed a linear relationship with metabolism only in temporal regions. **Conclusions:** Based on the results it is evident that in LMCI and AD stages, the rates of hypo-metabolism at temporo-parietal areas as well as in the precuneus depend on the local tissue amyloid burden, while in CN and EMCI stages, it is independent. Absence of a relationship in similar regions with the global measure amyloidosis suggests that a consolidated measure cannot represent the brain amyloid burden in all disease stages, and perhaps, a new consolidation masks need to be generated based on disease stage.

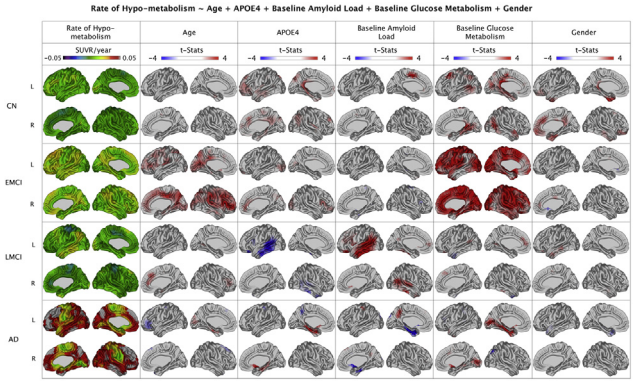


Figure 1. Vertex-based multivariate linear regression model showing the effect of amyloid load on the rate of hypo-metabolism in each disease stage, corrected for baseline glucose metabolism, age, gender and apoe genotype. Only LMCI and AD stages show positive effect from amyloid load on hypo-metabolism in temporo-parietal and precuneus regions.

IC-P-013 WITHDRAWN

IC-P-014 HOW TO FOLLOW UP AND CLUSTER SUBJECTS BY LONGITUDINAL CHANGES OF FIBRILLARY AMYLOID IMAGING AND CSF BIOMARKERS? A 24-MONTH FOLLOW UP

Sarinporn Manitsirikul[1,2], Sara Mohamedes[3], Sulantha S. Mathotaarachchi[3], Thomas Beaudry[3], Serge Gauthier[3], Pedro Rosa-Neto[3], *[1]McGill Centre for Studies in Aging/Translational Neuroimaging Laboratory, Montreal, QC, Canada; [2]Bangkok General Hospital, Payathai, Thailand; [3]McGill Centre for Studies in Aging, Montreal, QC, Canada. Contact e-mail: ju_sarinporn@yahoo.com*

Background: Presence of amyloid is associated with cognitive decline. Fibrillar amyloid deposition levels in brain can be detected by increase uptake of amyloid in [^{18}F] Florbetapir (AV45) PET and decrease of csfA$\beta_{1\text{-}42}$. Combination of biomarkers performed better for diagnosing AD. Tau was strongest predictor of conversion but Jack et al. propose that CSFA$\beta_{1\text{-}42}$ was abnormal more often than t-tau. Here, we studied relationship between regional distributions of brain fibrillar amyloid deposition, neurodegenerative biomarkers in brain(FDG) and CSF(tau), brain structural change and cognitive function at 24-month follow-up to find the best method to follow up the subjects. **Methods:** We analyzed 182 participants from ADNI and try to cluster the subjects by MCLUSTforR. We divided the