Background: Cognitively healthy asymptomatic elders (HC) with evidence of Alzheimer’s disease brain pathology are considered to be "preclinical AD" by research criteria. The current study had two objectives: 1) to evaluate the accuracy of volumetric MRI, FDG-PET and neuropsychological tests for predicting the conversion from HC to MCI and AD dementia. 2) To map MRI and FDG-PET brain differences between HC converters vs. stable HC. Methods: ROIs of FDG-PET and MRI grey matter volume were defined as spatial clusters of significant decreases in 78 prodromal AD patients compared to 30 HC subjects (CSF Aβ > 192 pg/ml), recruited in ADNI. This analysis resulted in a tempo-parietal FDG-PET ROI and a medial temporal grey matter ROI that subsequently were applied to baseline scans of 54 HC subjects for predicting the conversion to MCI and AD dementia (range of follow-up period: 36 - 54 months). In logistic regression analyses, the neuroimaging ROIs, free recall score and trail making test (TMT-B) were tested as predictors of conversion. Note that a subset of 15 HC subjects had been also used for defining the ROIs in the first step, but exclusion of these subjects in the logistic regression analyses did not alter the predictive value of the ROIs reported below. In voxel-based group comparisons, differences in MRI grey matter and FDG-PET between HC converters and stable HC were tested at α < 0.05 (cluster-corrected). Results: Eleven of 54 subjects converted to MCI (n = 9) or AD (n = 2). The FDG-PET (p = 0.004) but not MRI ROI was a significant predictor of HC conversion status. TMT-B (p = 0.03) but not free recall performance significantly predicted conversion. The combination of FDG-PET and TMT-B yielded a sensitivity of 82% and a specificity of 93%. Voxel-based group comparison of FDG-PET revealed reduced metabolism within the medial temporal and frontal cortex in HC converters compared to stable HC. No group differences in grey matter were detected. Conclusions: Reduced tempo-parietal FDG-PET and TMT-B performance may indicate preclinical AD. Our results suggest that FDG-PET abnormalities can be detected earlier than grey matter atrophy in the course of AD.

Table 1

| Predictor Variables          | ADNI          |          | Correct classification % |          |
|------------------------------|---------------|----------|--------------------------|----------|
|                              | AUC (SE)      | Sensitivity at 80% (90%) |                      | AUC (SE) | Sensitivity at 80% (90%) | 
| Age                          | 0.497         | 12.74 (5.73) | 55.67                    | 0.739    | 52.61 (29.85) | 
| MMSE                         | 0.655         | 37.88 (19.20) | 65.54                    | 0.778    | 41.41 (26.79) | 
| Hippocampal Vol.             | 0.725         | 48.05 (34.42) | 64.60                    | 0.753    | 62.07 (41.38) | 
| Entorhinal Volume            | 0.718         | 50.65 (35.71) | 67.16                    | 0.773    | 67.86 (50.00) | 
| AVLT                         | 0.756         | 49.47 (25.16) | 44.33                    | 0.849    | 71.63 (53.13) | 
| FAQ                          | 0.738         | 49.05 (35.90) | 44.33                    | 0.708    | 45.46 (32.83) | 
| Age, MMSE                    | 0.659         | 36.94 (18.79) | 63.48                    | 0.821    | 72.73 (39.39) | 
| Hippocampal and Entorhinal Volumes | 0.744 | 55.84 (35.71) | 68.98                    | 0.824    | 67.86 (67.86) | 
| AVLT/SRT and FAQ             | 0.811         | 62.74 (42.68) | 72.70                    | 0.879    | 78.13 (59.38) | 
| Model 1                      | 0.828 (.024) | 73.25 (49.05) | 73.40                    | 0.921 (.027) | 90.63 (81.25) | 
| Model 2                      | 0.783 (.028) | 57.79 (40.26) | 73.72                    | 0.866 (.046) | 82.14 (71.43) | 
| Model 3                      | 0.865 (.022) | 75.33 (55.20) | 77.01                    | 0.940 (.027) | 92.59 (88.89) | 
| Model Comparisons            | AUC Difference | .00428 | .0035 ** | AUC Difference | 0.0028 | .0710 .0254 * |
| Model 1 vs. Model 2          | 0.0396         | .2271     | 0.0428 | .0011 ** | 
| Model 1 vs. Model 3          | 0.0428         | .1979     | 0.0710 | .0254 * |
| Model 2 vs. Model 3          | 0.0824         | .3618     | 0.0042 | 

A threshold of 0.5 was used on predicted risk derived from the logistic regression models. Area under the curve (AUC) was derived from Receiver Operating Characteristic (ROC) analyses. N = 282 (157 converters) in ADNI and N=126 (33 converters) in QD. The differences between models in AUCs are slightly different from the direct subtraction of AUCs between models because of missing data that ranged from 1% to 4% for the variables examined in ADNI and 1% to 5% for the variables examined in QD.

*p < .05, ** p < .01.
Results: There were 126 patients in QD and 282 MCI patients in ADNI with follow-up by 3 years. Within each sample, the differences in AUCs between the statistical models were very similar. Adding hippocampal and entorhinal cortex volumes to the model containing age, Mini Cortex volumes to the model containing A VLT/SRT, FAQ, age and MMSE decreased AUC, with sensitivity increasing by 2% in ADNI and 2% in QD for a fixed specificity of 80%. Conversely, adding episodic verbal memory (SRT/AVLT) and FAQ to the model containing age, Mini Mental State Exam (MMSE), hippocampal and entorhinal cortex volumes increased the AUC in ADNI (P<0.0001) and QD (P=0.0254), with sensitivity increasing by 17% in ADNI and 10% in QD for 80% specificity.

Conclusions: The predictor models showed similar differences from each other in both studies, supporting independent validation. MRI hippocampal and entorhinal cortex volumes showed limited added predictive utility to assessment of memory and informant report of function. Evaluation of cognitive function and the informant’s report of functional decline is important, and validation of biomarkers with the use of the same cut-points and ranges for abnormality across studies is needed before considering widespread clinical application.

O3-03-03 COGNITION, HIPPOCAMPAL VOLUME AND FIBRILLAR Aβ BURDEN AS PREDICTORS OF COGNITIVE DECLINE: THREE-YEAR FOLLOW-UP RESULTS FROM AIBL

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Background: To evaluate imaging and cognitive measures in healthy controls (HC) and mild cognitive impairment (MCI) participants in the Australian Imaging Biomarkers and Lifestyle study of aging (AIBL), to assess their prognostic ability in relation to disease progression over 3 years. Methods: Episodic memory, hippocampal volume (HV), and Aβ burden were evaluated at enrollment with clinical follow-up at 20 and 36 months in 194 HC, 92 MCI, and 79 Alzheimer’s disease (AD) participants. C-11 PiB SUVR cut-off was 1.5 for high amyloid burden derived from previous studies, while cut-offs for HV and memory score were established using ROC analyses of the AIBL AD and HC. Cox proportional hazards were used to calculate risk ratios adjusted for age, gender and years of education. Results: At baseline, 74% of AD and 61% of MCI had significantly lower HV than HC, while 98% of AD, 65% of MCI and 31% of HC had high PiB (PiB+). At 3 years, 46 MCI (50%) met criteria for dementia (41 AD, 5 non-AD). Progression to AD occurred in 60% of PiB+ MCI vs. 10% of PiB- MCI (RR 8.7 P<0.0001), while 17% of PiB- MCI progressed to other dementias. Severe memory impairment predicted progression in MCI (RR 14.1 P=0.0002) and much more strongly than HV (RR 2.3). Of the PiB+ HC, 15% developed MCI or AD compared to 3% of PiB- (RR 2.7 P=0.05). Memory score and HV also predicted progression in HC (RR 3.4 P=0.04 and RR 2.7 P=0.05 respectively). With multivariate analysis PiB (RR 5.9) and memory score (RR 5.5) remained significant predictors in MCI but only memory score (RR 3.6) remained in HC. Conclusions: Extensive Aβ deposition precedes cognitive impairment and is associated with a higher risk of cognitive decline. High Aβ burden and low episodic memory were strongest predictors of progression of cognitive impairment in this large cohort with 3 year follow-up.

O3-03-04 COMBINED FORNIX DEGENERATION AND CA1 HIPPOCAMPAL LOSS PREDICT CONVERSION OF NORMAL TO MCI

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Background: Recent biomarker studies have suggested an ordered sequence of changes due to Alzheimer’s pathology. In this schema, regional brain atrophy is thought to precede earliest detectable cognitive changes, which signal conversion of normal to MCI. To date, studies of structural change in MCI have focused primarily on gray matter structures, although Fornix microstructure is known to change early in the course of AD. It has not yet been determined whether fornix microstructure and regional hippocampal atrophy contribute jointly or independently to earliest cognitive decline. Methods: 124 cognitively normal subjects were analyzed for fornix volume and FA, radial and total volume hippocampal values, as well as age, education, gender, ethnicity, episodic memory and non-fornix white matter FA and followed longitudinally. Within the time frame of the study, 104 subjects remained normal and 20 converted to MCI, based on an increase of CDR sum from 0 to 0.5. A parametric survival analysis model was used to identify significant predictors of conversion to MCI that included hippocampal volume, fornix volume, CA1 radial distance, whole brain FA and adjusting for age, education, gender and ethnicity. Results: Subjects converting to MCI had approximately 0.5 sd lower episodic memory (P=0.0003) and executive function performance (P=0.0006) at baseline. Average time of follow-up was 3.4 + 1.7 years. Significant independent predictors of conversion to MCI were age (P=0.002), episodic memory (P=0.03), average hippocampal CA1 radius (P=0.01) and fornix FA (P=0.04) in a parametric survival analysis. Hippocampal CA1 radii were also significantly associated with Fornix FA (P=0.002) independent of total hippocampal volume. Conclusions: The combined results suggest that decline of the entire CA1–fornix circuit, rather than CA1 alone, may be one of the earliest structural changes related to incipient cognitive loss. This is strengthened by the accompanying decline of episodic memory and the lack of significance of non-fornix FA, fornix volume or total hippocampal volume for predicting conversion. These results suggest that entire cognitive circuits may be specifically affected in the transition from normal cognition to MCI.

O3-03-05 A BLOOD-BASED GENE EXPRESSION TEST TO DETECT PRODROMAL ALZHEIMER’S DISEASE

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Background: A blood based test for prodromal Alzheimer’s disease (AD) will allow for early initiation of treatment before clinical symptoms of