(RAVLT and Trails B),hippocampal volume and cerebral glucose metabolism (CMRglu) with respect to APOE genotype (epsilon4+ or epsilon4-), age and AV-45 SUVR. The following path model was considered: APOE genotype and age as predictor variables; AV-45 SUVR as a mediator variable; and Trails B Score, RAVLT, hippocampal volume and mean FDG SUVR as outcomes. **Results:** Standardized regression weights for significant correlation are reported in Figure 1. In the path model, APOE genotype was strongly associated with amyloid SUVR, weakly associated with CMRglu and cognitive scores (and not at all to hippocampal volume). In contrast there was a stronger relationship between AV-45 SUVR, on the one hand, and CMRglu, hippocampal volume and cognitive function, on the other hand, independent of APOE genotype. Age was more strongly associated with hippocampal volume thanwith CMRglu and the cognitive measures. **Conclusions:** The effect of APOE genotype on cognition, hippocampal volume and CMRglu is mediated primarily by its effect on increasing amyloid deposition, with relatively little independent contribution by APOE genotype.

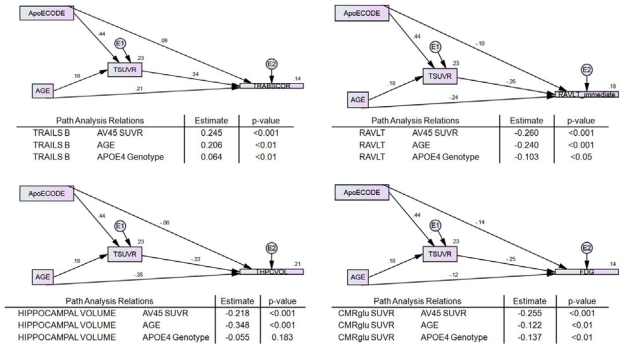

Figure 1. Path Analytic Models addressing dependencies of Cognitive Variables [Trails B (A) and RAVLT (B)], Volumetric variable [hippocampal volume] (C) and Metabolic variables [rCMRglu](D) to APOE e4 genotype, age and mean [18F]-florbetapir AV45 SUVRs, showing the Standardized Regression Weights for each correlation. The associations of Age (0.179, p<0.001) and APOE genotype (0.440 p<0.001) with AV-45 SUVR were found to be significant across all path models.

IC-P-004 THRESHOLDS FOR BRAIN AMYLOID CONCENTRATION IN RELATION TO DISEASE STAGE, COGNITION, BRAIN METABOLISM, BRAIN ATROPHY, AND APOE GENOTYPE IN THE ADNI COHORT

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Background: To determine vulnerability of cognitive, functional, cerebral metabolic rate of glucose (CMRglu) and brain volume variables to fibrillar amyloid burden, in relation to APOE genotype and disease stage in the ADNI Cohort. **Methods:** Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Baseline demographic, clinical, neuropsychological, and volumetric MRI data for 385 subjects [55 diagnosed with mild Alzheimer's disease (AD), 91 with late MCI (LMCI), 114 early MCI (EMCI), and 125 cognitively normal (CN) cases] were explored in relation to APOE genotype (ApoE4+ (n=136) versus ApoE4- (n=211)). Piecewise Linear Models were used to assess the concurrent relationships between mean brain standardized uptake value ratios (SUVRs) of [18F]-florbetapir (AV45) uptake, auditory verbal learning test (AVLT), CDR sum of boxes (CDRsb) scores, regional CMRglu values and brain volumes on MRI, as a function of e4 status. Inflection points for SUVR scores in relationship to each of these regression curves were identified by computing points on the linear models at which the second derivative changes sign. **Results:** Overall, the association of SUVR scores was stronger for ApoE4+ than ApoE4- subjects (p<0.01). The coefficients of determination were: entorhinal cortex volume (R 2 for ApoE4+ = 18.14% and ApoE4- = 9.91%), mean CMRglu (R 2 for ApoE4+ = 13.89% and ApoE4- = 13.38%), RAVLT (R 2 for ApoE4+ = 9.36% and ApoE4- = 5.79%), and Hippocampal volume (R 2 for ApoE4+ = 16.71% and ApoE4- = 7.06%). Inflection points were identifiable for all the variables (Figure 1), and were at higher SUVR scores in ApoE4+ (μ =1.298, f = 0.13) than ApoE4- (μ =1.072, f = 0.08) subjects (p<0.001). The SUVR at the inflection points among cognitive (μ =1.270, f = 0.13), atrophy (μ =1.230, f = 0.16) and CMRglu (μ =1.201, f = 0.20) variables were different. **Conclusions:** For a given level of neurodegeneration (as reflected in cognitive scores, CMRglu values and regional brain atrophy in AD affected regions), the corresponding AV45 SUVRs and inflection points are strongly influenced by factors such as APOE genotype. These findings indicate the absence of a fixed threshold for "positive" or "negative" amyloid PET s cans.

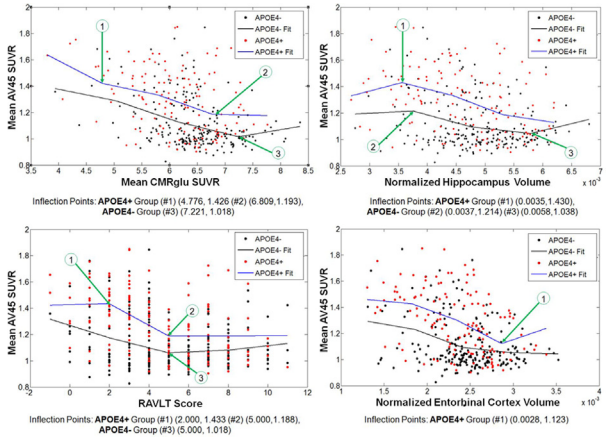

Figure 1. Fibrillar amyloid burden mean AV45 SUVR versus (A) Cerebral Metabolic Rate of glucose (CMRglu), (B) Rey Auditory Verbal Learning Test (RAVLT), (C) Normalized Hippocampus Volume and (D) Normalized Entorhinal Cortex Volume showing variations in mean AV45 SUVR for the inflection points of among cognitive, volumetric and functional measures. The inflection points are listed below each corresponding graph.

IC-P-005 DISCREPANCIES BETWEEN PIB AMYLOID IMAGING IN TYPICAL AND ATYPICAL CLINICAL DIAGNOSIS: PRACTICAL UTILITY IN A MEMORY CENTER

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Background: The 11C-PIB-PET is a tracer that specifically detects amyloid deposition in life. It has the advantage of being minimally invasive, but it is expensive and its use care in the clinical spectrum of degenerative diseases has not been stipulated. Our goal is to determine the utility of 11C-PIB-PET analyzing the presence of amyloid in patient groups high and low pretest probability. **Methods:** Observational cross-sectional study 144 patients underwent 11C-PIB-PET in our center. They were assigned into categories of high or low pretest probability according to clinical suspicion of AD pathology. The high probability group included: mild cognitive impairment (MCI), amnestic, amnestic and other domains MCI, Alzheimer disease (AD), posterior cortical atrophy (PCA), logopenic Primary Progressive Aphasia (PPA), amyloid angiopathy and mixed dementia. The low assumption group included: normal controls, non-amnestic MCI, non logopenic PPA and frontotemporal dementia (FTD). **Results:** 29.67% of patients with high pretest probability had 11C-PIB-PET negative, and 26.42% in

the low-probability was positive. The syndromic diagnoses that most discrepancies were found were: amnestic MCI (37% had negative PIB), amnestic and other domains (40%, negative PIB) into high probability group; non-amnestic MCI (33% positive PIB), and non-logopenic PPA and FTD (33% and 45% positive PIB) into low probability group. Normal controls and AD patients (typical and atypical presentation) were the most consistent across clinical and molecular diagnostics. **Conclusions:** There were discrepancies in molecular diagnosis in both high and low probability groups. The implications of these inconsistencies were different between each clinical category. The most important contribution to the diagnosis of 11C-PIB-PET is really significant in cases of early-onset AD, and atypical presentation (PPA, FTD and PCA).

IC-P-006 HIPPOCAMPAL ATROPHY: AUTOMATED VOLUMETRY VS VISUAL EXAMINATION—AN ARG ADNI COHORT ANALYSIS

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Background: Hippocampal atrophy is one of the earliest findings in Alzheimer Disease (AD). MRI volumetry is a low-cost in vivo study to quantify brain atrophy Our goal is to analyze MRI brain volumetry in Arg._ADNI cohort in order to determine the clinical usefullness. As a secondary objective a comparation between visual and automated analysis of the hippocampal atrophy was performed. **Methods:** 45 patients of the Argentina-ADNI database were included (12 controls, 12 early mild cognitive impairment (eMCI), 13 late MCI and 8 dementia AD). Neuropsichological assessment, labs, CSF biomarkers, fdg-PET and PiB-PET were performed. All of them had a MRI Brain Volumetry including Absolute Hippocampal volume, whole brain volume and a hippocampal/whole brain ratio (Hi/WBV). Study of correlation between hippocampal visual and automated examination was performed on 49 patients between cognitive neurologist and neuroradiologist. **Results:** Whole brain volume was similar between groups, but hippocampal volume was inversely related to clinical impairment. Specially Hi/WBV ratio. 88% of AD, 46% of LMCI and 42% of eMCI were below a cut-off point of 0.0025. In addition, 92% of control patients had a Hi/WBV superior to 0.0025 value. On the other hand, 68.4% of patients who had Hi/WBV<0.0025 had another positive AD biomarker (FDG-PET, Pib-PET or CSF profile) versus 34,6% of those >0.0025. With a specificity of 0.72, sensitivity 0.61, PPV 0.68 and NPV 0.66. A visual examination of hippocampal atrophy showed low concordance in the control group and a high influence of the years of training. **Conclusions:** A reliable cutoff point to measure hypocampal atrophy could be determined using MRI volumetry, this finding correlates with clinical impairment and the presence of other AD biomarkers. Visual examination of MRI seems to be insufficient to assess hyppocampal atrophy in the early stages of the disease even for a specialist in neuroradiology or cognitive neurology.

IC-P-007 PATTERNS OF [C-11]PIB AMYLOID BURDEN THAT ARE ASSOCIATED WITH CEREBROSPINAL FLUID AD BIOMARKERS IN PEOPLE AT RISK FOR ALZHEIMER'S DISEASE: FINDINGS FROM THE WRAP STUDY

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Background: Further research is needed on the full spectrum of cerebrospinal fluid (CSF) markers and their relationships to amyloid imaging in all stages of Alzheimer's disease (AD). This study examines a wide range of CSF markers in a relatively young, preclinical cohort enriched with risk factors (APOE4 and AD parental history) for AD in conjunction with [C-11]Pittsburgh Compound B (PiB) positron emission tomography (PET). **Methods:** N=106 Participants (mean age 60.43, SD 5.66) enriched with genetic and familial risk for AD from the Wisconsin Registry for Alzheimer's Prevention (WRAP) underwent PET-PiB imaging and lumbar puncture and were grouped as amyloid-positive (PiB+), amyloid-indeterminate (PiBi), or amyloid-negative (PiB-) based on the amount and pattern of amyloid deposition. ANOVAs were conducted on CSF Aß, tau, and CSF markers of inflammation (MCP-1, YKL-40) and axonal injury (NFL). Regional voxel-wise regression analyses of PiB scans were performed to examine the spatial relationship between CSF measures and amyloid load. **Results:** ANOVA indicated a pattern of lower Aß42 in PiB+ compared to PiBi or PiB- while the ratios of Aß40, p-tau, t-tau, MCP-1, YKL40, and NFL to Aß42 were all higher in PiB+ compared to PiBi or PiB-. Correlations with extracted PiB distribution volume ratio from precuneus, and voxel-wise regressions, p(FWE)<0.05, showed a negative relationship between Aß42 and PiB while the ratios to ABß42 all showed a positive relationship to PiB. A common voxel-wise pattern was observed for all CSF, but most notably in p-tau/Aß42 and t-tau/Aß42 in regions previously implicated in symptomatic AD. **Conclusions:** Group comparisons and voxel-based tests demonstrated that CSF ratios to Aß42 accounted for more variance than any single CSF measure alone. The positive relationship with PET-PiB likely reflects simultaneous amyloid deposition and early neurodegenerative processes. Voxel-based results are consistent with previous findings that the regions commonly labeled as the default mode network are functionally and anatomically affected in AD, even before symptom onset. An overlay of voxel-based results of Aß42, 1/Aß42 and p-tau/Aß42 indicate that Aß42 is likely driving the overall pattern, while tau provides additional sensitivity. This study shows that, together, CSF and PET-PiB provide critical and striking information about this important preclinical disease stage.

Table
CSF Statistical Contrasts by Amyloid Grouping

CSF marker	ANOVA	Group Contrast	Post-hoc T-test (Tukey-corrected)
Aß42	P=0.014	PiBi > PiB+	P=0.040
		PiB- > PiB+	P=0.013
Aß40/42	P=0.000	PiB+ > PiB-	P=0.000
		PiB+ >PiBi	P=0.000
t-tau/Aß42	P=0.000	PiB+ > PiB-	P=0.000
		PiB+ >PiBi	P=0.000
p-tau/Aß42	P=0.000	PiB+ > PiB-	P=0.000
		PiB+ >PiBi	P=0.000
MCP-1/Aß42	P=0.003	PiB+ > PiB-	P=0.002
		PiB+ >PiBi	P=0.045
YKL40/Aß42	P=0.000	PiB+ > PiB-	P=0.000
		PiB+ >PiBi	P=0.000
NFL/Aß42	P=0.000	PiB+ > PiB-	P=0.000
		PiB+ >PiBi	P=0.001
1/Aß42	P=0.000	PiB+ > PiB-	P=0.000
		PiB+ >PiBi	P=0.004