Recently, CAP deficits have also been shown to identify responders to donepezil treatment (Ouchi, 2015). Previously, we reported a relationship of CAP to age and genetic risk. We now report studies on the relationship between CAP and imaging markers of pre-symptomatic AD. **Methods**: Over 200 participants in the PREVENT-AD cohort of asymptomatic persons with a parental history of AD completed the Synthetic Sentence Identification with Ipsilateral Competing Message (SSI-ICM) task, a measure of speech comprehension with background noise. We explored whole brain cortical thickness in 148 of these subjects using CIVET 1.12 (Lerch, 2005). SurfStat was used to correct for multiple comparisons using Random Field Theory with \( p < 0.05 \). We extracted temporal gyrus functional connectivity with regions of interest selected a priori using NIAK (Bellec, 2011). **Results**: After controlling for age, cortical thickness analyses revealed association of SSI-ICM performance with thickness of rostral mid frontal cortex (rMFC) and the pars orbitalis (PO). In subjects who had a successful tone test (\( n = 43 \)), we found decreased resting state connectivity between the temporal gyri (TG) and dorsomedial prefrontal cortex (dMPFC) in persons with reduced performance on the SSI-ICM (age-corrected partial correlations \( r = 0.345 \) for left and \( r = 0.313 \) for right, \( p < 0.05 \) for both). We also found a correlation between decreased connectivity of the left TG and posterior cingulate cortex (PCC), and lower SSI-ICM scores (\( r = 0.328, p < 0.05 \)). **Conclusions**: Tests of central auditory processing appear to correlate with the thickness of several cortical structures, and with resting state connectivity between areas implicated in auditory scene analysis and speech processing. These areas are commonly affected by AD pathology, suggesting that CAP dysfunction may serve as an indicator of AD progression in pre-symptomatic disease.

**P2-140**

CONVERGENT EVIDENCE OF PUPILLARY RESPONSE AS AN EARLY INDICATOR OF LOCUS COERULEUS DYSFUNCTION AND RISK FOR MCI

Jeremy A. Elman¹, Matthew Panizzon¹, Donald J. Hagler, Jr.¹, Christine Fennema-Notestine¹, Carol Franz¹, Lisa T Eyler¹, Eric Granholm², Amy J. Jak³, Michael Lyons⁴, Anders M. Dale¹, William S. Kremen², ¹University of California, San Diego, La Jolla, CA, USA; ²University of California, San Diego/VA San Diego Healthcare System, La Jolla, CA, USA; ³University of California, San Diego/VA San Diego Healthcare System, La Jolla, CA, USA; ⁴Boston University, Boston, MA, USA. Contact e-mail: jaelman@ucsd.edu

**Background**: There is a great need for early screening tools of Alzheimer’s disease (AD) as pathology may be present decades before symptom onset. Task-evoked pupil dilation (TEPD) is a well-validated measure of mental effort which may detect subtle declines in cognitive efficiency prior to impaired performance. During a digit span task, TEPD increases with cognitive load but decreases after capacity is exceeded. TEPD is also linked to functioning of the locus coeruleus (LC) which has been proposed as an initial site of abnormal tau (Braak & del Tredici, 2010). Damage to the LC may also contribute to key aspects of AD pathophysiology, an increased inflammatory response and amyloid-beta deposition. We examined whether TEPD is related to measures of resting-state functional MRI (rs-fMRI), inflammation, and cognitive performance that can all be linked to LC functioning. **Methods**: 980 late middle-aged subjects (ages 56-65) in the Vietnam Era Twin Study of Aging were defined as cognitively normal or as having mild cognitive impairment (MCI). Pupil dilation was measured during a concurrent digit span task. These subjects also completed tests of processing speed and blood was collected to measure levels of C-reactive protein (CRP), a marker of inflammation. A subset of subjects (\( n = 447 \)) also received rs-MRI scans in which variance of the blood-oxygenation-level-dependent (BOLD) signal was measured in regions selected a priori that are modulated by the LC. **Results**: Consistent with previous findings by our group, subjects with MCI and lower working memory ability demonstrated greater drop-off in TEPD between moderate and high task loads, consistent with system capacity being overwhelmed. Higher BOLD variance, higher CRP, and slower processing speed were
associated with more dilation (effort) at low loads and less task appropriate increase in dilation at moderate loads. Conclusions: These results suggest that pupillometry is associated with altered brain activity, inflammatory state, and cognitive performance. This provides converging evidence for LC involvement, an early site of AD pathology which may provide the neural substrate linking these measures together. Given the relatively young age of the sample, TEPD may provide a simple and useful psychophysiological biomarker for early identification of AD risk.

**P2-142** COMPARISON OF T-TAU, NEUROGRANIN AND NFL AS CSF NEURODEGENERATION MARKERS IN ALZHEIMER’S DISEASE

Niklas Mattsson1,2,3, Philip S. Insel4,5, Sebastian Palmqvist1, Erik Portelius6, Henrik Zetterberg6,7, Michael W. Weiner8, Kaj Blennow6, Oskar Hansson1,8, Skåne University Hospital, Department of Neurology, Lund, Sweden; 2Clinical Memory Research Unit, Lund University, Lund, Sweden; 3Center for Imaging of Neurodegenerative Diseases, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; 4University College London, Institute of Neurology, London, United Kingdom; 5University of California, San Francisco, San Francisco, CA, USA. Contact e-mail: niklas.mattsson@med.lu.se

**Background:** Cerebrospinal fluid (CSF) levels of tau (total tau, T-tau) is a biomarker for neurodegeneration in Alzheimer’s disease (AD). Recently, other CSF biomarkers have been proposed for neurodegeneration in AD, including neuronfilament light (NFL) and the synaptic protein neurogranin (Ng). It is not clear if combinations of these biomarkers improve the diagnostic accuracy for AD, and to what degree they reflect similar or different aspects of the disease.

**Methods:** We examined 93 AD patients, 187 mild cognitive impairment (MCI) patients and 109 controls (CN) from Alzheimer’s Disease Neuroimaging Initiative (ADNI). We compared the diagnostic accuracy of T-tau, NFL and Ng for AD versus CN, and progressive versus stable MCI, and tested associations between baseline biomarkers and longitudinal outcomes (cognition, MRI volumetrics, FDG-PET, and white matter hyperintensities, WMH). Based on the theory that AD starts with amyloid-β (Aβ) accumulation and progresses with secondary pathologies, we tested if T-tau, Ng and NFL differed between Aβ-negative CN (based on CSF Aβ42) and Aβ-positive CN, MCI, and AD dementia subjects, and if Aβ-status had different associations with the different biomarkers at different clinical stages.

**Results:** T-tau, Ng and NFL were all significant pre-dictors of AD diagnosis and combinations improved the diagnostic accuracy compared to individual biomarkers. The biomarkers had different associations with different outcomes at baseline and longitudinally. T-tau and Ng were primarily associated with cognition and hippocampal atrophy, while NFL was also associated with baseline effects, and had stronger associations with ventricular volume and WMH. Several associations between biomarkers and outcomes were significant even when adjusting for the other biomarkers. When comparing Aβ-negative CN with Aβ-positive subjects, we found increased T-tau and Ng in Aβ-positive CN, MCI and AD, and increased NFL in all MCI and AD subjects, independent of Aβ-status. Within diagnostic groups, Aβ was more strongly associated with Ng and T-tau than with NFL. **Conclusions:** T-tau, Ng and NFL provide partly independent information in AD. Combinations of these biomarkers may increase the diagnostic accuracy for AD. T-tau and Ng are closely related to Aβ-dependent processes while NFL also reflects other processes related to subcortical atrophy and white matter pathology.