reference region. Quantitative MRI 3 measured the volumes of cerebral gray matter, hippocampi, and white matter hyperintensities (WMH) on MRI scans obtained nearest to PiB PET. Mixed effects regression models of individual trajectories of memory and executive functioning were estimated with random effects of baseline level and rate of change. Demographic variables, baseline clinical diagnosis, global amyloid burden defined as the average DVR from cortical regions associated with Alzheimer's amyloid pathology 1, MRI variables, and vascular risk factor burden defined as the simple sum of vascular risk factors present were entered into the model as fixed effects in a stepwise fashion. All fixed effects whose association with memory or executive function passed a p-value threshold of 0.01 were carried forward to subsequent models. **Results:** In the first model, baseline diagnosis was significantly associated with both baseline level and rate of change in memory and executive function. Global amyloid burden, when added to this model, was significantly associated with baseline level and rate of change in one or both cognitive domains. When MRI measures were further added to the model, only hippocampus volume was a significant predictor of baseline level and rate of change in cognitive domains. When total vascular risk factor burden was further added to the model, it significantly predicted baseline level of executive function. When total vascular risk factor burden was replaced with individual risks factors, only hyperlipidemia was significantly associated with baseline level of memory performance (Table). **Conclusions:** In a cohort of community based, predominantly nondemented individuals, greater vascular risk factor exposure was significantly associated with baseline level of executive function in a model that included amyloid burden and MRI measures of vascular and neurodegenerative disease. We conclude that modifiable vascular risk factors are important to cognitive health even after adjusting for the concurrent effects of cerebral amyloid burden.1. Marchant NL, Reed BR, DeCarli CS, et al. Cerebrovascular disease, beta-amyloid, and cognition in aging. Neurobiol Aging 2012;33:1006 e1025-1036.2. Marchant NL, Reed BR, Sanossian N, et al. The Aging Brain and Cognition: Contribution of Vascular Injury and Abeta to Mild Cognitive Dysfunction. JAMA neurology 2013:1-8.3. DeCarli C, Reed BR, Jagust W, Martinez O, Ortega M, Mungas D. Brain behavior relationships among African Americans, white, and Hispanics. Alzheimer Dis Assoc Disord 2008;22:382-391.

IC-01-05 REGIONAL CEREBRAL BLOOD FLOW PATTERN ASSOCIATED WITH SUBCLINICAL COGNITIVE DECLINE AND VASCULAR RISK FACTORS IN HEALTHY, MIDDLE-AGED MALES

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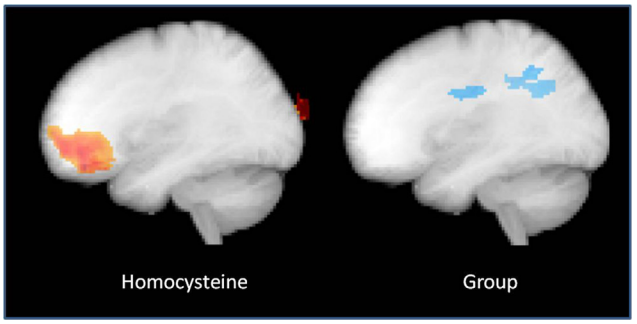
Background: Age related cognitive dysfunction and structural brain changes have been associated with both cerebral blood flow (CBF) changes and vascular risk factors such as homocysteine, suggesting a role of cerebrovascular function in the brain aging process and neurodegenerative disease. However, little is known about the interplay between these factors in normal brain aging preceding overt cognitive dysfunction. We investigated the relationship between cognitive function, structural brain changes, vascular risk factors and CBF in a group of 175 middle aged malesubject with or without life-time decline in cognitive function. **Methods:** The Metropolit cohort consists of all men born in Copenhagen in 1953, with a cognitive examination at age approx. 20 years. Among 2000 healthy participants retested at age 57, we included those with highest relative increase (Group A, n=87) or decrease (Group B, n=88) in cognitive function. Subjects underwent cognitive testing, blood sampling and structural MRI. Regional CBF measurements were obtained using the QUASAR arterial spin labeling sequence and boht absolute and normalized perfusion maps were calculated using FSL tools taking individual hematocrit values into account. Phase contrast mapping was used to measure global brain blood flow, and by normalizing to brain volume a measure of mean global CBF was obtained. Structural brain changes were assessed by calculation brain parenchymal fraction (BPF) and Fazeka's white matter lesion score. **Results:** The two groups did not significantly differ with regard to mean global CBF or structural brain changes. Also no correlation between vascular risk factors or structural brain changes with mean global CBF were observed. Cognitive decline was associated with significantly lower perfusion in the precuneal area in voxelwise analysis ($p<0.001$ uncorr), and in regional analysis ($p<0.05$) also in post. cingulate and calcarine areas. Further, homocysteine was associated with relative hyperperfusion in the inferior mesial frontal areas ($p<0.001$ uncorr.) independently of the group effect. **Conclusions:** The main findings are that both pre-symptomatic lifetime cognitive decline and homocysteine are independently associated with specific regional CBF patterns but not to global CBF changes or structural measures of brain aging.



IC-01-06 AORTIC BLOOD PRESSURE IS ASSOCIATED WITH WHITE MATTER HYPERINTENSITY FRACTION IN POSTMENOPAUSAL WOMEN WITH NORMAL BLOOD PRESSURE

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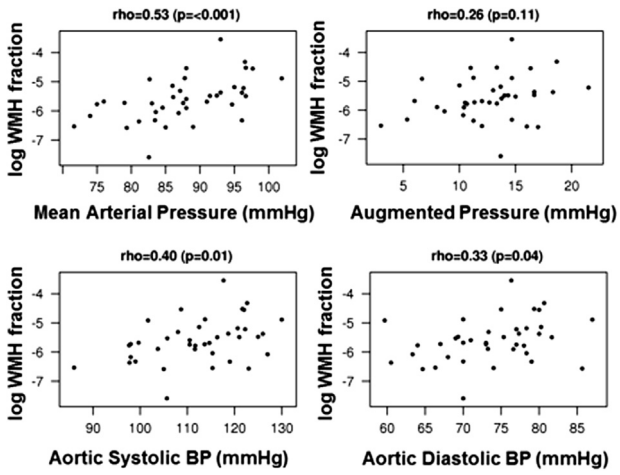
Background: White matter hyperintensity (WMH) load on T2-weighted MRI is a risk factor for cognitive impairment. Hypertension is associated with high WMH load, suggesting a vascular etiology. However, the relationship of blood pressure (BP) within the normal range and WMH is not established. Elevations in aortic hemodynamics precede the appearance of clinically-diagnosed hypertension. In normotensive individuals, noninvasive measurements of aortic hemodynamics provide information on vascular function. Early alterations in aortic hemodynamics may be mechanistically linked to the development of WMH. In this context, the hormonal shifts during menopause accelerate vascular dysfunction in women, putting postmenopausal women at increased risk for both hypertension and WMH. Our objective was to determine the association between aortic hemodynamics and WMH in healthy, postmenopausal women with normal blood pressure. **Methods:** We examined 39 nonhypertensive postmenopausal women (age 60±3 yrs; body mass index 27±4 kg/m 2). Mean arterial blood pressure (MAP) was determined using a brachial arm cuff and was within normal range (88±7 mmHg). Aortic hemodynamics were estimated using beat-by-beat tonometry (Sphygmocor). WMH was calculated from fluid-attenuated inversion recovery MRI using a semi-automated segmentation algorithm. WMH volume was divided by the total white matter volume to calculate WMH fraction in each subject. **Results:** Aortic hemodynamics included systolic BP (112±10 mmHg) and diastolic BP (74±7 mmHg). WMH fraction was positively associated with aortic systolic BP ($r=0.40$;$p<0.01$) and aortic diastolic BP ($r=0.33$;$p<0.05$). After adjusting for age, aortic systolic BP and WMH remained significantly associated ($p=0.03$). Age and diastolic BP had a significant interaction ($p=0.02$), with WMH fraction increasing less with aortic diastolic BP in older ages. **Conclusions:** In postmenopausal women with normal blood pressure, higher aortic systolic pressure was associated with greater WMH load. Because increases in aortic hemodynamics precede changes in brachial cuff BP measurements, our results suggest that monitoring aortic hemodynamics may identify individuals at accelerated risk for WMH and guide early treatment to reduce development of WMH and cognitive impairment.



SATURDAY, JULY 12, 2014
ALZHEIMER'S IMAGING CONSORTIUM (IC)
IC-02
PRECLINICAL ALZHEIMER'S DISEASE AND BIOMARKERS

IC-02-01 GREATER SUBJECTIVE COGNITIVE CONCERNS CORRESPOND WITH ADVANCING STAGES OF PRECLINICAL AD

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Background: Emerging evidence suggests that subjective cognitive concerns (SCC) may herald initial cognitive decline at the preclinical stage of Alzheimer's disease (AD). While previous studies have investigated the relationship between SCC and amyloid (A b) burden and neurodegeneration (ND) separately, it remains unclear if increased SCC correlates with successive stages of preclinical AD. **Methods:** We studied 186 CN individuals from the Harvard Aging Brain Study (Clinical Dementia Rating Scale = 0, Geriatric Depression Scale <11). A b status was determined with PIB-PET imaging and ND was measured using two a priori imaging markers: hippocampus volume and glucose metabolism extracted from AD-vulnerable regions. A subjective cognitive concerns composite was calculated using subscales from three questionnaires. Linear regression models with A b and ND status as simultaneous predictors were used to predict SCC, controlling for age, education, and gender. A secondary analysis included APOE ε4 carrier status as a predictor. SCC were also examined across groups based on joint A b and ND status (Stage 0: A b -/ND-; Stage 1: A b +/ND-, Stage 2: A b +/ND+, and SNAP: A b -/ND+). **Results:** SCC was not related to age, gender or education. Both A b (p=0.002) and ND (p=0.036) were independently associated with greater SCC. APOE ε4 carrier status was not related to SCC and did not impact results from the initial model. Examination across groups revealed that SCC was greater in stage 2 compared to stage 0 (p<0.001), stage 1 (p=0.20) and SNAP (p=0.03). Furthermore, Stage 0 had lower SCC than both SNAP (p = 0.07) and stage 1 (p=0.03). There was no difference between Stage 1 and SNAP (p=0.45). **Conclusions:** We demonstrate independent and additive contribution of A b and ND status in predicting SCC, unaffected by APOE ε4 carrier status, such that individuals who are positive on both biomarkers show the greatest SCC, while individuals positive for a single biomarker show intermediate levels of SCC. This pattern is consistent with the hypothesis that the combination of A b and ND markers increases likelihood of cognitive decline.

IC-02-02 THE USE OF NEUROIMAGING BIOMARKERS IN PRECLINICAL ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is a major public health issue. Atrophy assessed with structural MRI, hypometabolism and amyloid load have been recently proposed as neuroimaging biomarkers for the preclinical diagnosis of the disease, consistently with the amyloid cascade hypothesis. However the meaning and the relevance of each neuroimaging biomarker remain not completely understood. Our objective was to characterize populations defined according to each neuroimaging biomarker (i.e. positive vs negative cases) to further our understanding of their use in the preclinical diagnosis of AD. **Methods:** We prospectively included 54 healthy controls (HC) over 50 years old who all performed structural MRI, FDG-PET and Florbetapir-PET in the same neuroimaging center. All HC were then dichotomized into positive or negative independently for each of the three biomarkers considering the regions of greatest changes in AD. Then, demographic, neuropsychological and neuroimaging data were compared between positive and negative cases classified from MRI, FDG-PET or Florbetapir PET data. **Results:** Amongst the 54 HC, 12 (22%), 12 (22%) and 8 (15%) individuals were positive for atrophy, hypometabolism and amyloid deposition, respectively. Demographic and neuropsychological data were not statistically different between the positive and the negative subgroups, except for age that was higher in the amyloid positive versus negative subgroup. Interestingly, the atrophy positive subgroup showed both hippocampal and frontal atrophy, and posterior cingulate, temporoparietal and frontal hypometabolism compared to the atrophy negative subgroup. There was no difference in amyloid load between atrophy or hypometabolism positive versus negative subgroups and the amyloid positive group didn't differ from the amyloid negative in terms of grey matter atrophy or hypometabolism. However, when considering individuals with atrophy and/or hypometabolism together, there seems to be an inverse relationships between amyloid and neurodegenerative biomarkers such that those with more neurodegeneration tend to show lower amyloid deposition and reversely. **Conclusions:** The atrophy biomarker is associated with a mixed pattern of AD-like and frontal. The three biomarkers provide independent rather than redundant information. Our findings show that individuals tend to have either neurodegeneration or amyloid load but not both, suggesting additive rather than sequential/causative links between the current neuroimaging biomarkers in the pathological process of AD.

IC-02-03 EXISTING THRESHOLDS FOR PIB POSITIVITY ARE TOO HIGH

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Background: There is no consensus among researchers about the thresholds that define amyloid positivity and there is little known about the earliest phases of amyloid accumulation in older adults. The present study had two goals: first, to derive a cutoff that captures early accumulation using both DVR and SUVR data from our subjects and, secondly, to examine their pattern of amyloid accumulation. **Methods:** Amyloid accumulation was investigated in 152 cognitively