IC-01-03 PARTICIPATION IN COGNITIVELY STIMULATING ACTIVITIES IS ASSOCIATED WITH BRAIN STRUCTURE AND COGNITIVE FUNCTION IN PRECLINICAL ALZHEIMER'S DISEASE

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Background: Prior studies have shown that participation in cognitively-stimulating activities might delay the onset of Alzheimer's disease (AD). However, the mechanism underlying this effect is not well understood. In this study, we tested the hypothesis that frequent participation in cognitively-stimulating activities, specifically those related to playing games and puzzles, favorably alters brain structure and cognition in a sample of middle-aged adults at increased risk for AD. **Methods:** Three hundred twenty-nine cognitively normal, middle-aged adults (age=60.31±6.25 years, 69% women, 40% APOE4 positive, and 74% with family history of AD) enrolled in the Wisconsin Registry for Alzheimer's Prevention participated in this study. They reported their current engagement in cognitive activities using a modified version of the Cognitive Activity Scale (CAS), underwent a structural MRI scan, and completed a comprehensive cognitive battery. FreeSurfer was used to derive gray matter (GM) volumes from AD-related regions of interest (ROIs), and composite measures of episodic memory and executive function were obtained from the cognitive tests. Covariate-adjusted least squares analyses were used to examine the association between the Games item on the CAS (CAS-Games) and both GM volumes and cognitive composites. **Results:** Higher scores on CAS-Games were associated with greater GM volumes in several ROIs including the hippocampus, posterior cingulate, anterior cingulate, and middle frontal gyrus (p's<.04). Similarly, CAS-Games scores were positively associated with scores on the Immediate Memory, Verbal Learning & Memory, and Speed & Flexibility domains (p's<.02). These findings were not modified by known risk factors for AD, including age, APOE4, and family history of AD. In addition, the Total score on the CAS was not as sensitive as CAS-Games to the examined brain and cognitive measures. **Conclusions:** Engagement in cognitively-stimulating activities is associated with increased brain volume and higher cognitive test scores in middle-aged adults at risk for AD. These findings suggest that, for some individuals, participation in cognitive activities pertinent to game playing may help prevent AD by preserving brain structures and cognitive functions vulnerable to AD pathophysiology. More detailed studies investigating the effects of specific gaming activities would help further our understanding of how an active lifestyle might help delay the development of AD.

IC-01-04 VASCULAR RISK FACTORS IMPACT COGNITION INDEPENDENT OF PIB PET AND MRI MEASURES OF AD AND VASCULAR BRAIN INJURY

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Background: Alzheimer's and vascular disease are two common causes of cognitive decline among older individuals. The recent advent of amyloid imaging in combination with MRI markers of vascular brain injury and AD-associated neurodegeneration and detailed medical history allows for in vivo assessment of the combined influence of vascular and Alzheimer' s disease on cognitive decline. Recent work by our group finds evidence that vascular brain injury is significantly associated with cognitive ability independent of amyloid load among individuals selected for high vascular risk 1, 2. We extended this work by examining the impact of vascular risk factors, vascular brain injury, AD-associated neurodegeneration, and amyloid load in a community based cohort more representative of the general population. **Methods:** The study consisted of 65 subjects aged 73.2 + 7.2 years of age, 65% of whom were Caucasian, 17% Hispanic, 14% African American and 4% Asian with mean educational achievement of 15.5 + 3.3 years; 54% were female and 57% cognitively normal, 38% mild cognitively impaired 5% were demented at baseline assessment. Subjects received yearly psychometrically matched measures of memory and executive function over 5.2 + 2.3 years. A history of hypertension, diabetes, elevated cholesterol, coronary artery disease, or cerebrovascular disease was assessed at baseline evaluation and 79% had one or more risk factor, with a median of 2. All subjects underwent PiB PET imaging quantified using a distribution volume ratio with cerebellar

Table

	Episodic Memory			Executive Function		
Variable	Estimate	Std Error	Prob>|t|	Estimate	Std Error	Prob>|t|
Intercept	-0.695765	1.491768	0.6429	-1.288254	1.017152	0.2115
Time	-0.018035	0.047031	0.7021	-0.018371	0.032862	0.5771
Education	0.0736248	0.028469	0.0128*	0.0896571	0.019485	<.0001*
Dx[Demented]	0.0956777	0.358098	0.7900	-0.104587	0.244562	0.6700
Dx[MCI]	-0.497818	0.198377	0.0142*	-0.138016	0.135823	0.3129
Time*Dx[Demented]	0.1214084	0.087934	0.1697	0.0778725	0.062235	0.2125
Time*Dx[MCI]	-0.052757	0.047178	0.2656	-0.063648	0.033445	0.0590
Baseline Age	-0.012767	0.014517	0.3834	-0.016105	0.009934	0.1116
Global PiB DVR	-1.173637	0.373716	0.0027*	-0.191387	0.255029	0.4564
Time* Global PiB DVR	-0.229223	0.073818	0.0031*	-0.143367	0.048869	0.0058*
Hippocampal Volume	371.5397	140.2651	0.0109*	289.92276	96.18849	0.0042*
Time* Hippocampal Volume	13.263985	23.2546	0.5719	38.80356	15.05114	0.0167*
Vascular Burden	-0.138457	0.075923	0.0744	-0.127056	0.052021	0.0185*
Time* Vascular Burden	-0.00711	0.012867	0.5839	0.0093575	0.008315	0.2714
Hyperlipidemia	0.2122436	0.088242	0.0199*	0.1010828	0.064604	0.1242
Time* Hyperlipidemia	0.0234361	0.015491	0.1385	-0.002628	0.01073	0.8085

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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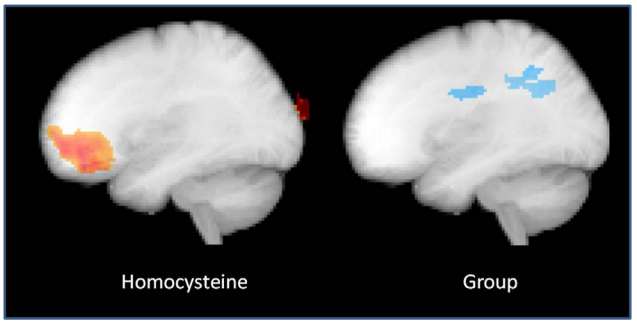
Background: Age related cognitive dysfunction and structural brain changes have been associated with both cerebral blood flow (CBF) changes and vascular risk factors such as homocysteine, suggesting a role of cerebrovascular function in the brain aging process and neurodegenerative disease. However, 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.