for improved cognitive aging, including in the presence of Alzheimer's disease, is warranted.

**Categories:** Aging
**Keyword 1:** brain plasticity
**Keyword 2:** dementia - Alzheimer's disease
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## 6 Pulse Pressure and APOE ε4 Dose Interact to Affect Cerebral Blood Flow in Older Adults Without Dementia

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**Objective:** Alterations in cerebral blood flow (CBF) are associated with risk of cognitive decline and Alzheimer's disease (AD). Although apolipoprotein E (APOE) ε4 and greater vascular risk burden have both been linked to reduced CBF in older adults, less is known about how APOE ε4 status and vascular risk may interact to influence CBF. We aimed to determine whether the effect of vascular risk on CBF varies by gene dose of APOE ε4 alleles (i.e., number of ε4 alleles) in older adults without dementia.
**Participants and Methods:** 144 older adults without dementia from the Alzheimer's Disease Neuroimaging Initiative (ADNI) underwent arterial spin labeling (ASL) and T1-weighted MRI, APOE genotyping, fluorodeoxyglucose positron emission tomography (FDG-PET), lumbar puncture, and blood pressure assessment. Vascular risk was assessed using pulse pressure (systolic blood pressure – diastolic blood pressure), which is thought to be a proxy for arterial stiffening. Participants were classified by number of APOE ε4 alleles ($n_{0\ alleles}$ = 87, $n_{1\ allele}$ = 46, $n_{2\ alleles}$ = 11). CBF in six FreeSurfer-derived *a priori* regions of interest (ROIs) vulnerable to AD were examined: entorhinal cortex, hippocampus, inferior temporal cortex, inferior parietal cortex, rostral middle frontal gyrus, and medial orbitofrontal cortex. Linear regression models tested the interaction between categorical APOE ε4 dose (0, 1, or 2 alleles) and continuous pulse pressure on CBF in each ROI, adjusting for age, sex, cognitive diagnosis (cognitively unimpaired vs. mild cognitive impairment), antihypertensive medication use, cerebral metabolism (FDG-PET composite), reference CBF region (precentral gyrus), and AD biomarker positivity defined using the ADNI-optimized phosphorylated tau/β-amyloid ratio cut-off of > 0.0251 pg/ml.
**Results:** A significant pulse pressure X APOE ε4 dose interaction was found on CBF in the entorhinal cortex, hippocampus, and inferior parietal cortex (*p*s ≤ .005). Among participants with two ε4 alleles, higher pulse pressure was significantly associated with lower CBF (*p*s ≤ .001). However, among participants with zero or one ε4 allele, there was no significant association between pulse pressure and CBF (*p*s ≥ .234). No significant pulse pressure X APOE ε4 dose interaction was found in the inferior temporal cortex, rostral middle frontal gyrus, or medial orbitofrontal cortex (*p*s ≥ .109). Results remained unchanged when additionally controlling for general vascular risk assessed via the modified Hachinski Ischemic Scale.
**Conclusions:** These findings demonstrate that the cross-sectional association between pulse pressure and region-specific CBF differs by APOE ε4 dose. In particular, a detrimental effect of elevated pulse pressure on CBF in AD-vulnerable regions was found only among participants with the ε4/ε4 genotype. Our findings suggest that pulse pressure may play a mechanistic role in neurovascular unit dysregulation for those genetically at greater risk for AD. Given that pulse pressure is just one of many potentially modifiable vascular risk factors for AD, future studies should seek to examine how these other factors (e.g., diabetes, high cholesterol) may interact with APOE genotype to affect cerebrovascular dysfunction.

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**Categories:** Neuroimaging
**Keyword 1:** apolipoprotein E
**Keyword 2:** cerebral blood flow
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## Paper Session 03: Parkinson's disease related topics

9:00 - 10:30am
Thursday, 2nd February, 2023
Pacific Ballroom E

Moderated by: Cady Block

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### 1 Basal Forebrain Free Water Fraction is Associated with Cortical Cholinergic Levels in Idiopathic Parkinson's Disease

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**Objective:** Cognitive dysfunction is a common non-motor symptom of Parkinson's disease (PD). Cognitive decline in PD is likely associated with dysfunction in the cholinergic system, which is affected by synuclein pathology early in the disease course. Recent studies have shown an association between reduced integrity of the basal forebrain (BF), which provides cholinergic innervation to most of cortex, and diminished cognitive functioning in PD. Specifically, those with PD and reduced cholinergic innervation also have higher rates of cognitive impairment. However, no study has directly investigated the relationship between basal forebrain integrity and cortical cholinergic levels. In the present study, we examined this relationship through measures of basal forebrain microstructural integrity and cholinergic nerve terminal density in cortical and subcortical gray matter.

**Participants and Methods:** Participants included 92 non-demented individuals with idiopathic PD (M:F=64:28; Age=67.0±7.1 yrs) who underwent structural MRI, diffusion MRI, and [18F] fluoroethoxybenzovesamicol (FEOBV) cholinergic PET imaging. We used a basal forebrain and region of interest defined by AssemblyNet, which uses ensembles of pretrained convolutional neural networks to create a full brain segmentation. Bilateral putamen from this atlas was also included as a control region. We measured microstructural integrity using free water fraction (FWF), a diffusion MRI-derived metric of extracellular water that associates with cellular density and neuroinflammation. For PET data, we computed the distribution volume ratio (DVR) by regions as defined by FreeSurfer. A factor analysis of DVR in all 88 FreeSurfer ROIs resulted in seven clusters of ROIs covering 1) widespread bilateral cortical regions (PC1); 2) subcortical and limbic regions (PC2); 3) bilateral cingulate regions (PC3); 4) left frontal regions (PC4); 5) right frontal and temporal regions (PC5); 6) cerebellum (PC6); and 7) bilateral entorhinal cortex and left temporal cortex (PC7). We performed seven separate regression analyses per ROI (controlling for age and disease duration) to evaluate the association between BF FWF and cholinergic levels in these regions. To determine if these ROIs showed unique associations with BF FWF, we then entered ROIs with a significant association with BF FWF as independent variables in a stepwise regression with forward selection with BF FWF as the dependent variable.
**Results:** BF FWF was significantly and negatively associated with cholinergic levels in PC1 (ΔR2=.042, β=-0.208, p=.04), PC3 (ΔR2=.044, β=-0.206, p=.03), PC4 (ΔR2=.056, β=-0.239, p=.02), and PC7 (β=-0.215, p=.04). BF FWF trended towards a negative association with cholinergic levels in PC5 (ΔR2=.045, β=-0.168, p=.09) and PC6 (β=-0.188, p=.09). Putamen FWF did not significantly associate with any of the ROIs. In the follow-up stepwise regression, only PC4 contributed significantly to the overall model (ΔR2=.061, β=-0.261, p=.02).
**Conclusions:** Basal forebrain FWF was inversely related to cholinergic levels in regions that are directly innervated by the basal forebrain (e.g., cingulate cortex, left frontal cortex, and bilateral entorhinal cortex). Future research should directly investigate the relationship between basal forebrain integrity, cortical cholinergic levels, and cognition.

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