football players. FLAIR WMH serves as a promising measure to further investigate the late multifactorial pathologies of RHI.

Categories: Neurodegenerative Disorders
Keyword 1: neuroimaging: structural
Keyword 2: head injury (closed)
Keyword 3: dementia - other cortical
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5 Associations Between Regional Perfusion and Locus Coeruleus MRI Contrast are Moderated by Plasma Alzheimer's Disease Biomarkers in Older Adults

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Objective: The locus coeruleus (LC) innervates the cerebrovasculature and plays a crucial role in optimal regulation of cerebral blood flow. However, no human studies to date have examined links between these systems with widely available neuroimaging methods. We quantified associations between LC structural integrity and regional cortical perfusion and probed whether varying levels of plasma Alzheimer's disease (AD) biomarkers (Aβ42/40 ratio and ptau181) moderated these relationships.
Participants and Methods: 64 dementia-free community-dwelling older adults (ages 55-87) recruited across two studies underwent structural and functional neuroimaging on the same MRI scanner. 3D-pCASL MRI measured regional cerebral blood flow in limbic and frontal cortical regions, while T1-FSE MRI quantified rostral LC-MRI contrast, a well-established proxy measure of LC structural integrity. A subset of participants underwent fasting blood draw to measure plasma AD biomarker concentrations (Aβ42/40 ratio and ptau181). Multiple linear regression models examined associations between perfusion and LC integrity, with rostral LC-MRI contrast as predictor, regional CBF as outcome, and age and study as covariates. Moderation analyses included additional terms for plasma AD biomarker concentration and plasma x LC interaction.
Results: Greater rostral LC-MRI contrast was linked to lower regional perfusion in limbic regions, such as the amygdala (β = -0.25, p = 0.049) and entorhinal cortex (β = -0.20, p = 0.042), but was linked to higher regional perfusion in frontal cortical regions, such as the lateral (β = 0.28, p = 0.003) and medial (β = 0.24, p = 0.05) orbitofrontal (OFC) cortices. Plasma amyloid levels moderated the relationship between rostral LC and amygdala CBF (Aβ42/40 ratio x rostral LC interaction term β = -0.31, p = 0.021), such that as plasma Aβ42/40 ratio decreased (i.e., greater pathology), the strength of the negative relationship between rostral LC integrity and amygdala perfusion decreased. Plasma ptau181levels moderated the relationship between rostral LC and entorhinal CBF (ptau181 x rostral LC interaction term β = 0.64, p = 0.001), such that as ptau181 increased (i.e., greater pathology), the strength of the negative relationship between rostral LC integrity and entorhinal perfusion decreased. For frontal cortical regions, ptau181 levels moderated the relationship between rostral LC and lateral OFC perfusion (ptau181 x rostral LC interaction term β = -0.54, p = .004), as well as between rostral LC and medial OFC perfusion (ptau181 x rostral LC interaction term β = -0.53, p = .005), such that as ptau181 increased (i.e., greater pathology), the strength of the positive relationship between rostral LC integrity and frontal perfusion decreased.
Conclusions: LC integrity is linked to regional cortical perfusion in non-demented older adults, and these relationships are moderated by plasma AD biomarker concentrations. Variable directionality of the associations between the LC and frontal versus limbic perfusion, as well as the differential moderating effects of plasma AD biomarkers, may signify a compensatory mechanism and a shifting pattern of hyperemia in the presence of aggregating AD pathology. Linking LC integrity and cerebrovascular regulation may represent an important understudied pathway of dementia risk and may

https://doi.org/10.1017/S1355617723007749 Published online by Cambridge University Press

help to bridge competing theories of dementia progression in preclinical AD studies.

Categories: Neuroimaging
Keyword 1: cerebral blood flow
Keyword 2: dementia - Alzheimer's disease
Keyword 3: neuroimaging: structural
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6 Posterior cerebral artery-defined white matter hyperintensities are associated with object domain memory and transentorhinal volume independently of global beta-amyloid burden

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Objective: White matter hyperintensities (WMH) are a radiological marker of small vessel cerebrovascular disease that are related to cognition and memory decline in aging and Alzheimer's disease (AD). However, the mechanisms that link WMH to memory impairment and whether they interact with or act independently of AD pathophysiology are unclear. The transentorhinal cortex (BA35) is among the earliest anatomical regions to show tau deposition and subsequent atrophy, and baseline posterior WMH is related to longitudinal cortical thinning of the entorhinal cortex. However, it is unclear whether regional WMH are related to BA35 volume specifically, and whether this relationship is influenced by amyloid-β (Aβ) burden. We hypothesized that WMH in the vascular territory of the posterior cerebral artery (PCA), which perfuses both posterior and medial temporal lobe regions, would be associated with reduced BA35 volume and with lower memory in older adults independently of Aβ.
Participants and Methods: 114 older adults without dementia, aged 60 to 98 years (mean (SD) = 78.31 (11.02), 71 (62.8%) women), were included. Regional WMH volumes were derived from T2-FLAIR images using ANTs, a vascular territory atlas and manual editing. Global Aβ was assessed with 18F-florbetapir PET, using SUVR of a cortical composite region (FBP mean SUVR) with a cerebellar reference region. Total transentorhinal (BA35) volume was derived using T1 and T2-weighted images using ASHS. To assess hippocampal pattern separation ability, an index of episodic memory, participants completed both object (MDT-O) and spatial (MDT-S) versions of a mnemonic discrimination task, with the lure discrimination index as the outcome. Using linear regressions, we first tested for associations among PCA-defined WMH, Aβ, BA35 volume, and MDT-S and MDT-O scores. We then tested whether the relationship between PCA-defined WMH and MDT-O performance was mediated by BA35 volume and whether this mediation was moderated by Aβ. All models adjusted for age, sex, and education.
Results: PCA-defined WMH were related to higher FBP mean SUVR (b=0.287, p=0.042) and lower BA35 volume (b=-0.222, p=0.038). PCA-defined WMH were also negatively related to MDT-O performance (b=-0.229, p=0.044), but not to MDT-S (b=-0.171, p=0.118). FBP mean SUVR was not related to BA35 volume (b=-0.131, p=0.344) or MDT performance (MDT-S: b=-0.138, p=0.348; MDT-O: b=0.059, p=0.690). Furthermore, FBP mean SUVR did not interact with PCA-defined WMH to predict memory performance (interaction b=-0.039, p=0.973), nor BA35 volume (interaction b=-0.140, p=0.894). The association of PCA-defined WMH to MDT-O was fully mediated by BA35 volume (indirect effect b=-0.0005, 95% CI (-0.0014, -0.0003)). This mediation was not moderated by FBP mean SUVR (indirect effect b=-0.00001, 95% CI (-0.001, 0.001)).
Conclusions: We found that PCA-defined WMH were related to memory performance in older adults, and this association is fully mediated by transentorhinal volume. While PCA-defined WMH are related to higher global Aβ burden, there is no interaction between PCA-defined WMH and Aβ on BA35 volume. These findings point to an amyloid-independent vascular pathway towards memory decline in aging and AD. Future work should examine whether the pathway linking PCA-defined WMH to transentorhinal cortex atrophy and subsequent memory decline is mediated by regional tau pathology.

Categories: Neuroimaging
Keyword 1: aging (normal)

https://doi.org/10.1017/S1355617723007749 Published online by Cambridge University Press