

Associations of Microglia Inflammation with Cognitive Changes in Older Black Adults

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BACKGROUND AND OBJECTIVE

- The prevalence and incidence of AD/ADRD is higher among Black older adults than among non-Hispanic White older adults.
- Chronic brain inflammation is one potential pathological mechanism that may underlying health outcomes disparities in Black populations.
- Studies have shown that microglia-driven inflammation is a common biological pathway associated with cognitive decline in aging. However, most clinicopathologic evidence linking microglia to cognitive outcomes has been derived from predominantly older White adults.
- The present study investigated the racial differences in hippocampal microglial density and test the association of microglia density with change in global cognition in Black older adults. The study also investigated whether the association between microglia density and cognitive decline varies by race.*

METHODS

Study Participants: Deceased participants from an ongoing longitudinal clinicopathologic cohort study, Rush Memory and Aging Project (MAP), Religious Orders Study (ROS), the Minority Aging Research Study (MARS), and the RADC Clinical Core **N=446 (153 Black and 293 White decedents)**

Characteristics	Black (N=153)	White (N=293)
Age-at-death (years), mean (SD)	84.7 (7.7)	86.1 (6.5)
Female, No (%)	116 (75.8)	219 (74.7)
Education (years), mean (SD)	15.1 (3.1)	15.1 (3.1)

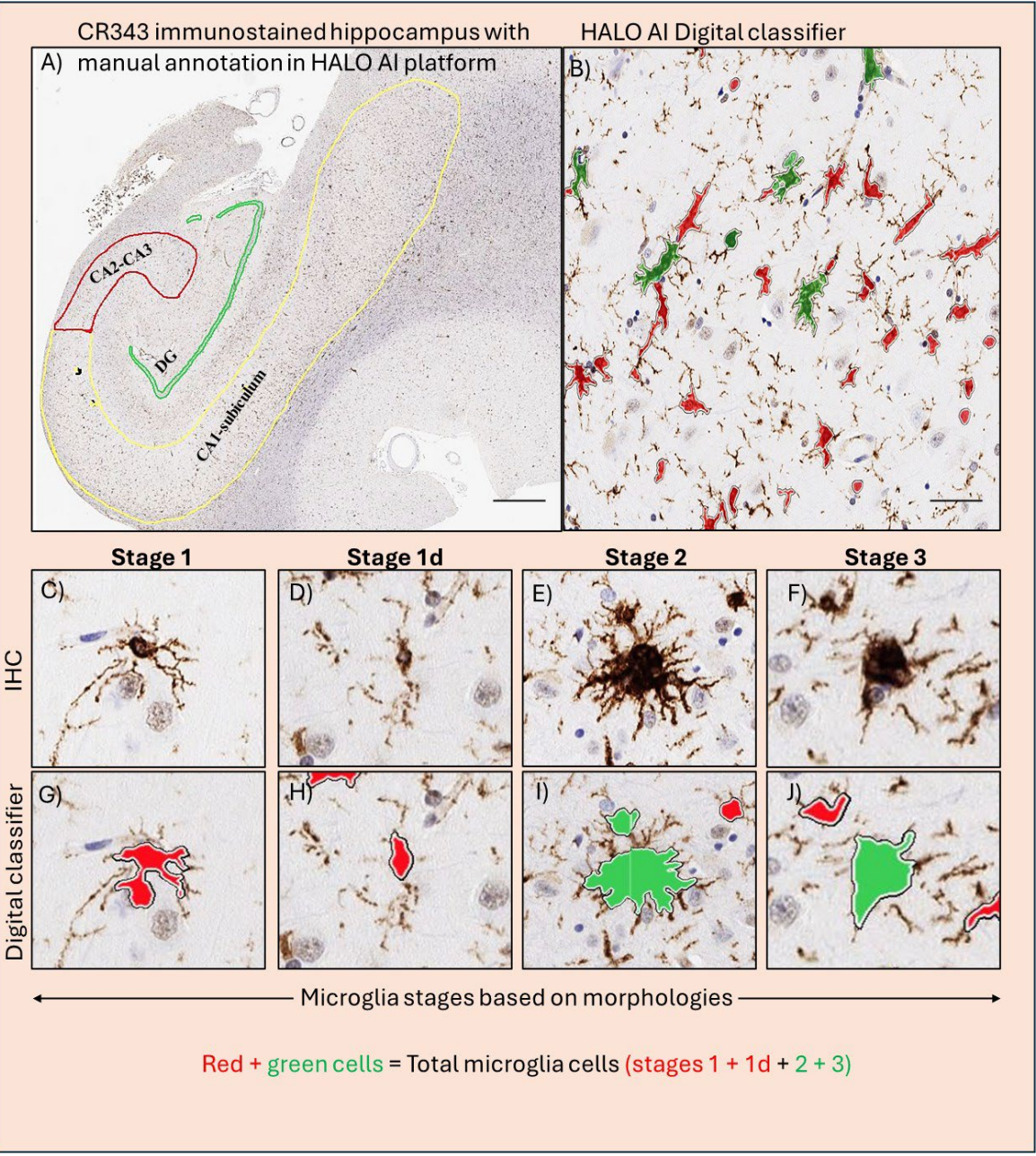
Clinical cognition assessment:

- 19 neuropsychological tests were used to generate a composite measure of global cognitive function as well 5 cognitive domains: episodic, working memory, semantic memory, perceptual speed, and perceptual orientation.

Neuropathology:

- Hippocampal microglia density** : CR343 immunohistochemistry and HALO AI Object Phenotype module, integrated with a nuclei segmentation classifier, was then used to quantify total microglial cells and stage 2/3 microglia (more reactive) from CA1-subiculum subregions of the mid hippocampus. **Median hippocampal microglial density : 96.8 (IQR: 23.2-173.9)**

Other brain pathologies : ADNC, LATE-NC, Lewy bodies, and cerebrovascular pathologies



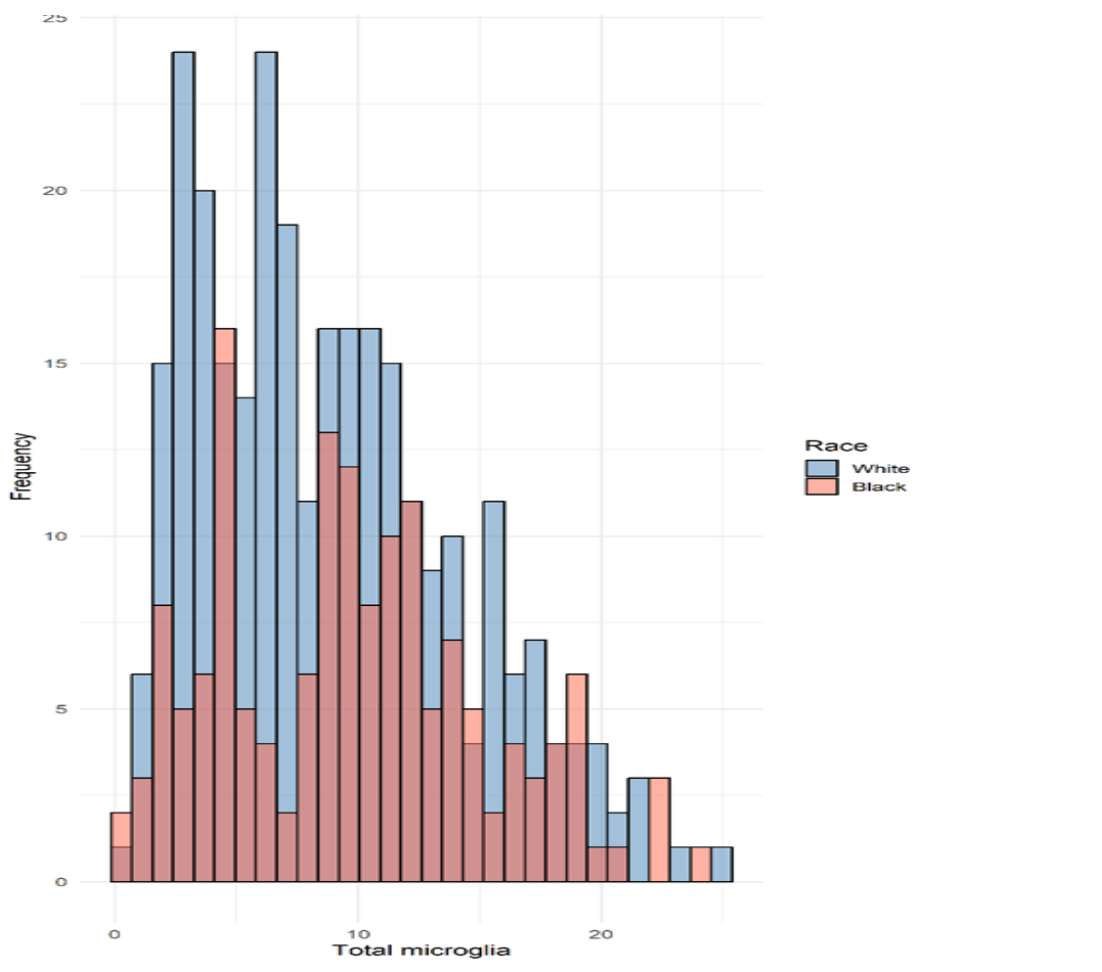
Statistical Methods:

- A. [Linear regression models](#) were applied to examine to assess the racial differences in hippocampal microglial density (total and stage 2/3).
- B. [Linear mixed models](#) were applied to examine that higher hippocampal microglia density (total and stage2/3) is associated with faster annual rates of decline in global cognition before death.
- C. [Linear mixed models](#) specified above the microglia by race interaction term, both as simple effect and in interaction with the time were applied to investigated whether the association between hippocampal microglia density and cognitive decline varies by race

RESULTS

Mean differences in the hippocampal (CA1-Subiculum) microglia density in Black decedents compared to White decedents

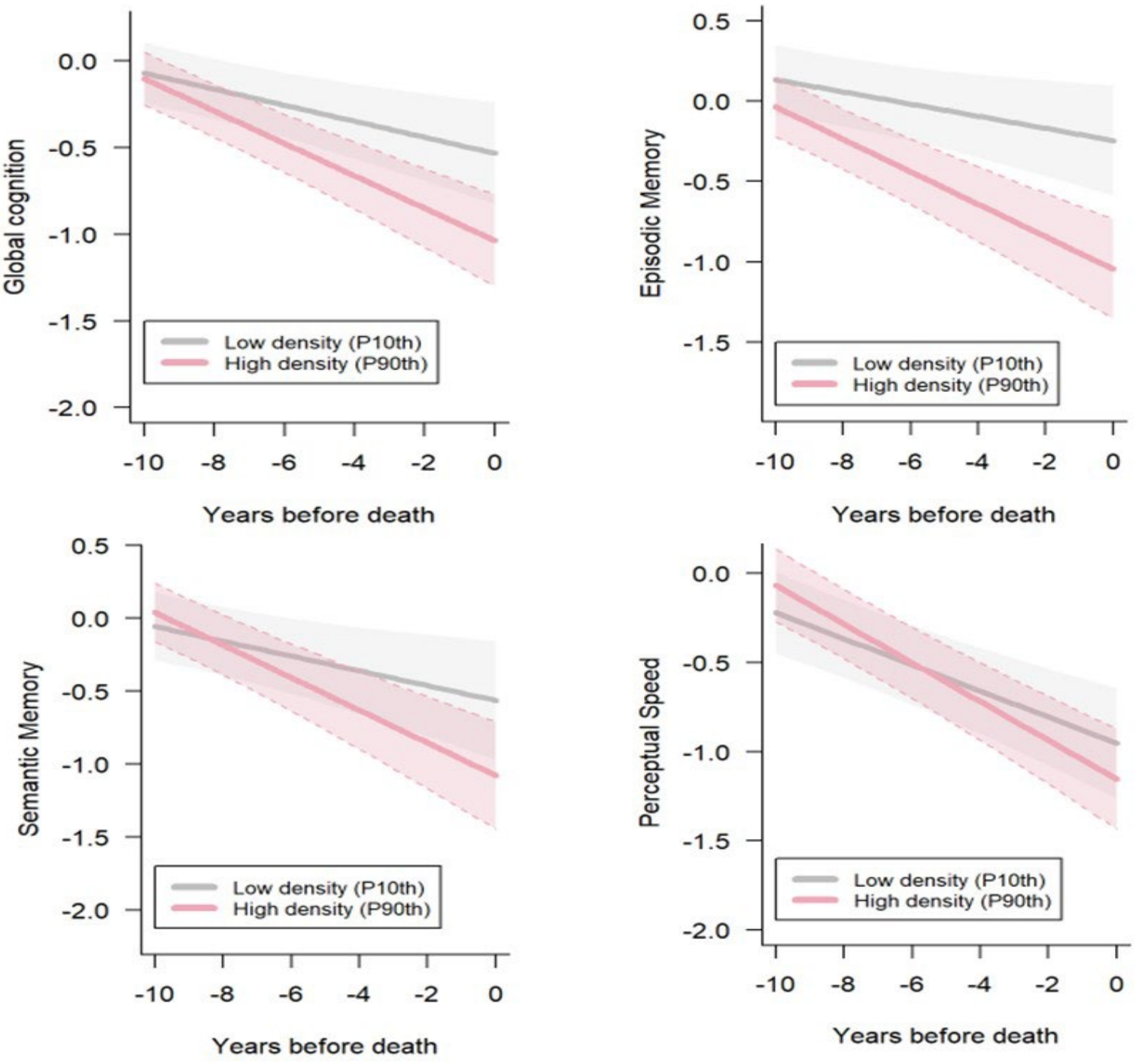
Model set	Outcome: Total microglia		Outcome: Stage 2/3 microglia	
	Adjusted R ² , %	Estimate (SE, p value)	Adjusted R ² , %	Estimate (SE, p value)
Model A	6.8	1.30 (0.51, 0.011)	4.9	0.10 (0.03, 0.008)
Model B	16.2	1.13 (0.49, 0.022)	14.5	0.09 (0.03, 0.016)
Model C	16.0	1.11 (0.51, 0.028)	14.6	0.10 (0.03, 0.009)



Linear regression models were applied. Models A was adjusted for age-at-death, sex, and education. Model B: Model A + ADNC + Lewy bodies, LATE-NC, HS-A, arteriolosclerosis, atherosclerosis, CAA, and cerebral infarcts. Model C: Model B + number of vascular disease risk factors (diabetes, hypertension, smoking history).

Association of hippocampal (CA1-Subiculum) microglia density with cognitive decline in black participants

Outcomes	Total microglia		Stage 2/3 microglia	
	Annual rate of decline	Level, proximate to death	Annual rate of decline	Level, proximate to death
Global cognition	-0.003 (0.001, <0.001)	-0.035 (0.010, <0.001)	-0.045 (0.013, <0.001)	-0.388 (0.138, 0.005)
Episodic memory	-0.004 (0.001, <0.001)	-0.056 (0.012, <0.001)	-0.059 (0.014, <0.001)	-0.680 (0.161, <0.001)
Semantic memory	-0.004 (0.001, 0.001)	-0.036 (0.014, 0.011)	-0.062 (0.017, <0.001)	-0.410 (0.192, 0.032)
Working memory	-0.001 (0.001, 0.056)	-0.019 (0.009, 0.039)	-0.022 (0.012, 0.085)	-0.167 (0.125, 0.182)
Perceptual speed	-0.002 (0.001, 0.015)	-0.014 (0.010, 0.193)	-0.039 (0.014, 0.005)	-0.144 (0.147, 0.329)
Visuospatial ability	-0.001 (0.001, 0.246)	-0.012 (0.009, 0.215)	-0.021 (0.013, 0.111)	-0.147 (0.130, 0.256)



Estimates are derived from six separate linear mixed effect models adjusted for age-at-death, sex, education, race, mode of cognitive assessment, ADNC, LATE-NC, LBs, HS-A, arteriolosclerosis, atherosclerosis, CAA, and cerebral infarcts and the interactions of all variables with the time before death. Cell values are interaction effects presented as estimate (SE, p-value).

Non-significant Interaction between microglia and Race

Outcomes	Total microglia x Race		Stage 2/3 microglia x Race	
	Annual rate of decline	Level, proximate to death	Annual rate of decline	Level, proximate to death
Global cognition ^a	-0.001 (0.001, 0.433)	-0.004 (0.022, 0.855)	-0.009 (0.025, 0.701)	0.265 (0.288, 0.357)
Global cognition ^b	-0.0001 (0.001, 0.985)	0.015 (0.019, 0.439)	0.020 (0.024, 0.390)	0.382 (0.255, 0.135)

^aEstimates derived from multiple linear mixed effect models with an interaction term between each microglia pathology and race, adjusted for demographics. ^bEstimates derived from multiple linear mixed effect models with an interaction term between each microglia pathology and race, adjusted for demographics and other cerebrovascular and neurodegenerative pathologies. Cell values are interaction effects presented as estimate (SE, p-value).

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CONCLUSIONS

- These findings suggest that neuroinflammation as an important contributor to cognitive decline in older Black decedents.
- Racial differences in neuroinflammatory burden represent a novel pathway that may contribute in late-life cognitive health disparities among older Black and White decedents.
- Future studies incorporating life-course measures of social and environmental exposures are needed to better understand the mechanisms underlying these racial differences in inflammation and to identify potential targets for intervention.