Title

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Journal

Alzheimer's & Dementia, 18(S6)

ISSN

1552-5260

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Publication Date

2022-12-01

DOI

10.1002/alz.062067

DOI: 10.1002/alz.062067

BIOMARKERS

PODIUM PRESENTATION

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THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

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Associations of Amyloid, White Matter Hyperintensities, and Hippocampal Volume with Cognitive Trajectories in the Oldest-Old: The 90+ Study

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Abstract

Background: Amyloid pathology, vascular disease pathology, and hippocampal atrophy are associated with cognitive trajectories in older adults. However, there is almost no prior evidence on how these pathologies influence cognition in the oldest-old.

Method: We included 216 individuals from The 90+ Study, a longitudinal study of aging and dementia in people aged 90 years and older, who had ^{18}F-florbetapir PET and MRI imaging. We examined the association of amyloid, white matter hyperintensities (WMH) volume, and hippocampal volume (HV) with baseline cognition and longitudinal cognitive decline. Amyloid burden was measured using the standardized uptake value ratio (SUVR) in the precuneus/posterior cingulate with white matter mask as reference. WMH volume and HV were normalized by intracranial volume (IV) and normalized WMH were log-transformed. SUVR and HV for each individual were Z-scored using the sample mean and standard deviation. Global cognitive performance was measured by Mental State Examination (MMSE) and modified MMSE (3MS) tests, repeated every six months. We defined baseline (time=0) as the visit closest to the PET imaging and included all visits starting from one year before baseline (time=-1). We used linear mixed-effects models with a random intercept to estimate the effect of pathologies on cognitive trajectories. All models included baseline age, sex, education, APOE-ε4, time, time squared, amyloid, WMH, HV, and interactions between linear time and pathology variables.

Result: At baseline, participants were 93.2 years old on average, 65.3% were females, 10.6% were APOE-ε4 carriers, and 66.2% had normal cognition (Table 1). Higher HV was associated with higher MMSE and 3MS scores at baseline. Both lower amyloid burden and higher HV were associated with slower rate of cognitive decline longitudinally. WMH was not associated with baseline cognition or cognitive trajectory. Parameter estimates are shown in Table 2 and illustrative cognitive trajectories predicted for a

93.2-year-old female with APOE-ε4 alleles and a college degree predicted at varying degrees of amyloid, HV, and WMH are shown in Figure 1.

Conclusion: Amyloid burden and HV are associated with longitudinal cognitive trajectories, highlighting the utility of amyloid and HV in predicting future cognitive decline for the oldest-old.

Table 1: Demographic, Clinical, and Pathological Characteristics of the Analytical Sample at Baseline

Characteristic	No. (%)[a]
Mean age (SD)	93.21 (2.69)
Sex	
Female	141 (65.28)
Male	75 (34.72)
Education	
Less than college	49 (22.69)
College degree	91 (42.13)
Beyond a college degree	76 (35.19)
APOE-ε4 carrier	
Yes	23 (10.65)
No	196 (89.35)
Race	
White	202 (93.52)
Other	14 (6.48)
Cognitive status	
Cognitively normal	143 (66.20)
CIND	63 (29.17)
Dementia	10 (4.63)
Median follow-up time in year (interquartile)	2.55 (1.50-4.20)
Mean amyloid (SD)	0.76 (0.07)
Mean HV as % of IV (SD)	0.41 (0.04)
Mean WMH as % of IV (SD)	1.20 (0.99)

Abbreviations: SD, standard deviation; CIND, cognitive impairment-no dementia; HV, hippocampal volume; IV, intracranial volume; WMH, white matter hyperintensities.

[a] Percentages may not sum to 100 because of rounding.

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Table 2: Parameter Estimates of the Linear Mixed-Effects Model for the Effect of Time and Pathology Variables on Cognitive Scores

	MMSE		3MS	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Linear time	-0.38 (0.20)	0.066	-1.53 (0.59)	0.009
Quadratic time	-0.04 (0.02)	0.024	-0.11 (0.05)	0.043
Baseline age	-0.17 (0.07)	0.012	-0.56 (0.19)	0.003
Amyloid	-0.20 (0.19)	0.292	-0.71 (0.53)	0.184
WMH	-0.13 (0.14)	0.350	-0.28 (0.38)	0.457
HV	0.62 (0.19)	0.001	2.24 (0.52)	< 0.001
Amyloid*Time	-0.41 (0.05)	< 0.001	-1.24 (0.15)	< 0.001
WMH*Time	0.02 (0.04)	0.498	-0.02 (0.11)	0.887
HV*Time	0.21 (0.05)	< 0.001	0.61 (0.14)	< 0.001

Abbreviations: MMSE, Mini-Mental State Examination; 3MS, modified MMSE; SE, standard error; WMH, white matter hyperintensities; HV, hippocampal volume.
Model included time, time squared, amyloid, WMH, HV, and interactions between linear time and pathology variables, baseline age, sex, education, and APOE-ε4.

Figure 1: Comparison of cognitive trajectories predicted for a 93.2-year-old female with APOE-ε4 alleles and a college degree with high or low values of amyloid, HV, and WMH.