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INTRODUCTION

The *APOE3* Christchurch (*APOE3^{Ch}*) is a rare genetic variant associated with marked protection against autosomal dominant Alzheimer's disease (ADAD) due to the *PSEN1^{E280A}* variant (1,2)

- **Delayed onset of clinical symptoms** in *APOE3^{Ch}* carriers
- Despite high amyloid- β burden, tau pathology and glucose metabolism remained preserved
- Glucose metabolism, measured with FDG-PET, is markedly reduced in ADAD (3) and is sensitive to age-related changes in healthy aging, being highly correlated with cognitive performance

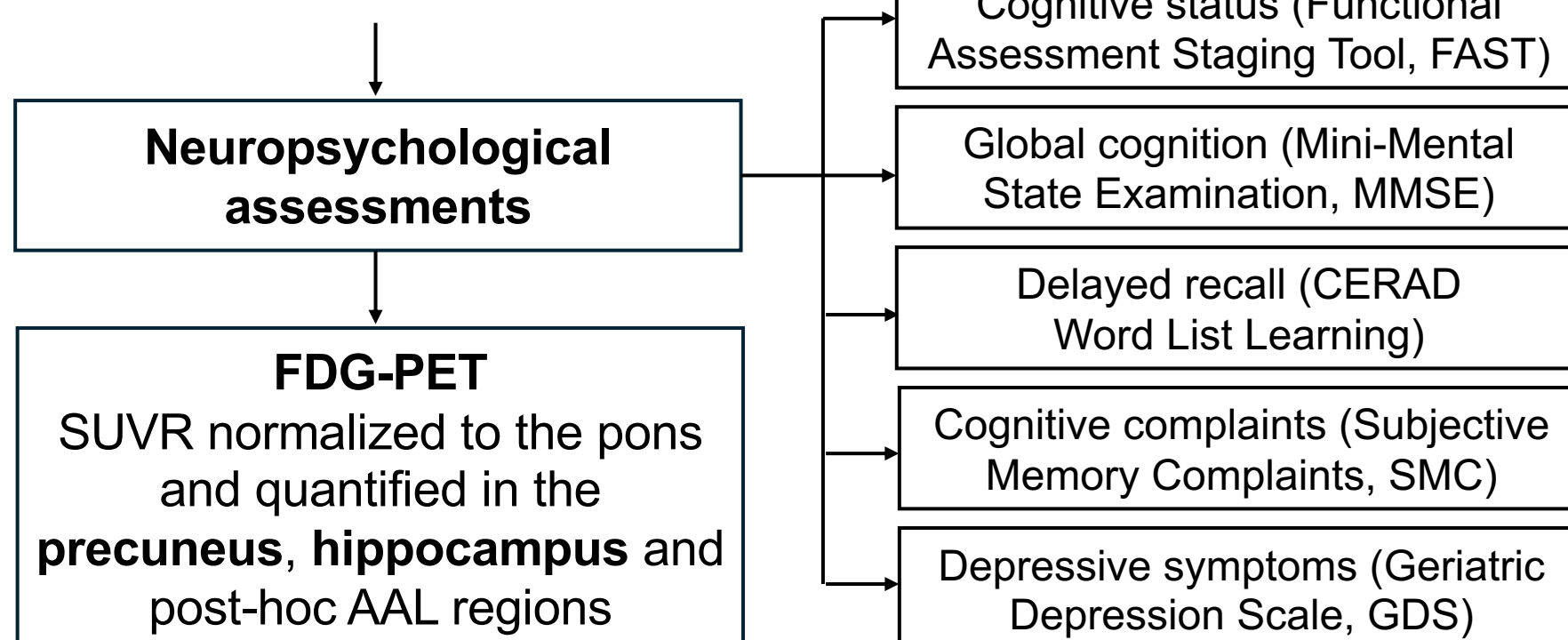
OBJECTIVES

To investigate **age-related alterations in cerebral glucose metabolism** and cognitive function in:

- 1) *APOE3^{Ch}*-*PSEN1^{E280A}* carriers compared to typical *PSEN1^{E280A}* carriers across the ADAD continuum
- 2) cognitively unimpaired *APOE3^{Ch}* carriers compared to non-carriers across the healthy adult lifespan

METHODS

Colombian ADAD kindred



Statistical analysis

- Robust linear regression with age by group interactions and adjusted for age, sex and education years
- Region-of-interest and FDR-corrected voxelwise models
- Z-scored FDG-PET SUVR and cognition relative to non-carriers

Groups demographics

	<i>APOE3^{Ch}</i> - <i>PSEN1^{E280A}</i> N = 7	<i>PSEN1^{E280A}</i> N = 48	P	<i>APOE3^{Ch}</i> Carriers N = 29	Non-Carriers N = 43	P
Age (years)	49 (35, 53)	39 (32, 45)	0.10	43 (35, 50)	40 (36, 44)	0.3
Female sex (n)	2 (29%)	30 (63%)	0.12	15 (52%)	26 (60%)	0.5
Education (years)	11 (7, 11)	11 (7, 13)	0.2	11 (5, 13)	12 (8, 15)	0.034
Cognitively impaired (n)	2 (29%)	17 (35%)	>0.9	0 (0%)	0 (0%)	>0.9
MMSE score	27 (19, 28)	27 (23, 29)	0.7	28 (28, 29)	28 (28, 29)	>0.9
CERAD WLL delayed recall	5 (1, 8)	7 (2, 8)	0.6	7 (6, 8)	8 (6, 9)	0.3
Precuneus FDG SUVR	1.49 (1.36, 1.57)	1.53 (1.42, 1.65)	0.5	1.60 (1.55, 1.69)	1.58 (1.52, 1.71)	0.7

CONCLUSIONS

- **Metabolic resilience patterns** conferred by the *APOE3^{Ch}* variant are notably different across groups, suggesting dissociation between processes of **resilience to AD-specific pathology** and **healthy aging**
- Structural and functional role of the **anterior cingulate cortex (ACC)** in this population may shed light on cognitive reserve and aging-resilience mechanisms
- Understanding the pathways through which *APOE3^{Ch}* confers protection could **inform novel therapeutic avenues** to enhance resilience against AD and neurodegeneration and **promote healthy brain aging** (4)

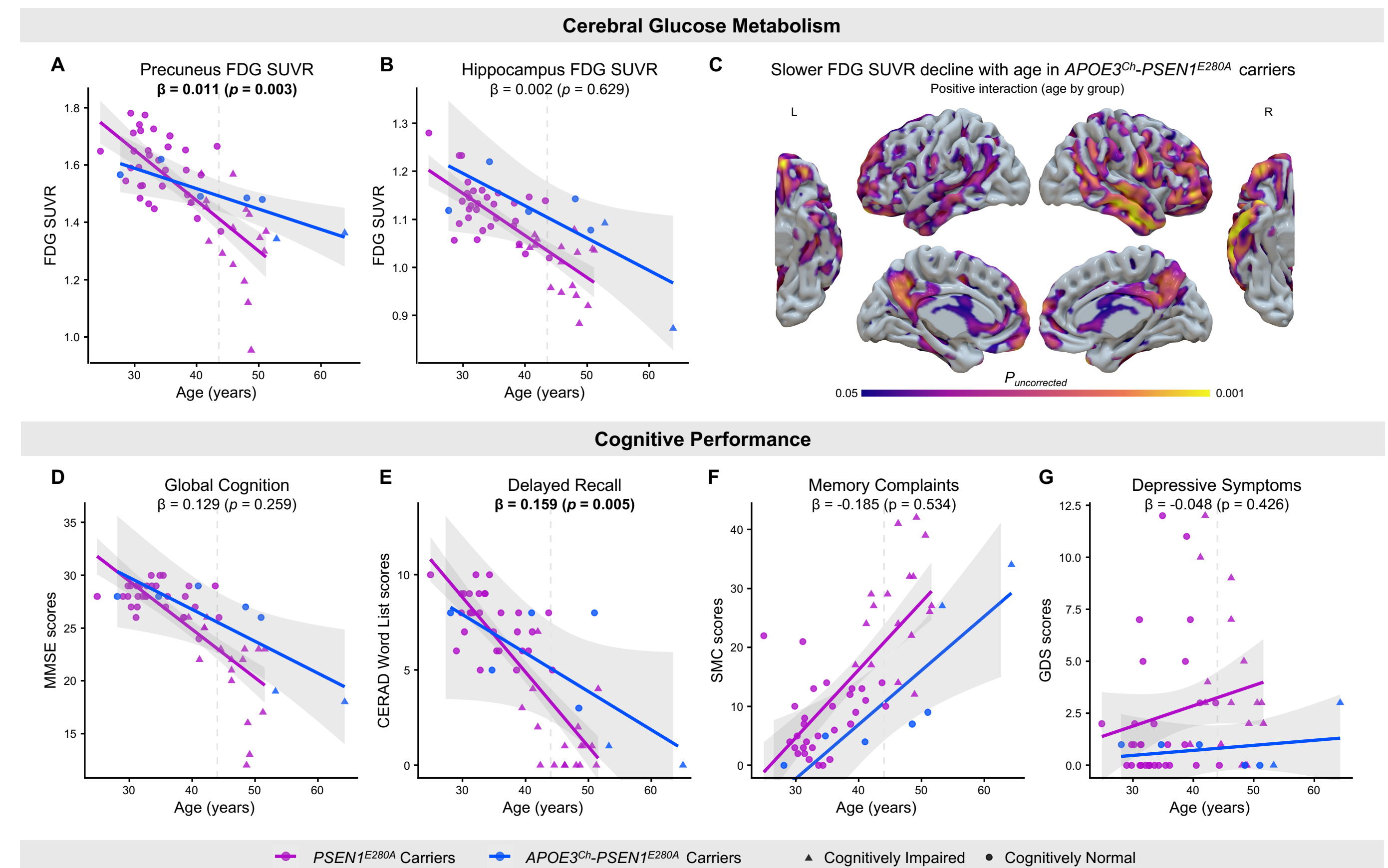
The *APOE3^{Ch}* variant may be protective against brain metabolic changes both in ADAD and across the disease-free adult lifespan, with corresponding benefits in cognitive function.

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References: (1) Arboleda-Velasquez et al. *Nat Med* **25**, 1680–1683 (2019); Quiroz et al. *N Engl J Med* **390**, 2156–2164 (2024); (3) Tristão-Pereira et al. *Brain Commun* fcaf508 (2026); (4) Marino et al. *Alzheimers Dement* **20**, 819–836 (2024)

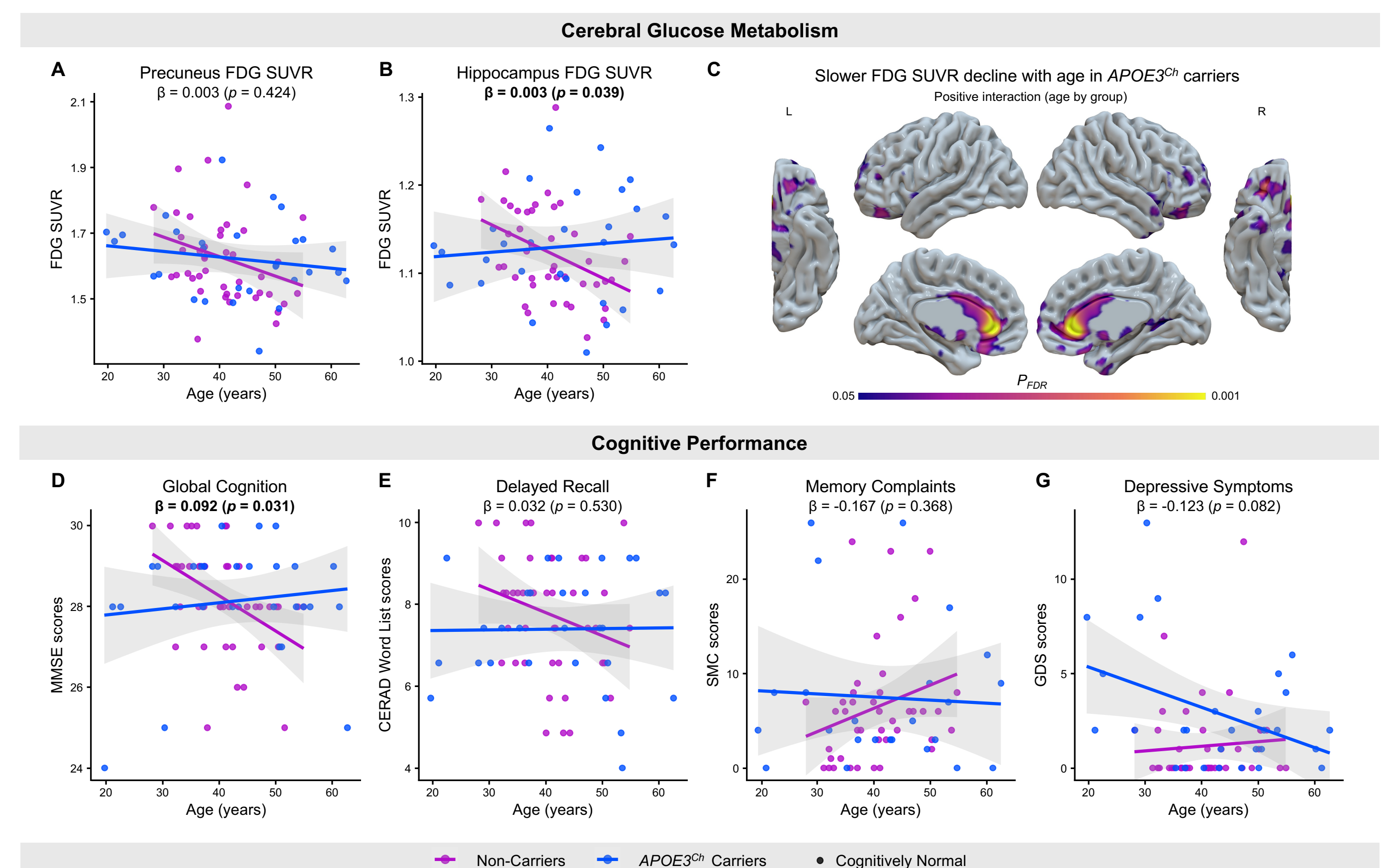
RESULTS

APOE3^{Ch}-*PSEN1^{E280A}* vs typical *PSEN1^{E280A}* carriers (ADAD)



APOE3^{Ch}-*PSEN1^{E280A}* carriers had a **58% smaller age-related reduction in precuneus metabolism**, along with a 50% smaller reduction in episodic memory, compared to typical *PSEN1^{E280A}* carriers

APOE3^{Ch} vs non-carriers (healthy adult lifespan)



ACC FDG-PET SUVR Correlations (z-scores):

Mini-Mental State Examination	$\beta = 0.494$ ($P = 0.023$)
CERAD WLL Delayed Recall	$\beta = 0.280$ ($P = 0.014$)
Subjective Memory Complaints	$\beta = -0.312$ ($P = 0.009$)
Geriatric Depression Scale	$\beta = -0.312$ ($P = 0.047$)

Across the adult lifespan, *APOE3^{Ch}* carriers had **preserved glucose metabolism** in the **ACC** compared to non-carriers (slope: 0.001 vs -0.009), which **correlated with greater global cognition** and episodic memory and fewer memory complaints and depressive symptoms.