

Effects of APOE ε4 on neuronal and glial alterations in Alzheimer’s disease: A whole-brain high-resolution 3D-MRSI study

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Using whole-brain high-resolution 3D-MRSI technique, we provide the first in vivo human evidence supporting the cell-specific cascading model, where APOE ε4 is associated with neuronal injury in early Braak stage-defined regions followed by glial response in later Braak stage-defined regions, and ultimately contributing to cognitive decline.

INTRODUCTION

- APOE is the strongest genetic risk factor for late-onset AD.
- The cell-specific cascading model: neuronal APOE ε4 acts as a pathological initiator, driving subsequent glial responses and neurodegeneration.[1]
- This model motivates new therapeutic strategies targeting specific cellular sources of APOE ε4, but has not yet been directly tested in humans.
- Magnetic resonance spectroscopic imaging (MRSI) enables noninvasive quantification of N-acetylaspartate (NAA) and myo-inositol (ml), markers of neuronal integrity and glial viability, respectively.
- Our high-resolution 3D-MRSI technique—allow whole-brain mapping of NAA and ml at 2×3×3 mm³ resolution, providing a unique opportunity to investigate cell-specific effects of APOE ε4 in vivo.[2]

METHODS

Table 1. Demographic of participants

Variable	CU	CI
n	69	174
Age, years	65.2 ± 8.0	69.2 ± 7.9
Sex, male, n (%)	31 (44.9)	65 (37.4)
Years of education	13.3 ± 3.3	10.9 ± 3.7
MMSE score	29.1 ± 1.2	21.4 ± 5.6
APOE ε4 carrier, n (%)	15 (21.7)	97 (55.7)
APOE genotype distribution, n (%)		
ε2ε2	0 (0.0)	2 (1.1)
ε2ε3	3 (4.3)	10 (5.7)
ε3ε3	51 (73.9)	65 (37.4)
ε3ε4	15 (21.7)	80 (46.0)
ε4ε4	0 (0.0)	17 (9.8)
Aβ positivity, n (%)	2 (2.9)	128 (73.6)

Data analysis:

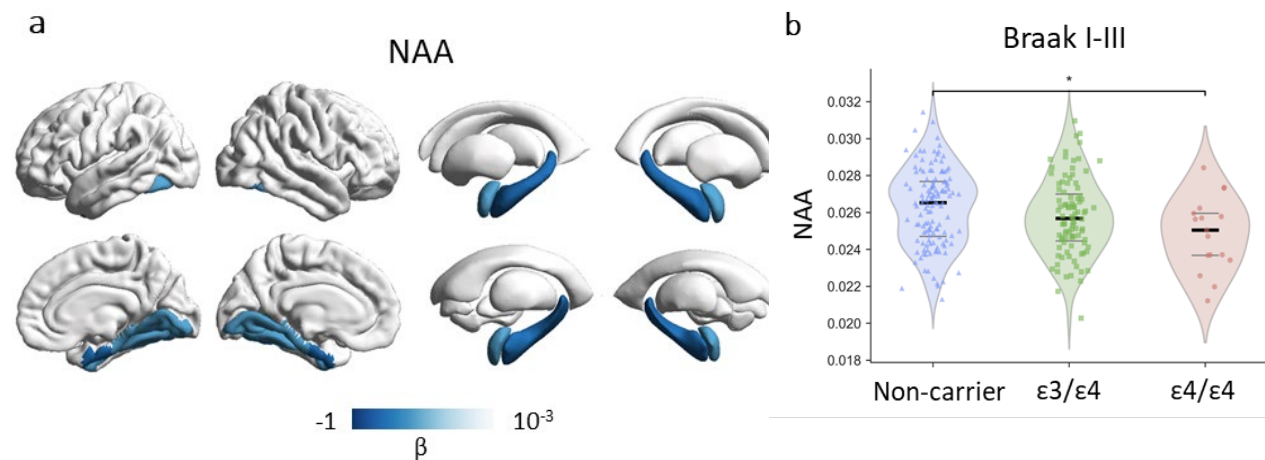
- ROI: Braak stage-defined regions
- GLM to assess effects of APOE4 on NAA and ml
- Genetic analysis to link NAA and ml distribution to APOE and cell-type expressions
- Mediation analysis to explore relationship among APOE4, NAA, ml and MMSE

Table 2. Imaging parameters

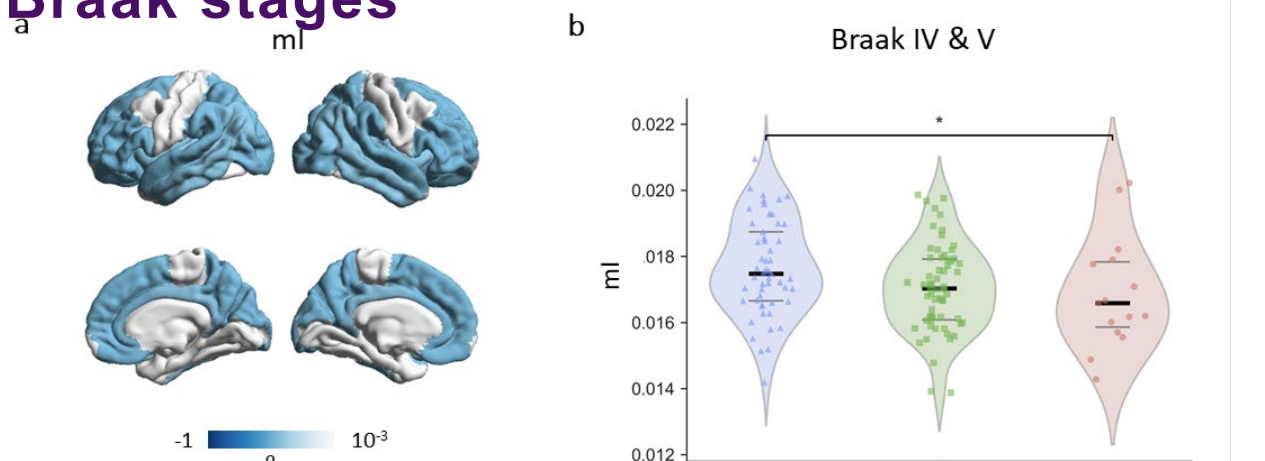
Modality	Voxel size	Matrix size	Scan time
[¹⁸ F] AV-45 PET	2.1 × 2.1 × 2.0 mm ³	344 × 344 × 127	15 min
3D MRSI	2.0 × 3.1 × 3.8 mm ³	122 × 78 × 42	9 min 55 sec
MPRAGE	1.0 × 1.0 × 1.0 mm ³	256 × 256 × 192	5 min 04 sec

RESULTS

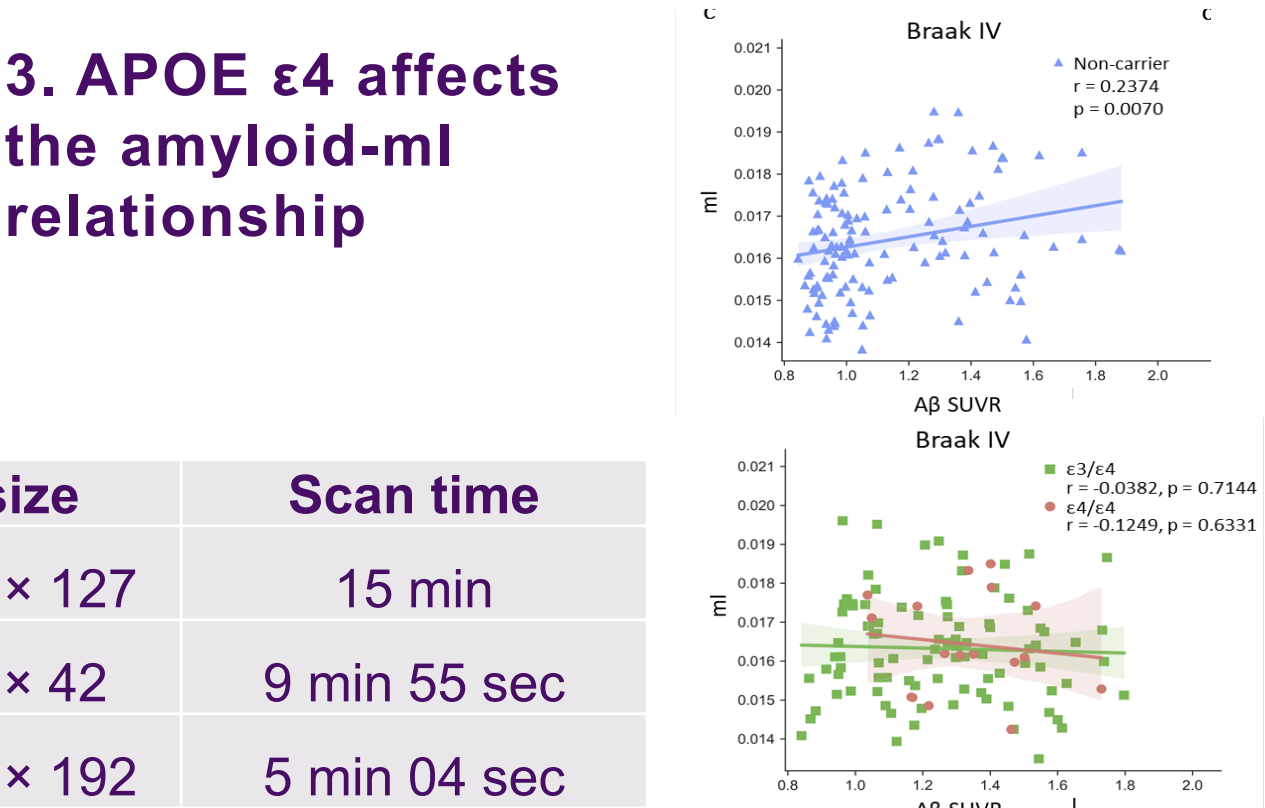
1. Effects of APOE4 dosage on NAA in early Braak stages



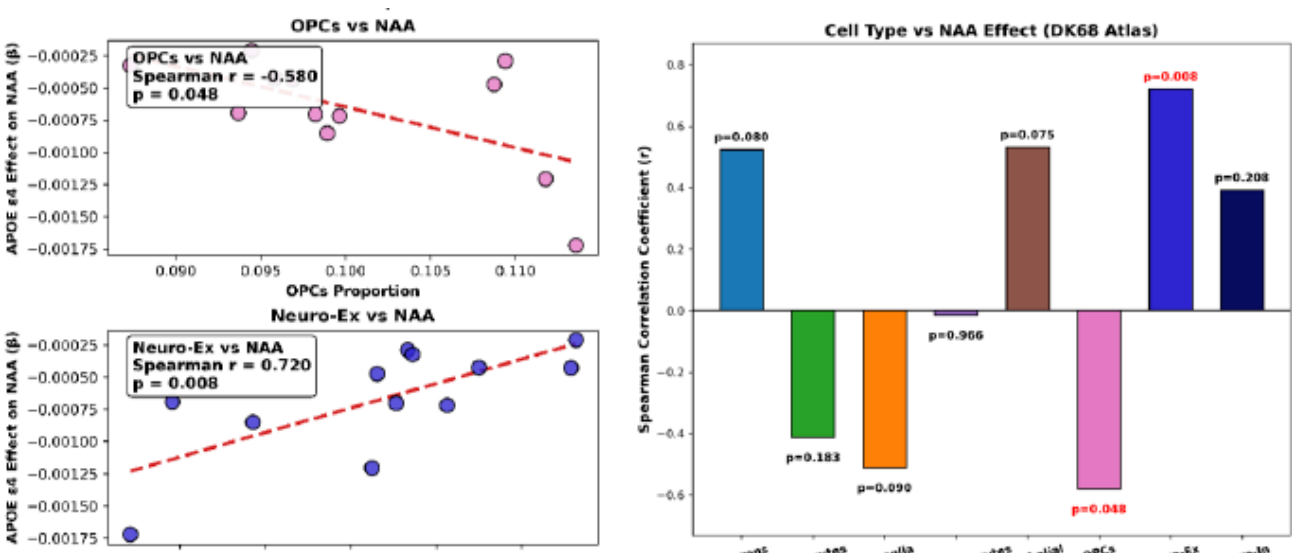
2. Effects of APOE4 dosage on ml in later Braak stages



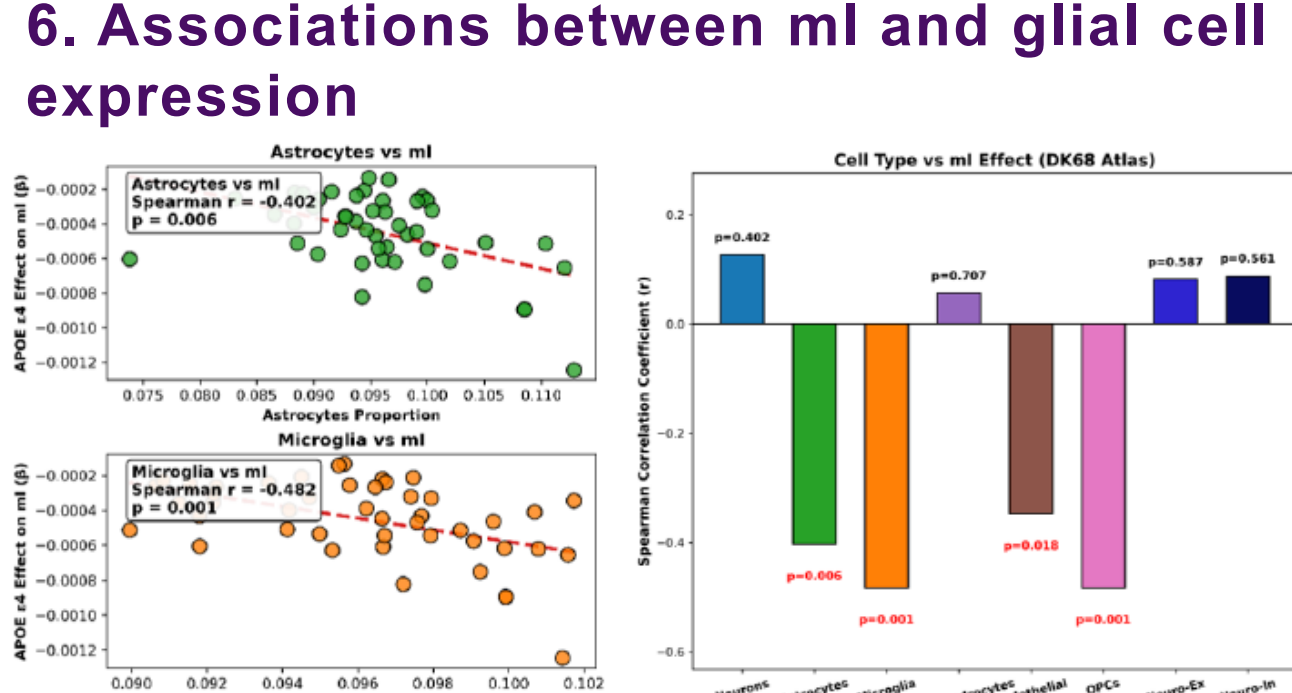
3. APOE ε4 affects the amyloid-ml relationship



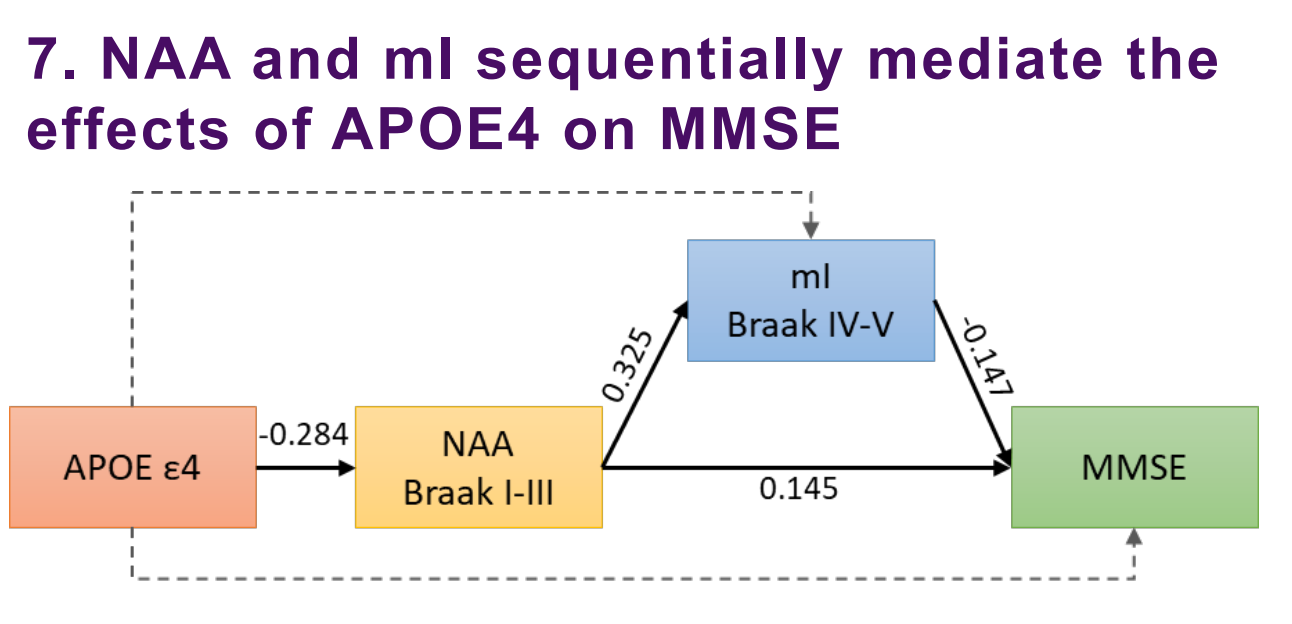
5. Associations between NAA and excitatory neurons and OPCs expression



6. Associations between ml and glial cell expression



7. NAA and ml sequentially mediate the effects of APOE4 on MMSE



CONCLUSIONS

APOE4 is associated with neuronal injury in early Braak stage-defined regions followed by glial response in later Braak stage-defined regions, and ultimately contributing to cognitive decline. These findings provide in vivo human evidence supporting a cell-specific cascading model of AD pathogenesis and have important implications for APOE-directed therapies.

REFERENCES

[1] Blumenfeld J, Yip O, Kim MJ, Huang Y. Cell type-specific roles of APOE4 in Alzheimer disease. Nature Reviews Neuroscience. 2024;25:91–110.

[2] Zhao YB, Li YD, Jin W, Guo R, Ma C, Tang WJ, et al. Ultrafast J-resolved magnetic resonance spectroscopic imaging for high-resolution metabolic brain imaging. Nat Biomed Eng. 2025;Published online on June 20, 2025.

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