

MR Elastography Reveals Lower Hippocampal Stiffness in Middle-Aged *APOE* ϵ 4 Carriers Without Cognitive Impairment

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Synopsis

Motivation: Brain tissue softening is well documented in dementia populations. However, preclinical changes to tissue mechanical properties are currently unknown, despite the impact it may have on Alzheimer's disease (AD) development through mechanobiological signalling pathways.

Goal(s): To establish whether brain mechanical properties differ in asymptomatic individuals who may be in the preclinical stages of AD.

Approach: Apply validated, high-resolution MR elastography methods to cognitively unimpaired, middle-aged *APOE*- ϵ 4 carriers and *APOE*- ϵ 3 homozygotes.

Results: Lower hippocampal tissue stiffness was observed in *APOE*- ϵ 4 carriers relative to *APOE*- ϵ 3 homozygotes, despite the absence of cognitive impairment. There was also a trend to suggest higher thalamus stiffness in *APOE*- ϵ 4 carriers.

Impact: MR elastography is a valuable tool for studying at-risk populations. Future research should determine if the observed preclinical changes in tissue mechanics influence Alzheimer's disease pathogenesis. Findings also have broader implications for precision medicine and risk stratification in dementia research.

Introduction: The ϵ 4 allele of the Apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for late-onset Alzheimer's disease (AD)¹, increasing the risk threefold in heterozygous carriers and up to 15-fold in homozygotes²⁻⁴. The mechanisms linking *APOE* ϵ 4 with AD are complex but are likely to involve disruptions to amyloid- β peptide clearance, tau phosphorylation, and cerebrovascular dysfunction⁵⁻⁷. Research efforts have increasingly focused on the study of asymptomatic middle-aged populations with the *APOE* ϵ 4 genotype to identify subtle neurological changes that may drive later pathophysiology. In a recent study of $N=28,494$ cognitively healthy participants from the UK Biobank, *APOE* ϵ 4 carriers exhibited microstructural changes within white matter, relative to noncarriers, as revealed through diffusion imaging, indicating early disruptions in neuronal connectivity⁸. The same study found no significant effects of *APOE* genotype on grey matter volume or median T2* measurements within subcortical regions, possibly because microstructural alterations are too subtle to be observed with conventional volumetric MRI. Instead, the mechanical properties of tissues represent microstructural health and integrity on the macroscopic scale and can be quantified noninvasively with magnetic resonance elastography (MRE)⁹. Changes in neuronal cell type, size, and organization have all been shown to influence MRE-derived parameters¹⁰. Numerous studies have documented brain tissue softening in patients with clinically defined or biomarker-confirmed AD and mild cognitive impairment, particularly within the hippocampal region¹¹⁻¹⁴. However, it is currently unknown whether the mechanical properties of the brain differ in asymptomatic middle-aged individuals with and without an inherited risk for AD.

Aims: To quantify the mechanical properties of the brain in asymptomatic mid-life *APOE* $\epsilon 4$ carriers and compare these to age-matched *APOE* $\epsilon 3$ homozygotes, using high-resolution MRE methods. We focus our preliminary analyses on four regions of interest: the hippocampus, thalamus, posterior cingulate cortex, and the postcentral gyrus.

Methods: Four *APOE* $\epsilon 4$ carriers (mean age: 59.8 $\pm$ 1.0 years, 2M/2F) and four *APOE* $\epsilon 3$ homozygotes (mean age: 59.7 $\pm$ 0.9 years, 3M/1F) were recruited from the PROTECT cohort. All participants were cognitively healthy based on scores from the Addenbrooke's Cognitive Examination (ACE-III-R, *APOE* $\epsilon 4$ =96.3/100, *APOE* $\epsilon 3$ homozygotes=95.3/100). Imaging data were collected on a 3T Siemens Prisma MRI scanner, with tissue displacements generated at 50 Hz using the Resoundant actuator. MRE data at a 1.5 mm isotropic resolution were acquired using a 3D multiband, multishot spiral sequence with OSCILLATE acceleration¹⁵ and MRE data quality was measured through OSS-SNR¹⁶. Displacement data were analysed with a nonlinear inversion (NLI) algorithm to produce shear stiffness and damping ratio parameter maps¹⁷. MP2RAGE images (1 mm isotropic resolution) were processed with *Freesurfer* to segment four regions of interest. Advanced normalisation tools were used to co-register the ROIs into MRE native space for the purpose of extracting quantitative measurements. *HippUnfold*, a tool for hippocampal subfield segmentation and surface generation, was used to map stiffness and damping ratio across the full spatial extent of the hippocampal midthickness surface for each participant¹⁸ (Figure 1). Independent t-tests with two-tailed values of $p < 0.05$ were considered statistically significant and performed in Stata 17.

Results: The right hippocampus was >20% softer in *APOE* $\epsilon 4$ carriers compared to *APOE* $\epsilon 3$ homozygotes ($p=0.013$; Cohen's $d = 2.08$; Table 1). The left hippocampus showed a similar trend but did not reach statistical significance ($p=0.131$). There was some indication that the thalamus was stiffer in *APOE* $\epsilon 4$ carriers relative to non-carriers ($p=0.058$). There were no significant group differences in damping ratio, or within the two cortical areas.

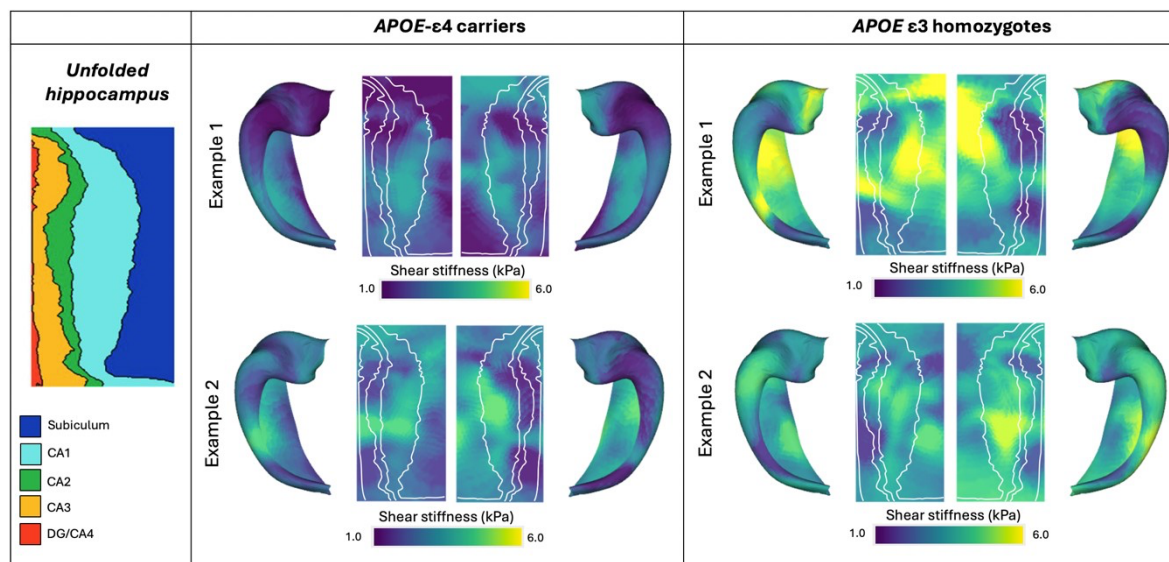


Figure 1. Examples of shear stiffness measurements (scaled from 1-6 kPa) resampled onto the midthickness surface of the hippocampus. Both left and right hemispheres and the folded and unfolded hippocampus are shown. On visual inspection, it appears as though hippocampal tissue is softer in *APOE* $\epsilon 4$ carriers relative to *APOE* $\epsilon 3$ homozygotes.

Table 1. Summary statistics for *APOE* $\epsilon 4$ carriers and *APOE* $\epsilon 3$ homozygotes.

Brain region		<i>APOE</i> $\epsilon 4$ carriers (M $\pm$ SD)	<i>APOE</i> $\epsilon 3$ homozygotes (M $\pm$ SD)	T-test (p value)	Cohen's <i>d</i>	Difference
Shear stiffness (kPa)						
Hippocampus	L	2.530 $\pm$ 0.70	3.060 $\pm$ 0.48	0.131	N/A	-18.96%
	R	2.567 $\pm$ 0.31	3.178 $\pm$ 0.27	0.013*	2.082	-21.27%
Thalamus	L	3.322 $\pm$ 0.20	2.935 $\pm$ 0.27	0.058	1.652	+12.37%
	R	3.017 $\pm$ 0.18	2.942 $\pm$ 0.49	0.780	N/A	+2.52%
Posterior cingulate	L	3.700 $\pm$ 0.66	3.397 $\pm$ 0.37	0.453	N/A	+8.54%
	R	3.554 $\pm$ 0.56	3.319 $\pm$ 0.40	0.523	N/A	+6.84%
Postcentral gyrus	L	2.119 $\pm$ 0.20	2.178 $\pm$ 0.13	0.634	N/A	-2.75%
	R	2.117 $\pm$ 0.17	2.138 $\pm$ 0.30	0.904	N/A	0.99%
Damping ratio, ξ						
Hippocampus	L	0.212 $\pm$ 0.04	0.209 $\pm$ 0.04	0.905	N/A	+1.43%
	R	0.240 $\pm$ 0.04	0.224 $\pm$ 0.05	0.628	N/A	+6.89%
Thalamus	L	0.240 $\pm$ 0.03	0.283 $\pm$ 0.04	0.119	N/A	-16.44%
	R	0.274 $\pm$ 0.03	0.304 $\pm$ 0.04	0.253	N/A	-10.38%
Posterior cingulate	L	0.131 $\pm$ 0.08	0.102 $\pm$ 0.05	0.524	N/A	+24.89%
	R	0.143 $\pm$ 0.13	0.120 $\pm$ 0.10	0.789	N/A	+17.49%
Postcentral gyrus	L	0.325 $\pm$ 0.04	0.307 $\pm$ 0.04	0.571	N/A	+5.70%
	R	0.318 $\pm$ 0.05	0.319 $\pm$ 0.07	0.982	N/A	-0.31%

*Statistically significant at $p < 0.05$.

Discussion: Among cognitively healthy, mid-life participants, *APOE* $\epsilon 4$ carriers exhibit reduced mechanical integrity in the hippocampus, evidenced through lower tissue stiffness. Given that a reduction in grey matter cerebral blood flow has been reported in young *APOE* $\epsilon 4$ carriers in their twenties¹⁹, suggests changes in cerebral vasculature may act as a mechanism for AD risk alleles to influence tissue mechanics²⁰. Preliminary signs of an increase in the stiffness of the left thalamus in *APOE* $\epsilon 4$ carriers warrants further study but complements findings of lower qMRT-based macromolecular proton fraction in the left thalamus in a similar demographic²¹. This work establishes a crucial foundation for future research by demonstrating that MRE can be used effectively to study at-risk populations. A limitation here is the preliminary sample size of $N=8$; but the results support the need to extend this work to larger cohorts of high-risk populations identified through AD polygenic risk scores and environmental risk factors. Importantly, tissue mechanical properties have a profound effect on other biological and chemical systems through mechanobiological signalling pathways²², and this early change in mechanics in at-risk individuals could play a key role in AD development.

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