

Lower state anxiety and white matter hyperintensity volumes characterize SuperAgers identified through multiple verbal memory tests

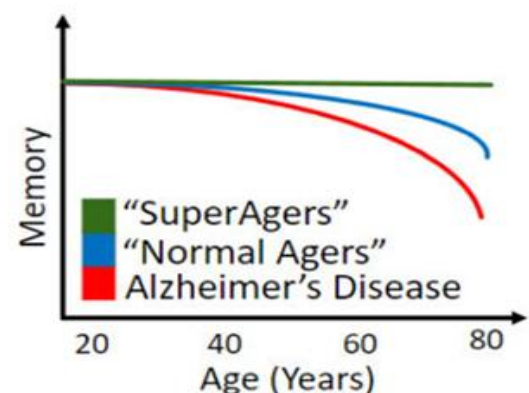


Niklas Behrenbruch^{1,2,3}, Beate Schumann-Werner^{1,3}, Svenja Schwarck^{1,3}, Eóin N. Molloy^{1,4}, Berta Garcia-Garcia^{1,4}, Larissa Fischer^{1,5}, Anna-Therese Büchel¹, Jose Bernal^{1,3,6,7}, Niklas Vockert¹, Patrick Müller^{1,8}, Hermann Esselmann⁹, Constanze I. Seidenbecher^{10,11}, Björn H. Schott^{9,10,12}, Henryk Barthel^{13,14}, Osama Sabri¹³, Jens Wiltfang^{9,12,15}, Michael C. Kreissl^{1,4}, Emrah Düzel^{1,2,3,11}, and Anne Maass^{1,2,11}



Introduction

- SuperAgers:** Individuals aged ≥ 80 years with exceptional episodic memory performance, comparable to cognitively healthy individuals aged **50–65 years**¹.
- The challenge:** Identification often relies on a **single verbal memory test**, which varies across studies and limits comparability².
- Aim:** To identify the lifestyle, health, brain, and biomarker characteristics of **"robust" verbal SuperAgers**, defined as meeting the memory criterion in **at least 2 out of 3 verbal memory tests**.



Methods

- SuperAger classification:** 106 cognitively normal elderly (≥ 79.5 y; Z03 CRC1436 cohort³); "robust" verbal SuperAging defined by sex/education-adjusted performance matching ≥ 50 –65y norms in at least 2 out of 3 verbal memory tests (VLMT/CVLT, CERAD+, FCSRT) and $\geq$ age/sex/education-norms for non-memory criteria (adapted Northwestern criteria).
- Statistical analysis:** Biopsychosocial and brain variables modeled via Elastic Net (glmnet; 10-fold CV, 50 repeats) predicting "robust" verbal SuperAging vs. typical aging (fulfilling zero memory criteria); validated via AUC (95% CI). Plasma biomarkers (FDR-corrected) and Tau-PET MetaROI burden compared via one-tailed Welch's t-tests. APOE $\epsilon 2$ and $\epsilon 4$ carriers and cumulative risk trends mapped via Fisher's exact tests and binomial logistic regression.

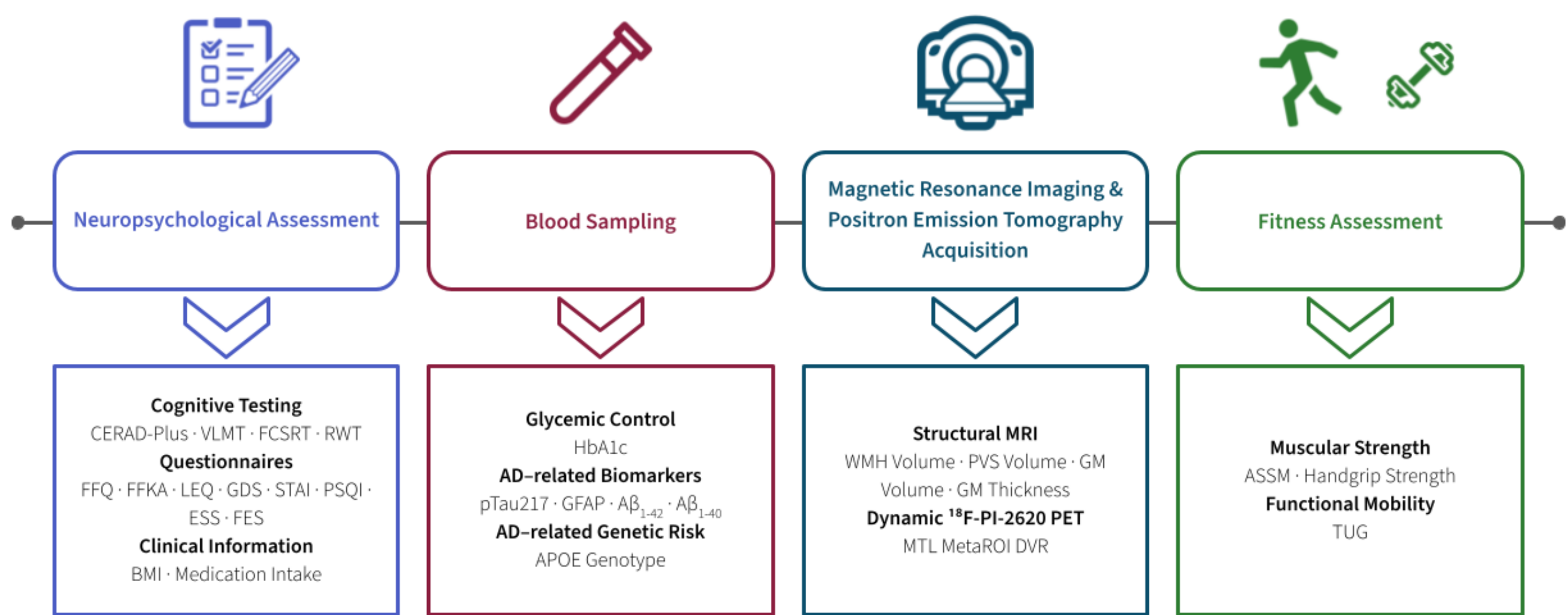
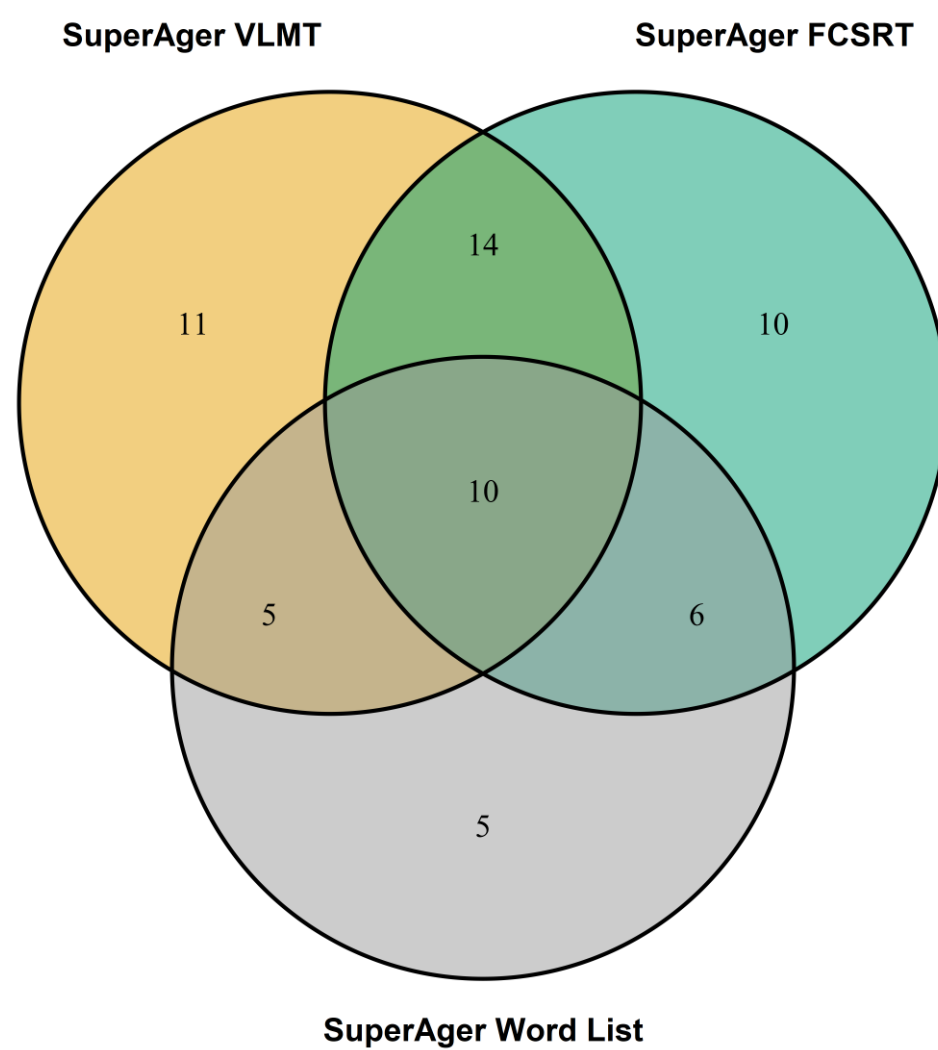


Figure 1. Study Overview. During test days one and two, cognitive testing was conducted and health-related information was collected, including questionnaires completed at home. On test day three, blood samples were collected for HbA1c analysis at a local clinical routine laboratory, for Alzheimer's disease-related plasma biomarkers using the fully automated Lumipulse G600II platform, and for APOE genotyping from whole blood using a PCR-based restriction fragment length polymorphism (RFLP) approach. During test days four and five, MRI data were acquired, including T1-weighted Multi-echo magnetization-prepared rapid gradient echo (MPRAGE) and Fluid-attenuated inversion recovery (FLAIR) sequences to estimate brain structural properties. In a subsample, dynamic ¹⁸F-Pi-2620 PET was obtained to assess tau burden. During test day six, participants underwent a short fitness assessment probing muscular strength, functional mobility, and vascular function. CERAD, Consortium to Establish a Registry for Alzheimer's Disease; VLMT, Verbal Lern- und Merkfähigkeitstest (German version of the Rey Auditory Verbal Learning Test); FCSRT, Free and Cued Selective Reminding Test; RWL, Regensburger Wortflüssigkeitstest (word fluency); FFQ, Food Frequency Questionnaire; FFKA, Freiburger Fragebogen zur körperlichen Aktivität (physical activity); LEQ, Lifetime of Experiences Questionnaire; GDS, Geriatric Depression Scale; STAI, State-Trait Anxiety Inventory; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; FES, Falls Efficacy Scale; BMI, Body Mass Index; AD, Alzheimer's disease; GFAP, Glial Fibrillary Acidic Protein; APOE, Apolipoprotein E; WMH, White Matter Hyperintensities; PVS, Perivascular Spaces; GM, Gray Matter; MTL, Medial Temporal Lobe; metaROI, meta-Region Of Interest; DVR, Distribution Volume Ratio; ASSM, Appendicular Skeletal Muscle Mass; TUG, Timed Up and Go test; P_{aor} , Pulse Wave Velocity of the aorta.

Discussion

- SuperAger status varies across verbal memory tests and may reflect a **graded** rather than unitary **phenomenon**.
- We found **minimal differences** in lifestyle, health, personality, or brain structure between robust verbal SuperAgers and typical agers.
- However, robust SuperAgers exhibited **lower anxiety, faster motor speed, lower WMH volume, and trends toward lower AD genetic risk and MTL tau burden**, collectively suggesting **brain maintenance** as a potentially underlying mechanism.

Results



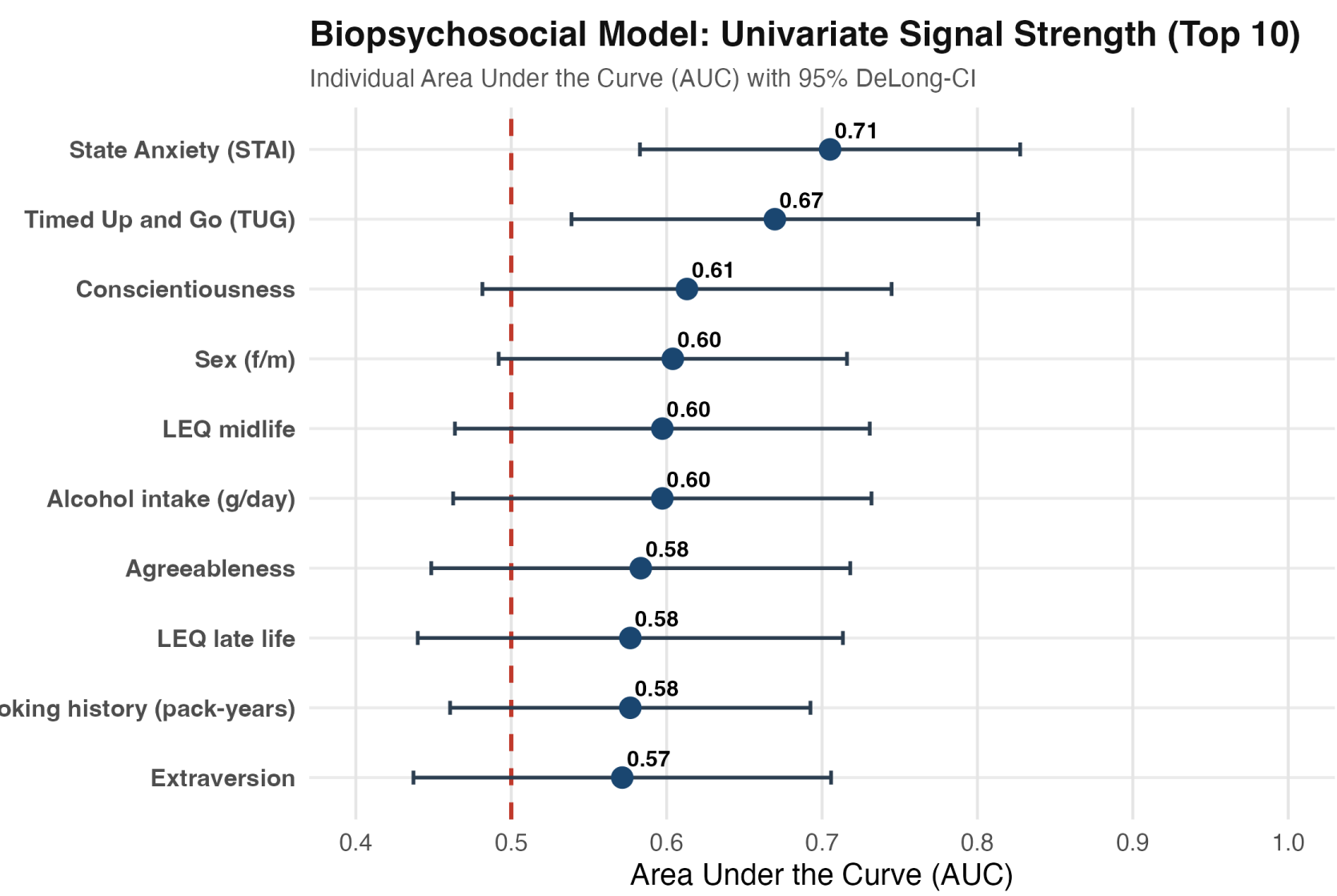
Variable	Overall	Robust SuperAger	Typical Ager	p
n	71	35	36	
age (median [IQR])	82.91 [81.21, 84.67]	82.90 [81.31, 84.24]	83.54 [81.21, 85.03]	0.314
sex = female (%)	27 (38.0)	17 (48.6)	10 (27.8)	0.119
Education years (median [IQR])	15.00 [13.00, 17.00]	15.00 [13.00, 16.00]	15.00 [13.00, 17.00]	0.424
MMSE (median [IQR])	29.00 [28.00, 29.00]	29.00 [28.00, 29.00]	28.00 [28.00, 29.00]	0.793
CERAD+ total z-value (median [IQR])	0.46 [0.32, 0.77]	0.70 [0.52, 0.94]	0.35 [0.05, 0.44]	<0.001
VLMT delayed recall (median [IQR])	9.00 [7.00, 11.00]	11.00 [10.00, 13.00]	7.50 [6.75, 8.00]	<0.001
CERAD word list recall (median [IQR])	7.00 [6.50, 8.00]	8.00 [8.00, 9.00]	7.00 [6.00, 7.00]	<0.001
FCSRT free recall (median [IQR])	32.00 [27.00, 36.00]	36.00 [33.50, 38.00]	27.50 [24.00, 29.00]	<0.001

Lifestyle, health & personality

Predictors:

Age, sex, education years, healthy eating index DEGS, FFKA sports, appendicular skeletal muscle mass (ASMM), handgrip strength, timed up and go (TUG), lifetime of experiences questionnaire (LEQ) early life, LEQ midlife, LEQ late life, openness (BFI), neuroticism (BFI), conscientiousness (BFI), extraversion (BFI), agreeableness (BFI), body mass index (BMI), HbA1c, dyslipidemia status, number of antihypertensive drugs, smoking pack-years, alcohol intake, geriatric depression scale (GDS), trait anxiety (STAI), state anxiety (STAI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Falls Efficacy Scale (FES)

N = 71; Alpha = 1; Lambda = 0.11
CV-AUC [95%-CI]:
0.602 [0.403-0.981]

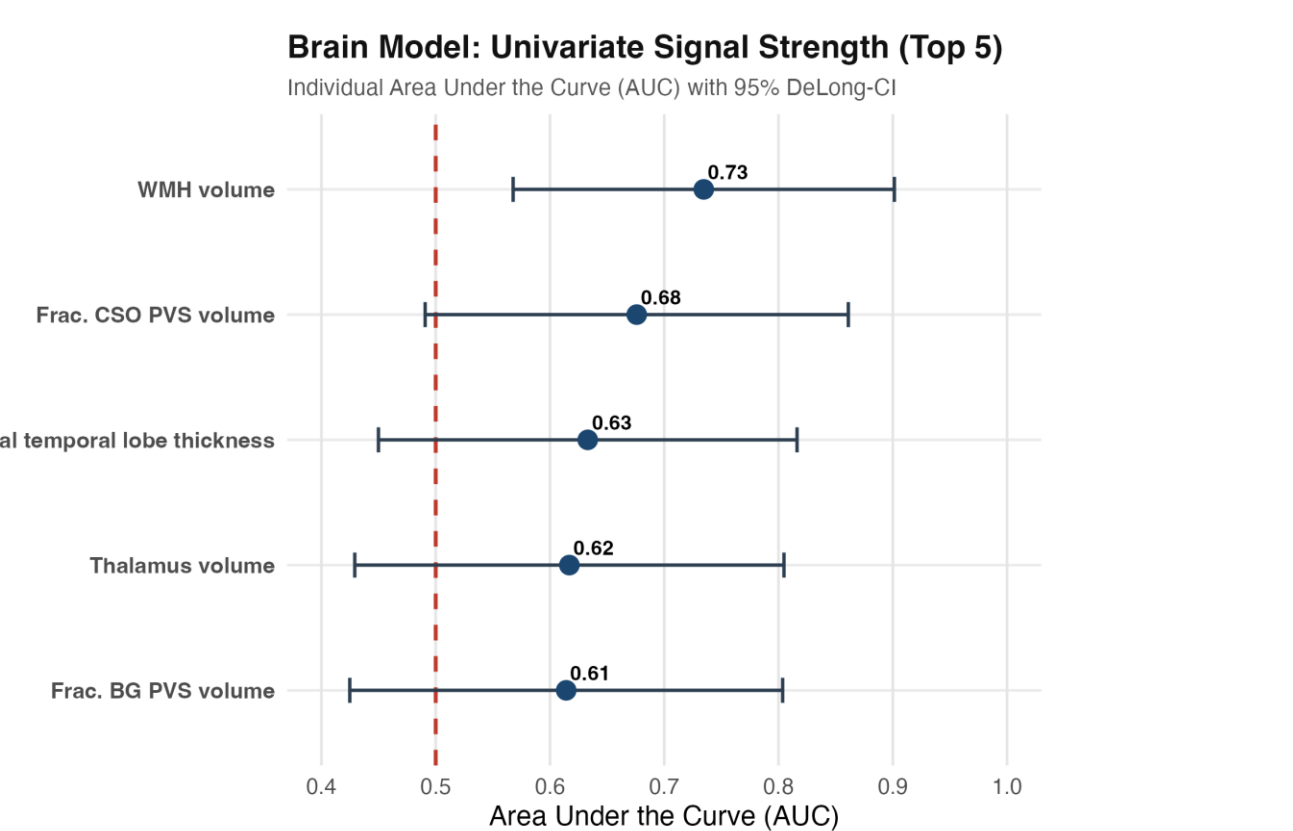


Brain

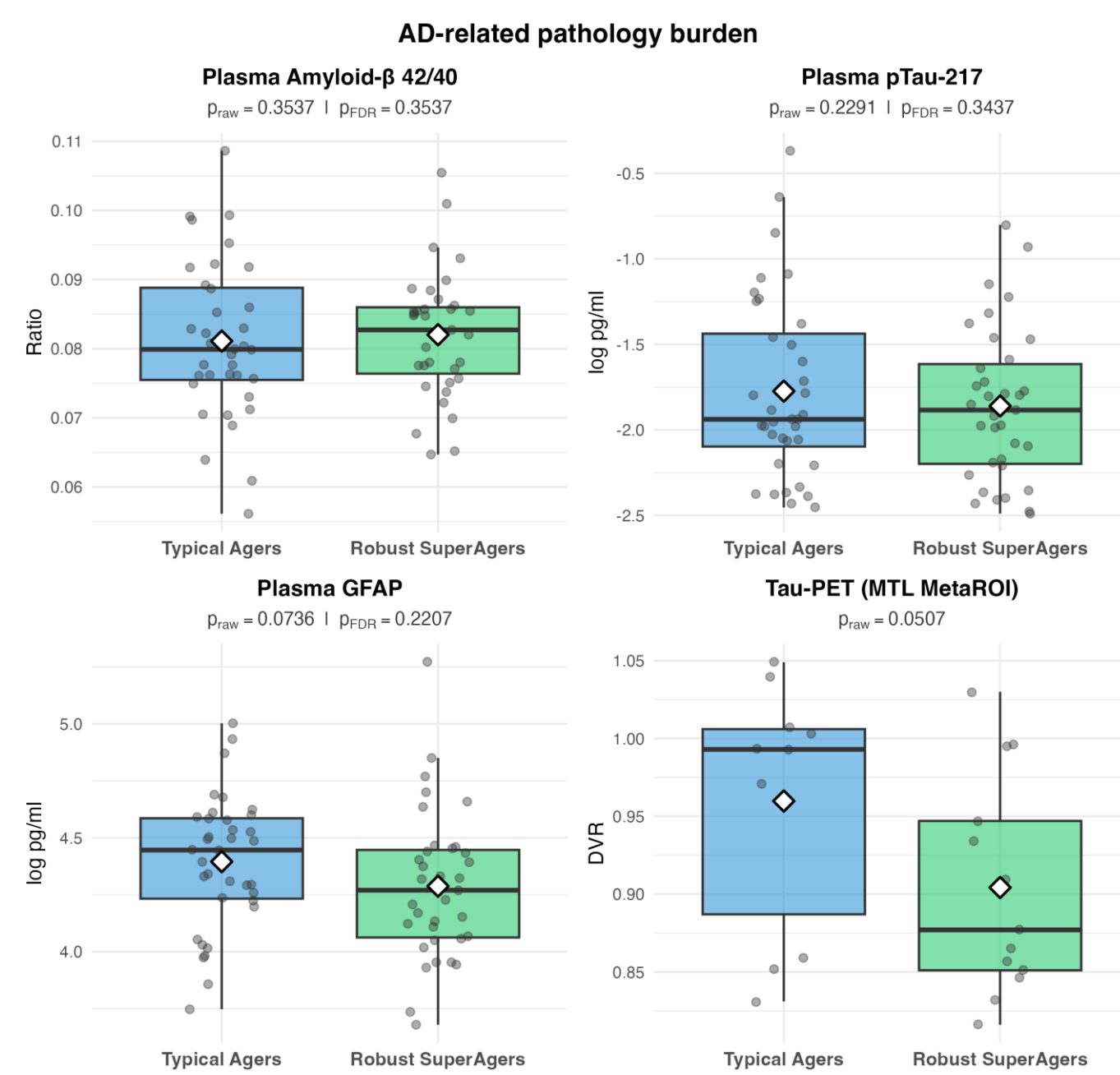
Predictors:

Age, sex, education years, white matter hyperintensity (WMH) volume, basal ganglia perivascular space (PVS) volume, centrum semiovale PVS volume, midbrain PVS volume, hippocampal volume, anterior cingulate cortex thickness, medial temporal lobe thickness, thalamus volume

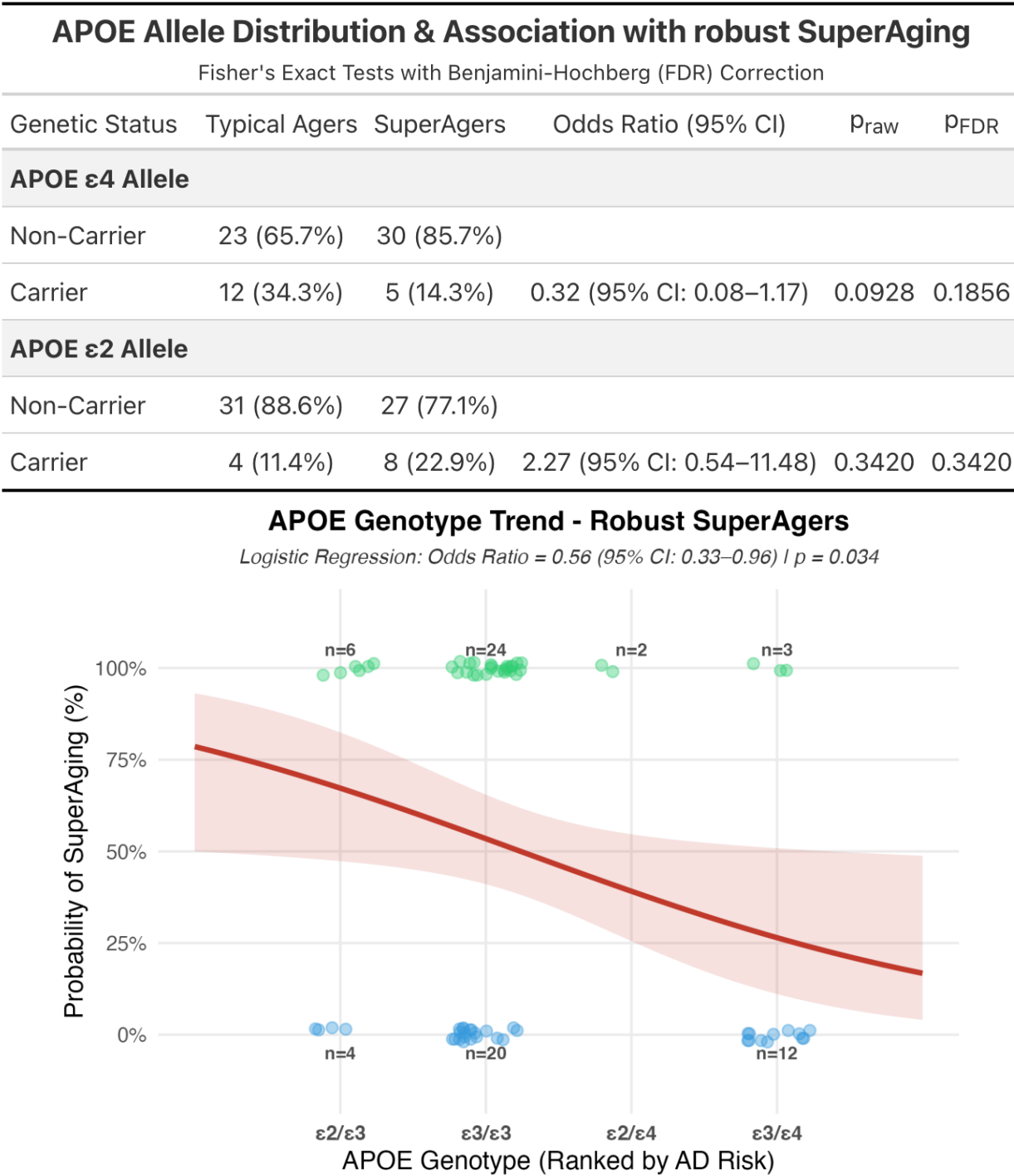
N = 36; Alpha = 0; Lambda = 0.53
CV-AUC [95%-CI]:
0.537 [0.500-1.000]



Blood markers



APOE genotype



Affiliations:
1 German Center for Neurodegenerative Diseases (DZNE), Leipzig Str. 44, Magdeburg, 39120, Germany
2 Institute of Biology (IBIO), Otto von Guericke University Magdeburg, Leipzig Str. 44, Magdeburg, 39106, Germany
3 Institute of Cognitive Neurology and Dementia Research (IKND), Otto von Guericke University Magdeburg, Leipzig Str. 44, Magdeburg, 39120, Germany
4 Division of Nuclear Medicine, Department of Radiology & Nuclear Medicine, Faculty of Medicine, Otto von Guericke University Magdeburg
5 Department of Neurobiology and Behavior, University of California, Irvine, 92697, USA
6 Institute for Neuroscience and Cardiovascular Research, Row Fogo Centre for Research into Ageing and The Brain, Department of Neuroimaging Sciences, The University of Edinburgh, UK
7 Department Artificial Intelligence in Biomedical Engineering (AIBE), Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany
8 University Hospital Magdeburg, Division of Cardiology and Angiology, Leipzig Str. 44, Magdeburg, 39120, Germany
9 Department for Psychiatry and Psychotherapy, University Medical Center Göttingen (UMG), Von-Siebold-Str. 5, Göttingen, 37075, Germany
10 Leibniz Institute for Neurobiology (LIN), Brenneckestraße 6, Magdeburg, 39118, Germany
11 Center for Behavioral Brain Sciences (CBBS), Universitätsplatz 2, Magdeburg, 39106 Germany
12 German Center for Neurodegenerative Diseases, Göttingen, Von-Siebold-Straße 3A, 37075, Germany
13 Department of Nuclear Medicine, University Hospital Leipzig, Liebigstraße 18, Leipzig, 04103, Germany
14 Department of Nuclear Medicine, Municipal Hospital Dessau
15 Neurosciences & Signaling Group, Institute of Biomedicine (BIMED), Department of Medical Sciences, University of Aveiro, Aveiro, 3810-193 Portugal

References:
[1] Harrison TM, Weintraub S, Mesulam MM, Rogalski E. Superior memory and higher cortical volumes in unusually successful cognitive aging. J Int Neuropsychol Soc. 2012 Nov;18(6):1081-5. doi: 10.1017/S1558517112000847. PMID: 23156231. PMCID: PMC3547607.
[2] Caro-Pascual M, Frank D, Ramponi C, Draganski B. Defining 'successful' episodic memory ageing: Implications of methodological heterogeneity. Neurosci Biobehav Rev. 2026 Jul;186:106707. doi: 10.1016/j.neurobiorev.2026.106707. Epub 2026 Apr 25. PMID: 42044759.
[3] Behrenbruch N, Schwarck S, Schumann-Werner B, Molloy EN, Garcia-Garcia B, Hochkeppeler A, Fischer L, Büchel AT, Incesoy EI, Bernal J, Vockert N, Müller P, Behnisch G, Morgado B, Esselmann H, Seidenbecher CI, Schott BH, Barthel H, Sabri O, Wiltfang J, Kreissl MC, Düzel E, Maass A. A physically and mentally active lifestyle relates to younger brain and cognitive age. Geroscience. 2026 Apr;48(2):1853-1873. doi: 10.1007/s11357-025-01764-w. Epub 2025 Jul 7. PMID: 40619559. PMCID: PMC12972277.