

Laura Lang^{1,2}, Alejandro Valenzuela^{23,24}, Pamela Martino-Adami³, Oliver Peters^{4,5}, Julian Hellmann-Regen^{4,5}, Josef Priller^{5,6}, Anja Schneider^{1,2}, Jens Wiltfang^{7,8}, Katharina Buerger^{9,10}, Robert Perneczky^{9,11}, Stefan Teipel^{12,13}, Christoph Laske^{14,15}, Annika Spottke^{2,16}, Frederic Brosseron², Michael Wagner^{1,2}, Emrah Düzel^{17,18}, Frank Jessen^{2,19}, Agustin Ruiz^{23,25}, Amanda Cano²³, Raquel Puerta^{23,26}, Natalie Marchant²⁰, Ruth Frikke-Schmidt²¹, Jean-Charles Lambert²², Victoria Fernandez^{23,24}, Alfredo Ramirez³, Luca Kleineidam^{1,2}

1. Department of Old Age Psychiatry and Cognitive Disorders, University Hospital Bonn, Germany, 2. German Center for Neurodegenerative Disease (DZNE), Bonn, Germany, 3. Division of Neurogenetics and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany, 4. Charité Universitätsmedizin Berlin, Department of Psychiatry and Neurosciences, Berlin, Germany, 5. German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany, 6. Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany, 7. Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, University of Goettingen, Goettingen, Germany, 8. German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany, 9. German Center for Neurodegenerative Diseases (DZNE), Munich, Germany, 10. Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany, 11. Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, 12. Department of Psychosomatic Medicine, Rostock University Medical Center, Rostock, Germany, 13. German Center for Neurodegenerative Diseases (DZNE), Rostock-Greifswald, Germany, 14. German Center for Neurodegenerative Diseases (DZNE), Tuebingen, Germany, 15. Section for Dementia Research, Department of Psychiatry and Psychotherapy, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany, 16. Clinic for Parkinson's, Sleep and Movement Disorders, Centre for Neurology, University Hospital Bonn, Bonn, Germany, 17. German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany, 18. Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany, 19. Department of Psychiatry and Psychotherapy, University of Cologne, Medical Faculty, Cologne, Germany, 20. Division of Psychiatry, University College London, London, UK, 21. Department of Clinical Biochemistry, Copenhagen University Hospital - Rigshospitalet, Copenhagen N, Denmark, 22. Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, LabEx DISTALZ - U1167-RID-AGE Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, Lille, France, 23. Ace Alzheimer Center Barcelona, Universitat Internacional de Catalunya (UIC), Barcelona, Spain, 24. Networking Research Center on Neurodegenerative Diseases (CIBERNED), Instituto de Salud Carlos III, Madrid, Spain, 25. Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Science Center, San Antonio, Texas, USA, 26. PhD Program in Biotechnology, Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain

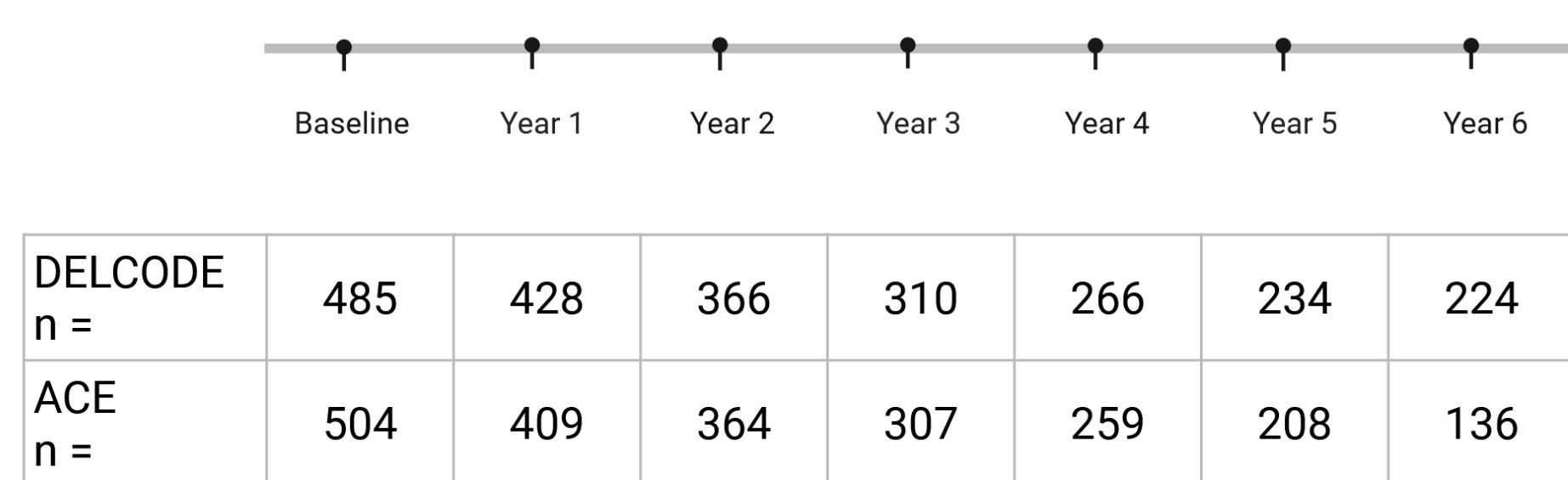
Background

- Shared markers change during Age and with AD status while simultaneously they are associated with memory decline
- They help prioritize pathways related to Age and AD pathology that both are major risk factors of cognitive loss

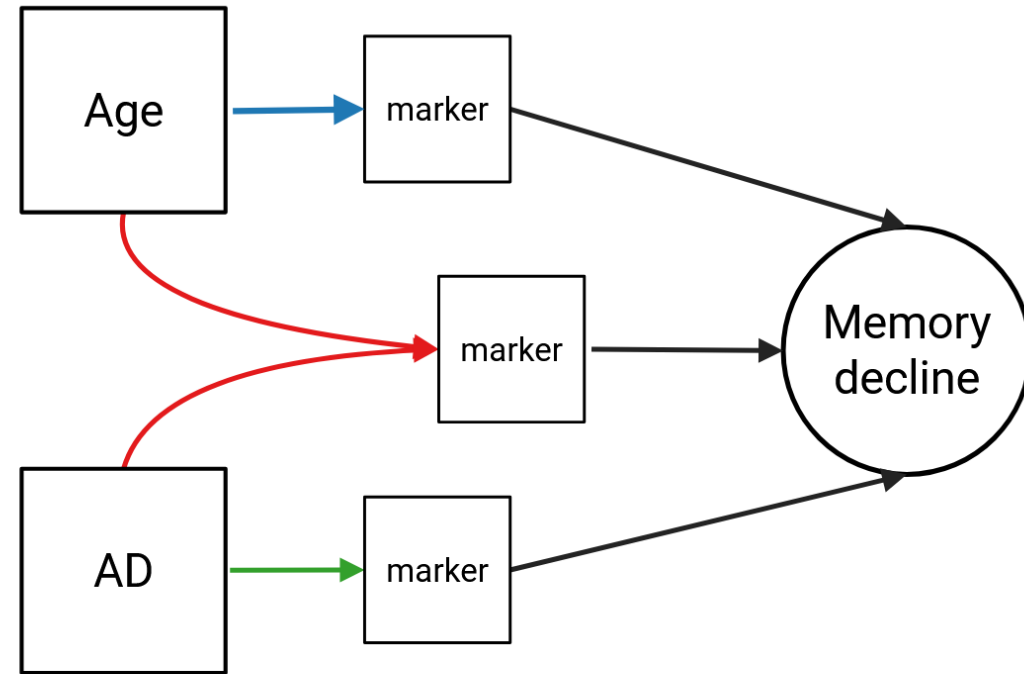
Analysis design

CSF proteins (OLINK explore)

memory word list

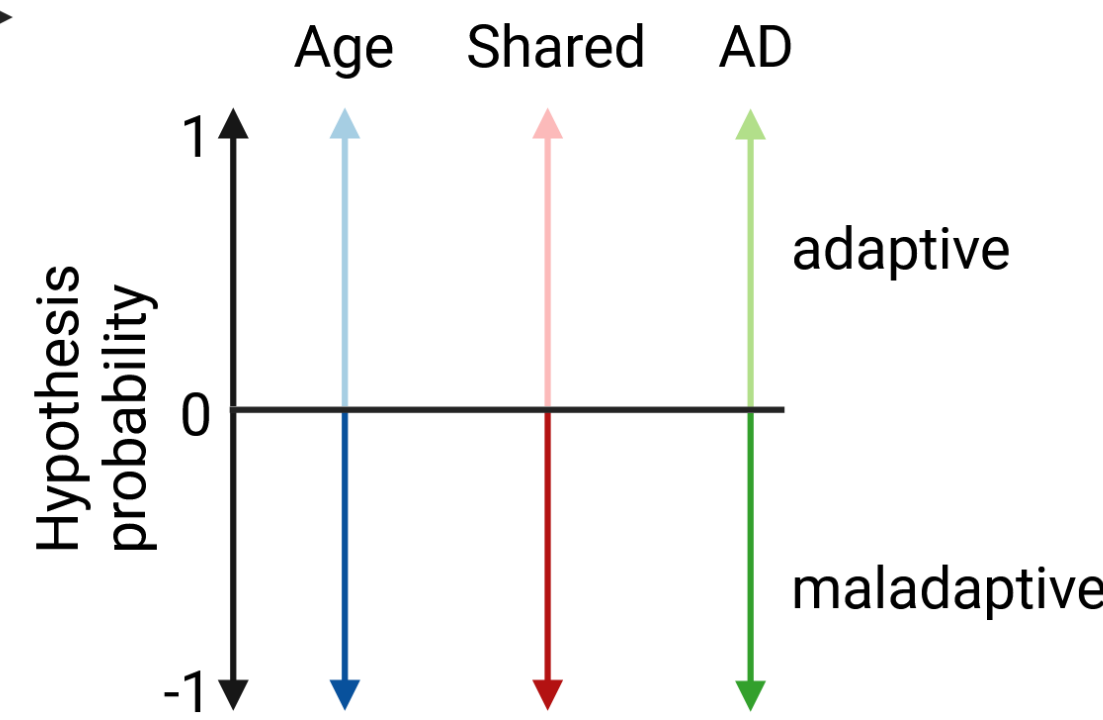


Structural equation model:
Latent growth model to estimate the effects of AD and Age on the marker and marker effect on memory



* model corrected for sex, education and CSF reference proteins (Karlsson et al., 2024)

Bayesian statistic:
Combines Age, AD and Memory estimate in hypotheses probabilities

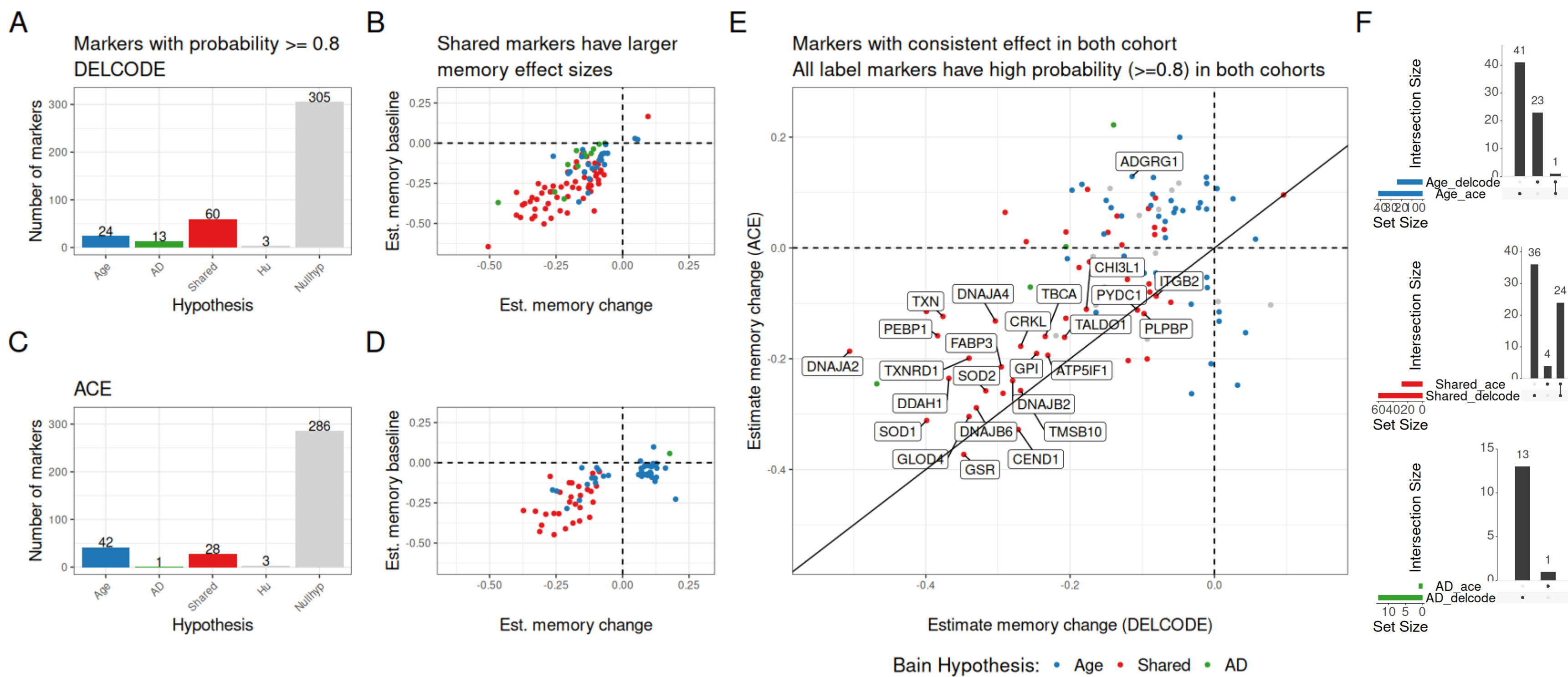


Cohort details

		DELCODE	ACE
	Age	71 [59-89]	72 [51-92]
Sex	Male	253	250
	Female	235	269
Diagnosis	Healthy	126	--
	SCD	197	44
	MCI	105	465
	AD	60	--
AD (Aβeta42 /pTau181)	Negative	310	280
	Positive	176	229

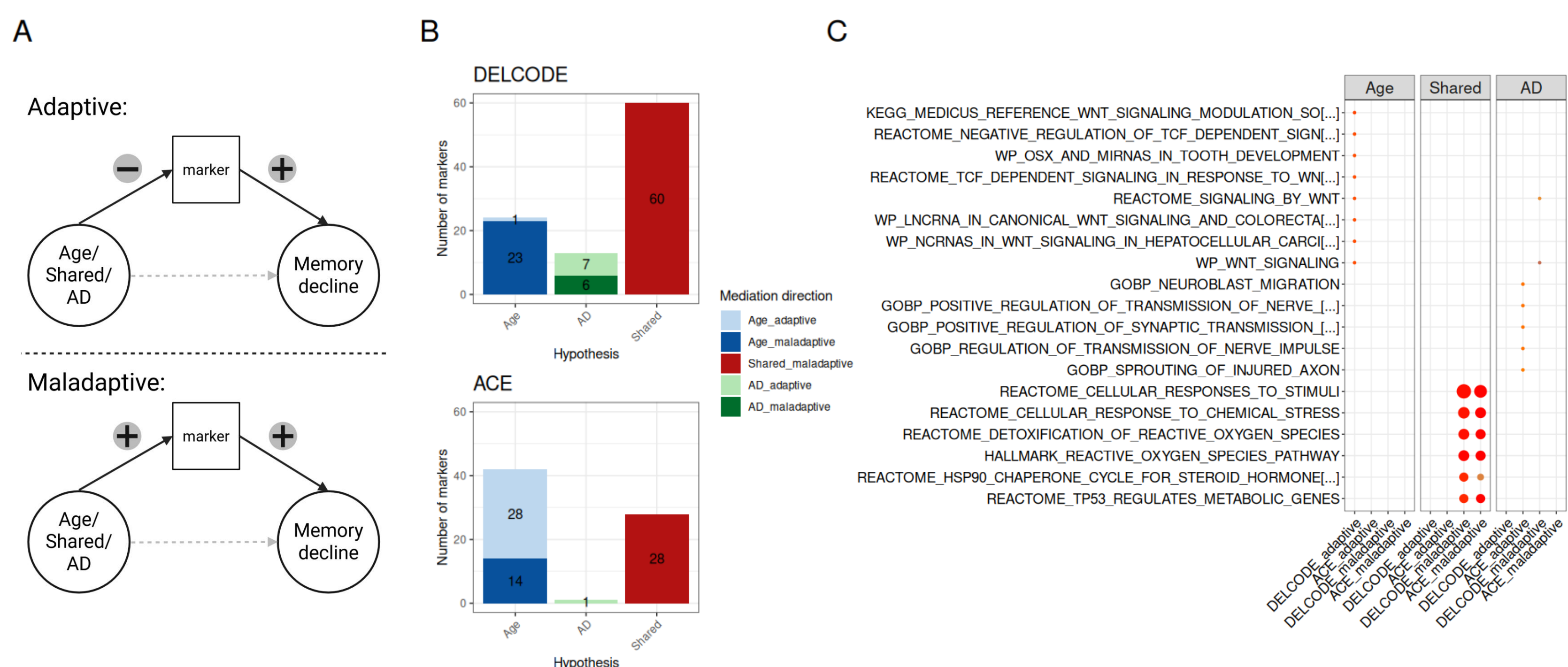
The OLINK explore panel was measured in CSF at baseline and memory was assessed using a word list memory task a with up to 6 yearly follow ups. At baseline 485 and 504 participants were included in DELCODE and ACE study cohort, respectively. Lavaan was used to set up a structural equation model to estimate the effects of Age and AD on the marker and marker effects on memory at baseline (intercept) and memory decline (sum of total change in linear and quadratic slope at year 6). Using the Bayesian statistic tool bain the model estimates were combined in hypothesis probabilities using the direction of effect of Age, AD and memory decline to assign the markers to the Age only, AD only and shared effects and give them the direction of adaptive and maladaptive.

CSF proteins linked to shared downstream processes of AD and aging show more consistent cross-sectional and longitudinal associations with memory function across cohorts



A: Number of markers assigned to a specific hypothesis with 0.8 or higher probability in DELCODE. B: Model effect strength of marker with regard to memory at baseline and memory change in DELCODE. C: Number of markers assigned to a specific hypothesis with 0.8 or higher probability in ACE. D: Model effect strength of marker with regard to memory at baseline and memory change in ACE. E: Markers assigned to the same hypothesis in both cohorts and non-matching hypothesis in grey. Labeled markers reach a probability of 0.8 or higher in both cohorts. F: Number of markers overlapping between cohorts for Age, Shared and AD group respectively.

Shared markers mediating maladaptive responses to Age and AD processes related to cellular stress and ROS leading to more memory decline



A: Grouping the markers by direction of mediation effect based on the sign of the indicated model estimate. Adaptive is indicated when the mediation effects have different signs. Maladaptive is indicated when the mediation effects have similar signs. B: Number of Age, Shared and AD markers in the adaptive and maladaptive group. C: Overrepresentation analysis of the markers in each category and direction performed using Reaction, KEGG, Hallmark and GOBP databases.

Summary & Conclusion

- Out of 1056 CSF markers 60 and 28 markers were identified as shared between Age and AD in DELCODE and ACE, respectively, with 24 markers overlapping
- Shared markers showed more consistent and stronger effects on memory function at baseline and memory decline in both cohorts
- Proteins related to maladaptive processes in both, AD and aging are enriched for key pathways of cellular stress and reactive oxygen species (ROS)
- The identified proteins nominate biomarkers for indexing AD and aging driven memory decline related to cellular stress and ROS