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Hippocampal Amyloid-Beta And Tau Distributions Differentially Affect Cognition In Centenarians

Susan K. Rohde[1,2,3,4] | Maruelle C. Luimes[2,3,4] | Annemieke J.M. Rozemuller[5,6] | Marieke J.I. Graat[7] | Myke E. van der Hoorn[7] | Dominique A.H. Daatselaar[7] | Marc Hulsman[7,8,9] | Sietske A.M Sikkes[10] | Timothy E. Richardson[11] | Jeroen J.M. Hoozemans[4,12] | Jamie M. Walker[11] | Henne Holstege[3,13,14,15]

[1]Amsterdam UMC, location VUmc, Amsterdam, Netherlands, Amsterdam, Netherlands, Amsterdam, Netherlands

[2]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands, Amsterdam, Netherlands

[3]Section Genomics of Neurodegenerative Diseases and Aging, Department of Clinical Genetics, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands, Amsterdam, Netherlands

[4]Department of Pathology, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Netherlands, Amsterdam, Netherlands, Amsterdam, Netherlands

[5]Netherlands Institute for Neuroscience, Amsterdam, Netherlands

[6]Department of Pathology, Amsterdam Neuroscience, Amsterdam UMC, Amsterdam, Noord-Holland, Netherlands

[7]Amsterdam UMC, Amsterdam, Netherlands

[8]Genomics of Neurodegenerative Diseases and Aging, Human Genetics, Amsterdam UMC, Amsterdam, Netherlands

[9]Alzheimer Centre, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands, Amsterdam, Netherlands

[10]Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands

[11]Icahn School of Medicine at Mount Sinai, New York, NY, USA

Abstract

Background: The hippocampus is differentially affected in Alzheimer's disease neuropathologic change (ADNC) versus primary age-related tauopathy (PART), an amyloid-beta (Aβ)-independent tauopathy: the CA2/CA1 hyperphosphorylated tau (pTau)-ratio is higher in PART, which inversely correlates with Aβ-burden. However, as the aging brain often presents mixed rather than uniform pathologies, we questioned whether these distinct hippocampal pTau distributions persist into extreme ages and how hippocampal Aβ- and pTau-distributions correlate with cognition in centenarians.

Method: We quantified Aβ- (6F/3D) and pTau (AT8)-burdens across eight hippocampal and parahippocampal subregions in 112 centenarians (median age 104, IQR 102-105), alongside 11 AD (median age 84, IQR 72-86) and 7 PART cases for comparison (median age 88, IQR 78-92; Figure 1). We compared CA2/CA1-pTau-ratio in centenarians who met PART criteria (Thal phase ≤2, Braak stage I-IV; n = 49) with centenarians who met ADNC criteria (intermediate/high according to NIA-AA guidelines; Thal phase ≥3, Braak stage III-VI; n = 50). Cognitive performance was assessed using 13 neuropsychological tests shortly before brain donation (median 10 months, IQR5-14, n = 72). Robust linear regression models were used to associate subregional Aβ- and pTau-burdens with cognitive performance, while adjusting for age, sex, and education.

Result: In line with previous findings, CA2/CA1-pTau-ratios were higher in younger PART cases compared to AD patients (median 3.0, IQR 2.1-3.6, min-max 1.6-4.2 vs. median 1.2, IQR 0.9-1.4, min-max 0.8-1.4; p <0.001). Surprisingly, CA2/CA1-pTau-ratios in centenarians with PART were comparable to centenarians with ADNC (median 1.3, IQR 1.1-2.0, min-max 0.3-10.8 vs. median 1.2, IQR 1.0-1.8, min-max 0.2-6.2; p = 0.684). Accordingly, CA2/CA1-pTau-ratio in centenarians was unrelated to

[12]Roche Pharma Research and Early Development, Basel, Switzerland

[13]Delft Bioinformatics Lab, Delft University of Technology, Delft, The Netherlands, Delft, Netherlands, Delft, Netherlands

[14]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, Netherlands

[15]VIB-KU Leuven Center for Brain & Disease Research, Leuven, Belgium

Correspondence
Susan K. Rohde, Amsterdam UMC, location VUmc, Amsterdam, Netherlands, Amsterdam, Netherlands, Amsterdam, Netherlands.
Email: s.rohde@amsterdamumc.nl

Aβ-burden, Thal phase or Braak stage. Higher Aβ- and pTau-burdens associated with lower cognition, though through different subregions: cognition associated with Aβ-burden in the hippocampus (CA4, CA3, CA2, CA1/subiculum), whereas pTau-burden in the parahippocampus (presubiculum, entorhinal cortex, fusiform gyrus) associated with cognition.

Conclusion: In the oldest-old, PART and ADNC are less distinguishable by determinants observed in younger individuals: centenarians with ADNC may show age-related Aβ accumulation alongside PART-like pTau patterns, while centenarians meeting PART criteria do not always show PART-like pTau patterns. However, hippocampal Aβ-burden and parahippocampal pTau-burden associate with cognitive decline, highlighting subregional-specific vulnerability to pathology-driven cognitive decline.