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Volumetric Characterization of Medial Temporal Lobe in Down Syndrome Along the Alzheimer's Disease Continuum

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Abstract

Background: Individuals with Down Syndrome (DS) almost invariably develop Alzheimer's Disease (AD), but detecting early clinical changes is challenging due to comorbid intellectual disability, highlighting the importance of non-invasive biomarkers. Neuroimaging of the medial temporal lobe (MTL), a key site of tau pathology, shows promise as an early AD biomarker. Here, we aimed to characterise volumetric patterns of the MTL in DS across the AD clinical continuum, and define associations with AD cerebrospinal fluid (CSF) biomarkers.

Method: 253 adults with DS and 190 euploid controls from the Down Alzheimer Barcelona Neuroimaging Initiative underwent a 3T-MRI protocol, and a comprehensive clinical assessment. T1-weighted images were used to parse the medial temporal lobe using the Automated Segmentation of Hippocampal Subfields (ASHS) pipeline. Segmentation quality was visually inspected and W-scores were computed for MTL subregions (anterior and posterior hippocampus, entorhinal cortex (ERC), parahippocampal cortex (PHC), and Brodmann areas Br35 and Br36) to adjust volumes for total intracranial volume, age and MRI scanner. Non-parametric statistical tests were employed to assess volumes by AD clinical stage, age, and CSF biomarkers of AD.

Result: Hippocampal and Br36 volumes gradually decreased with AD clinical stage, and all subregions were decreased at the dementia stage (dDS) compared to asymptomatic (aDS) and prodromal (pDS) stages (Fig. 1). Surprisingly, significantly larger ERC, PHC and Br35 volumes were found at the asymptomatic DS stage compared to controls. All subregions had decreased volumes with age, with inflexion points around 40y

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for the hippocampus, ERC and Br36, 45y for Br35 and 50y for PHC (Fig. 2). Most subregions exhibited significant correlations with CSF Aß42/40 ratio, p-tau-181 and neurofilament light chain, and the strongest associations were found with anterior and posterior hippocampus (Fig. 3).

Conclusion: AD clinical stage and age are associated with progressive decreasing MTL volumes. Among all subregions, the hippocampus correlated best with CSF measures and appears particularly sensitive to detect early disease processes. These results indicate effectiveness of MTL volumes as a biomarker of early AD pathological changes in DS. Further studies are required to determine the pathological substrate of MTL atrophy and understand the increased volumes in some subregions.

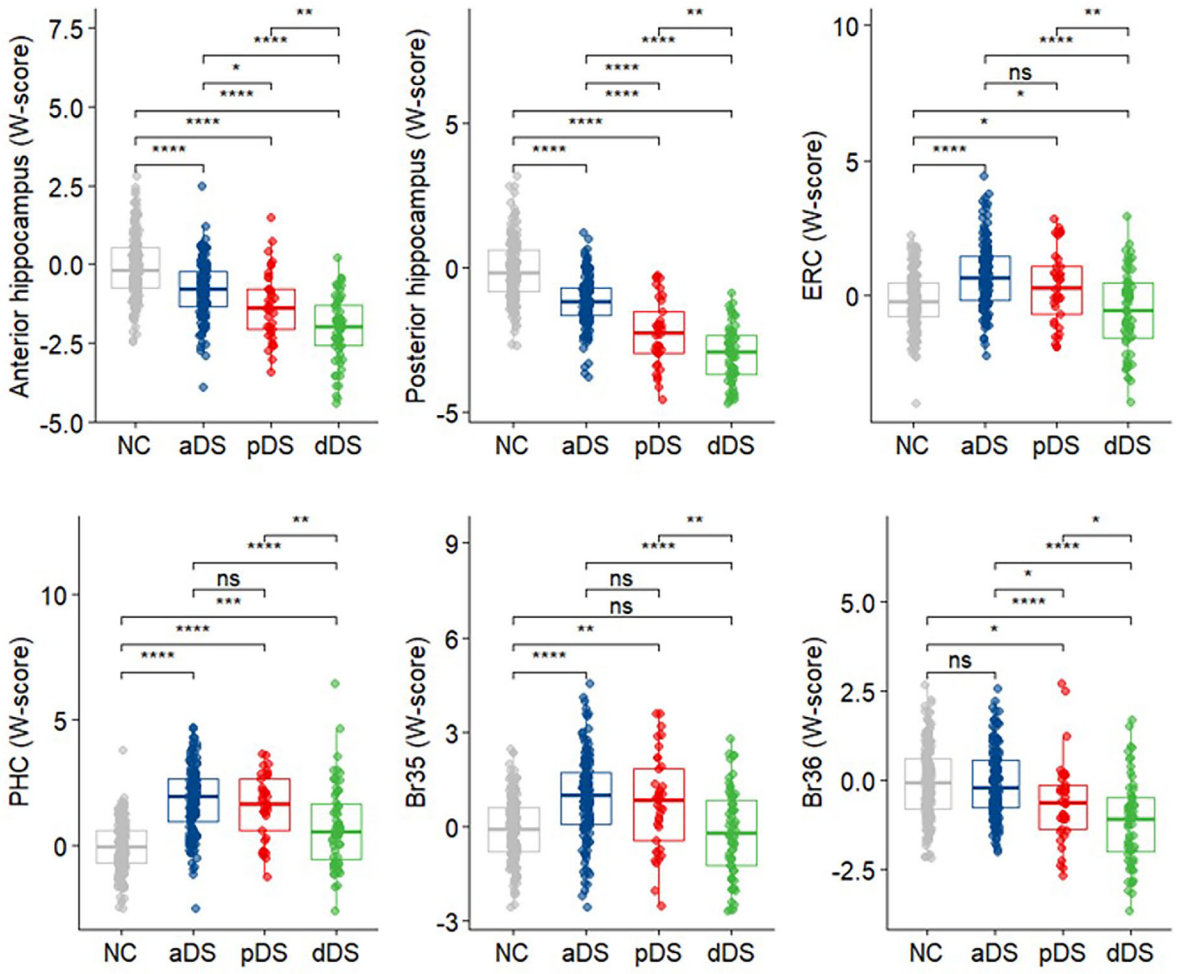

Figure 1: Regional volumes of the Medial Temporal Lobe across the AD continuum. *Regional MTL volumes by Alzheimer's Disease diagnosis in A) Anterior hippocampus, B) Posterior Hippocampus, C) Entorhinal cortex, D) Parahippocampal Cortex, D) Brodmann Area 35, and E) Brodmann Area 36. Values represent W-scored regional volumes. Significance values are expressed as * p=0.05, ** p<0.01, *** p<0.005 and **** p<0.001.* Abbreviations: *aDS/pDS/dDS = Asymptomatic/Prodromal/Demented Down syndrome, Br 35 & Br 36 = Brodmann Areas 35 & 36, ERC = Entorhinal Cortex, NC = Normal Controls (Euploid), PHC = Parahippocampal Cortex.*

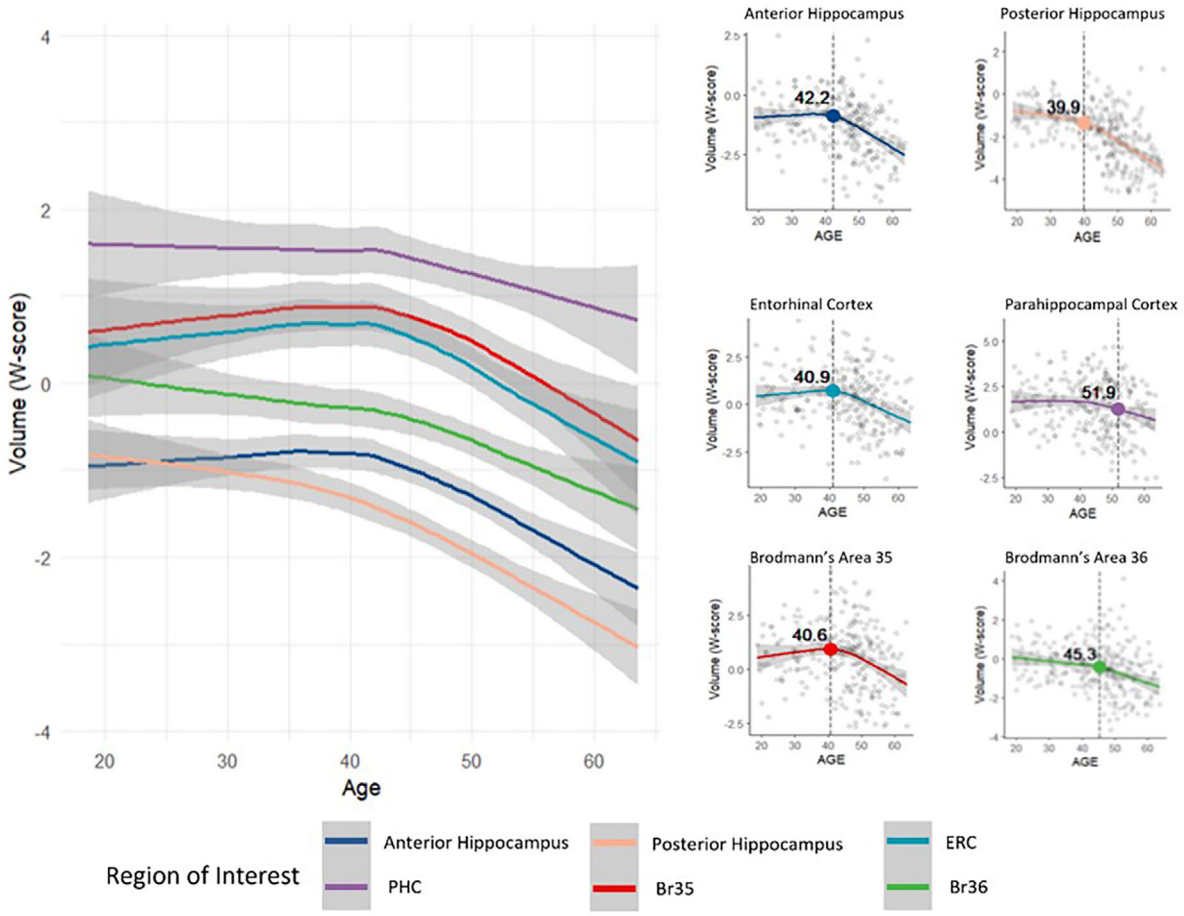

Figure 2: Regional volumes of the Medial Temporal Lobe across age. *Regional MTL volumes (W-score) by age in A) All MTL regions, and with estimated inflexion point in B) Anterior hippocampus, C) Posterior Hippocampus, D) Entorhinal cortex, E) Parahippocampal Cortex, F) Brodmann Area 35, and G) Brodmann Area 36. Lines computed using estimated scatterplot smoothing (LOESS) curves, shaded areas represent the 95% confidence interval. Points represent linear model inflection values. Visual significant difference was considered when the 95% confidence intervals did not overlap.* Abbreviations: *aDS/pDS/dDS = Asymptomatic/Prodromal/Demented Down syndrome, Br 35 & Br 36 = Brodmann Areas 35 & 36, ERC = Entorhinal Cortex, NC = Normal Controls (Euploid), PHC = Parahippocampal Cortex.*

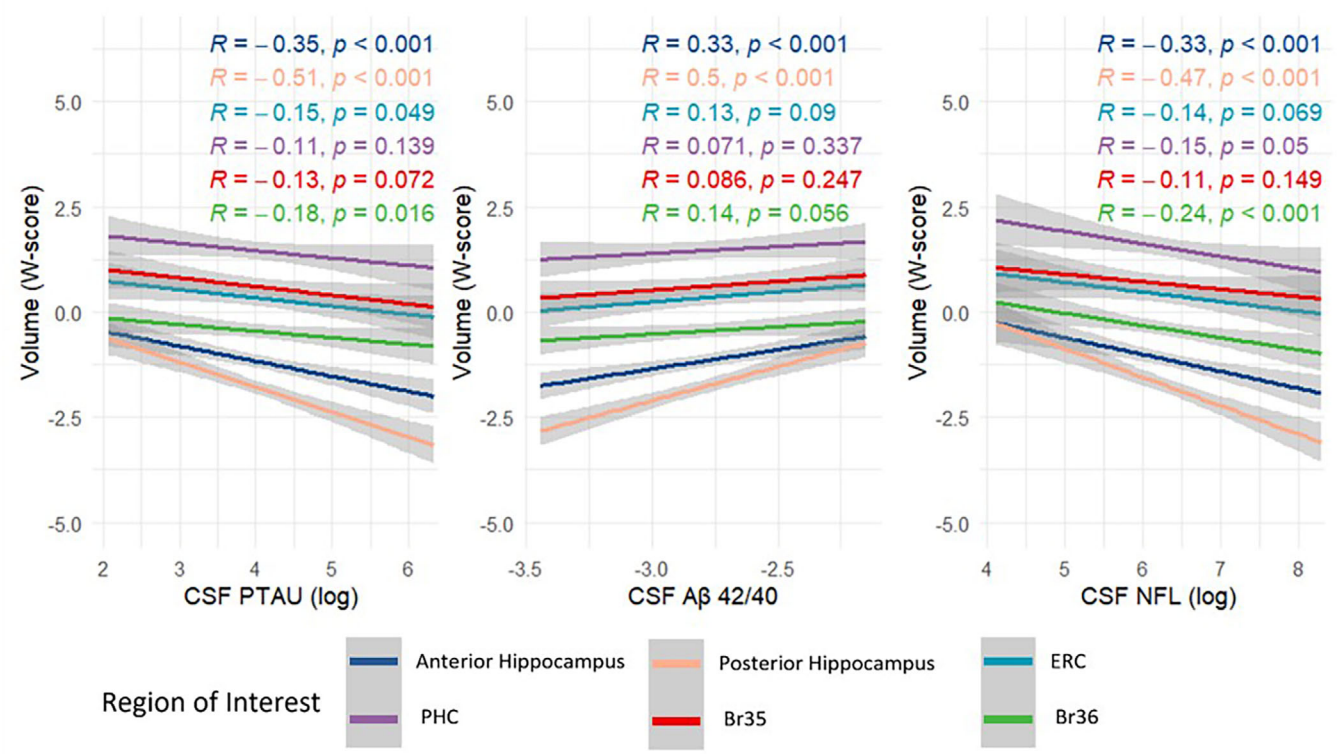

Figure 3: Correlations between regional MTL volumes and CSF biomarkers in DS*. c by CSF biomarkers of AD: A) CSF PTau, B) CSF Aβ42/40, and C) CSF NfL. CSF values are* log_{10} *scaled. p and r values obtained using Spearman correlation.* Abbreviations: *Aβ42/40 = Amyloid beta 42/40 ratio, CSF = Cerebrospinal Fluid, Br 35 & Br 36 = Brodmann Areas 35 & 36, ERC = Entorhinal Cortex, NFL = Neurofilament light chain, PHC = Parahippocampal Cortex, PTAU = Phosphorylated Tau.*