

P2-226 CROSS-SECTIONAL CEREBRAL VOLUMETRIC DIFFERENCES AND ASSOCIATIONS WITH ESTIMATED TIME TO AGE-AT-ONSET IN FAMILIAL ALZHEIMER'S DISEASE: FINDINGS FROM THE DIAN STUDY

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**Background:** A key challenge for Alzheimer's disease (AD) research is to identify the most reliable markers of early disease progression. Autosomal dominant AD provides a unique opportunity to study the earliest changes. We assessed cross-sectional volumes of whole brain, ventricles, and hippocampi within the Dominantly Inherited Alzheimer Network (DIAN) cohort. **Methods:** 158 participants were included: 55 of whom were non-carriers (NC); 59 were asymptomatic carriers (aMut+) with Clinical Dementia Rating (CDR) of 0; and 44 were symptomatic carriers (sMut+) with CDR>0. All participants underwent volumetric T1-weighted MRI. Automated segmentation techniques were used to delineate the whole brain, ventricles, and hippocampi. All volumes were adjusted for total intracranial volume and age. Ventricular and hippocampal volumes were additionally adjusted for sex. The relationships with time to expected age-at-onset, estimated from affected parent's age-at-onset, were also examined. **Results:** Statistically significant ( $P < 0.001$ ) differences were observed in brain, ventricles and hippocampi between the sMut+ and both NC and aMut+. There were no significant differences between the aMut+ and the NC, although a trend was observed for whole-brain volumes. The Figure shows average corrected volumes in each group. In addition, the aMut+ showed significant ( $P < 0.05$ ) correlations between time to expected age-at-onset and whole-brain and ventricular volumes. For the sMut+, similar significant correlations ( $P < 0.05$ ) were observed between the predicted age-at-onset and whole-brain and hippocampal volumes. **Conclusions:** Participants with dementia already had significantly greater atrophy: smaller brain and hippocampal volumes and larger ventricles. Unaffected carriers did not show significant differences compared to non-carriers: this overlap may be due to the wide normal range in regional brain volumes, and the inclusion of carriers who are many years before expected age-at-onset. Notably there was a significant association between estimated age-at-onset and brain volume in asymptomatic carriers suggesting atrophy increases (possibly non-linearly) prior to symptoms. Longitudinal measurements of atrophy may be a more sensitive biomarker than cross-sectional measures: the ongoing follow-up of DIAN subjects will allow this to be assessed.

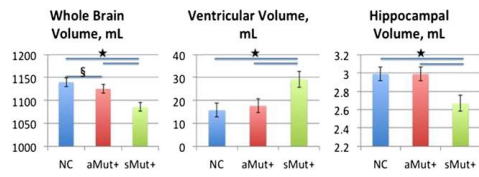


Figure 1. Average volumes (error bars represent 95% confidence intervals) for the structures of interest. All volumes have been adjusted for covariates of Total Intracranial Volume and Age. The Ventricles and Hippocampi have additionally been adjusted for gender. \*indicates  $P < 0.001$ . - x indicates ( $P > 0.075$ ) between aMut+ brain volume vs. NC brain volume.