

## **Choroid plexus volume is associated with levels of CSF proteins predominantly expressed by the choroid plexus in non-demented individuals with AD pathophysiology.**

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**Background:** The choroid plexus (CP) is a structure located inside the brain ventricles and is responsible for the production of cerebrospinal fluid (CSF), transport of proteins across the epithelium to the CSF and clearance of proteins from the CSF. The CP undergoes changes with aging, which are exacerbated in Alzheimer's disease (AD) and could alter CP functioning. Nonetheless, the relation between CP functioning and AD pathophysiology is still unclear. Here, we investigated the association of CP volume with levels of CSF proteins predominantly expressed by the CP and amyloid positivity in non-demented individuals.

**Methods:** We included 235 individuals with normal cognition (NC) or mild cognitive impairment (MCI) from the European EMIF-AD MBD study (49% women, mean age 67.9 (SD 7.9) years). Based on CSF A $\beta$ 1-42 (A, data-driven cut-offs) and p-tau (T, center-specific cut-offs), individuals were classified as cognitively normal with normal A and T (controls, n=54). Based on CSF A $\beta$ 1-42, individuals with NC or MCI were classified as amyloid-positive (CN A+, n=61; MCI A+, n=67). CSF proteomic data were centrally generated using TMT mass spectrometry and 5 CSF proteins with predominantly expression in the CP were selected based on the Protein Atlas, Harmonizome and literature (TTR, MFRP, SLC5A5, FOLR1, SOD3). CP and hippocampal volumes on MRI were quantified using FreeSurfer 7.2. We used non-parametric (Spearman) partial correlations corrected for age, gender and TIV.

**Results:** Lower A $\beta$ 42 levels were associated with higher CP volume in MCI. Higher levels of CP predominant expressed proteins were generally associated with increased CP volume in persons with amyloid positivity, in both preclinical and prodromal AD. Lower A $\beta$ 42 levels were associated with lower hippocampal volume in MCI. Lower hippocampal volumes were associated with higher CP volumes in MCI. Nonetheless, hippocampal volume and the levels of CP predominant expressed proteins were generally not correlated.

**Conclusion:** Our findings suggest that CP volume is associated with levels of proteins predominantly expressed by the CP in predementia stages of AD. This would suggest CP dysfunction in early AD. This is important for future research and AD treatment development.

**Keywords:** Choroid plexus, hippocampus, Alzheimer's disease.