Neurophysiological markers of early Alzheimer's Disease proteinopathy in the human brain

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Background: Alzheimer's Disease (AD) is characterized by the pathological accumulation of amyloid-beta (Aβ) and hyperphosphorylated tau proteins in the brain. Animal models have demonstrated that early Aβ accumulation induces neuronal hyperexcitability, whereas later additive effects of Aβ and tau lead to suppression of neuronal activity that parallels disease severity. Although neural hypoactivity has been reported in the later stages of AD, it remains unknow if such a shift from hyper to hypoactivity exists at the macroscopic level in the human brain of asymptomatic individuals.

Aim: The aim of this study was to evaluate the neurophysiological changes associated with the early deposition of Aβ and tau in asymptomatic older adults with familial history of AD and to address its implications for longitudinal cognitive performance.

Methods: We used Positron Emission Tomography to measure the deposition of whole-brain Aβ ([18F] NAV4694) and medial temporal tau ([18F] Flortaucipir) and resting-state Magnetoencephalography (MEG) to capture the neurophysiological changes linked to AD pathology in a group of clinically unimpaired older adults with family history of AD (PREVENT-AD cohort). We used nested linear mixed effects models to test the association between MEG spectral power and Aβ across cortical regions, and the interactive effect of tau accumulation on this relationship. We then used linear regression models to test if the observed associations between MEG spectral power and AD pathology were associated with longitudinal cognitive performance, evaluated annually using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).

Results: Aβ deposition was associated with neural hyperactivity, as reflected by a positive association between Aβ SUVR values and MEG spectral power in higher frequencies (alpha [8 - 12 Hz]) and a negative association in slow frequencies (delta [2 – 4 Hz]). The accumulation of medial temporal tau predicted a shift in these associations towards a hypoactivation pattern (increased neural slowing), which was associated with longitudinal decreases in attention scores.

Conclusion: Our results support the hypothesis that Aβ induces neural hyperactivity, while the additive effects of Aβ and tau lead to a shift towards neural slowing that relates to cognitive deficits in clinically unimpaired individuals. These findings contribute to the mechanistic understanding of the pathophysiology underlying early AD and the neurophysiological changes linked to early Aβ and tau accumulation may represent novel non-invasive biomarkers of the preclinical stage of AD.