**Is the presubiculum protected from neurodegenerative changes? A pathological and biochemical investigation.**

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**Background:** Aggregation and deposition of β-amyloid (Aβ) is believed to initiate the disease process in Alzheimer's disease (AD), resulting in neurodegeneration and downstream tau pathology. A characteristic feature of the presubiculum in AD is the presence of a large evenly distributed Aβ deposit ('smudge') that occupies the majority of this anatomical area. Previous studies have shown that the presubiculum has unique properties; absence of activated microglia in association with the Aβ deposits and only a small proportion of neurons affected by neurofibrillary pathology. This is in stark contrast to the neighbouring entorhinal cortex and subiculum that display structured Aβ plaques, severe microglial activation and neuronal loss due to tau accumulation. Using post-mortem brain samples from AD and other neurodegenerative diseases affected by extracellular amyloid deposition we aimed to characterise whether this 'smudge' phenomenon of the presubiculum is a unique feature of AD or is also apparent in other neurodegenerative diseases and characterise pathologically and biochemically.

**Methods:** Immunohistochemical analysis was performed on AD (n=30), familial British dementia (FBD, n=4) and familial Danish dementia (FDD, n=4) to assess the presence of the diffuse amyloid deposits in the presubiculum, the amyloid and tau loads and the level of microglial activation. Biochemical analysis was used to determine whether the Aβ peptide composition of the presubiculum differs from the entorhinal cortex.

**Results:** The presubiculum showed a different pattern of protein deposition in AD, FBD and FDD compared with the surrounding subiculum and entorhinal cortex, with significantly less phosphorylated tau and microglial activation. In addition, mass spectrometric analysis revealed less N-terminally truncated and pyro-glutamate-modified Aβ peptides in the entorhinal cortex.

**Conclusions:** Understanding why this region has less truncated forms of Aβ peptides and less microglial activation may provide insight into the pathophysiology of AD and other neurodegenerative disorders.

**Learning objective:** To understand why these diffuse amyloid deposits are occurring in the presubiculum and to identify their Aβ peptide composition.

**Keywords (max 3):** presubiculum; Alzheimer's disease; amyloid peptides