

EDITORIAL COMMENTARY

What is the molecular pathology that underlies hippocampal memory decline?

C R Harrington

Correspondence to:

Dr Charles R. Harrington
School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD,
United Kingdom

Tel: +44 1224 555801

Fax: +44 1224 555194

E-mail: c.harrington@abdn.ac.uk

Amyloid deposition and tau pathology are both associated with memory decline in early and late stages of Alzheimer's disease

Keywords: Alzheimer's disease; memory; amyloid; tau protein; neuropathology

Over a century ago Alois Alzheimer described the importance of neurofibrillary tangles in a woman who died with dementia at the age of 55 years; plaques having already been observed in brains by Blocq and Marinesco. In the 1960s, Martin Roth and colleagues at Newcastle were first to look at the pathological basis of dementia in AD and they identified neuritic plaques and tangles as the key determinants of clinical dementia. Although recent advances have since established the molecular basis for the pathological hallmarks of the disease, several studies have been contradictory in terms of whether it is amyloid or tau pathology that is critical in determining clinical deterioration. Intraneuronal accumulations of tau within the neurofibrillary pathology of AD (tangles, neuritic plaques and dystrophic neurites) are closely linked with the symptoms of dementia^{1,2}, but what initiates the process that leads to these intracellular lesions is uncertain. In some cases, this might be precipitated by abnormal deposition of amyloid β -protein while in others, some different factor may be involved. The absence of tools that are sensitive enough to detect subtle clinical changes in key aspects of AD has made it difficult to interpret correlations with global indices of cognitive function.

In this issue, Reitz et al³ (**see pp XXXX-XX**) describe specific losses in memory function that are associated with both amyloid and tau pathology in the hippocampus. They have taken specific components from a neuropsychological test battery to identify three mutually exclusive factors (memory, visuospatial/cognitive and language functions) and examined these in both cross-sectional and longitudinal analyses of cases. Braak staging shows a spread of tau pathology from hippocampus to medial temporal lobe and then on to parietal and then occipital cortices. The original Braak study⁴ was based upon patients presented at autopsy in the absence of psychometric data. Quantitative analysis of both hippocampus and neocortex reveals that the pathology of both amyloid and tau in the hippocampal formation was found to be associated with memory decline. There was no association between such pathology in other neocortical brain regions and memory function and, conversely, no relation between hippocampal pathology and visuospatial or language functions was found.

Some questions remain unanswered. This study does not claim to show the sequence of molecular events that lead to neuronal dysfunction. Are the soluble oligomers of tau and amyloid responsible for memory impairment prior to the development of tangles and plaques? How might the early abnormal processing of these proteins be linked and at what stage do these events give rise to clinical symptoms? These are important questions for therapeutic strategies if we want to prevent the disease becoming clinically overt.

Theories on the molecular pathogenesis of AD are largely based upon cellular and animal models that cannot necessarily explain the regional selectivity of the disease process and so clinicopathological studies such as those of Reitz *et al* are a valuable contribution to the debate surrounding these theories.

REFERENCES

1. **Wilcock GK, Esiri MM**, Plaques, tangles and dementia: a quantitative study. *J. Neurol. Sci.*1982;**56**:407-417.
2. **Arriagada PW, Growdon JH, Hedley-White ET, Hyman BT**, Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 1992;**42**:631-639.
3. **Reitz C**, Honig L, Vonsattel JP, *et al*. Memory Performance is related to amyloid and tau pathology in the hippocampus. *J Neurol Neurosurg Psychiatry* 2009;**XX**:XXXX-XX.
4. **Braak H and Braak E**, Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991;**82**:239–59.