Reactive astrocytes are highly activated in cases without dementia and do not seem to be associated with cognitive decline – Libby Finnigan

Introduction

Alzheimer's Disease (AD)

- Most common neurodegenerative disease that leads to dementia
- Build up of toxic proteins **tau** and **amyloid-beta** in the brain
- Typical clinical symptoms include decline in short term memory and general cognitive functioning
- The progression of AD correlates with Braak NFT stages
- Typically an individual without dementia will be a Braak 0-III (see Figure 1) and an individual with AD will be a Braak V/VI
- However Braak IV (intermediate) may or may not have dementia

Astrocytes

- Astrocytes are a type of brain cell which support neurones.
- During times of disease, as a defensive response astrocytes can 'transform' to a pro-inflammatory version called a **reactive astrocyte**.
- Could this lead to a decrease in support of neurones and trigger the decline into dementia?

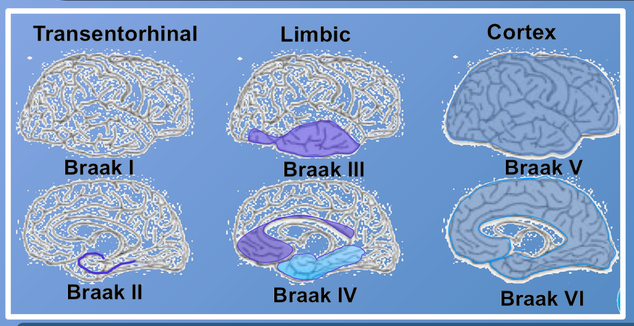

Figure 1 – NFT stage labelling and brain regions I n AD. Braak IV cases are usually diagnosed as intermediate

Aims

Using *post-mortem* human donor brains, we aim to microscopically measure the amount of AD pathology as well as the amount of reactive astrocytes in many regions of the brain.

- We will determine in Braak stage IV cases with dementia compared to those without dementia
  - If higher numbers of reactive astrocytes are present
  - If tau and Aβ pathology burden is higher
  - If tau and Aβ pathology and reactive astrocytes are associated with clinical measures of dementia

Methods

- 21 donated human brains from the Newcastle Brain Tissue Resource (NBTR). Case characteristics:
  - Braak NFT stage IV with dementia (BIV-D), n=4: mean age 90.5 years ± 11.56, 2M:2F; Braak NFT stage IV without dementia (BIV-ND), n=6: mean age 85.5 years ± 8.40, 4M:2F; AD (Braak NFT VI), n=5: mean age 80.6 years ± 3.97, 3M:2F; non-demented (Braak NFT 0-I), n=6; mean age 77.17 years ± 5.71, 3M:3F.
- We employed a **Tissue microarray (TMA)** to analyses the donated tissue (see Figure 2)
  - technique that enabled analysis of 40 punches of tissue from various regions of the same brain
  - We performed **immunohistochemistry** on the TMA sections in order to measure tau, Abeta plaques and reactive astrocytes
  - We utilised 3 different antibodies for tau (AT8), Abeta (4G8) and reactive astrocytes (GFAP)

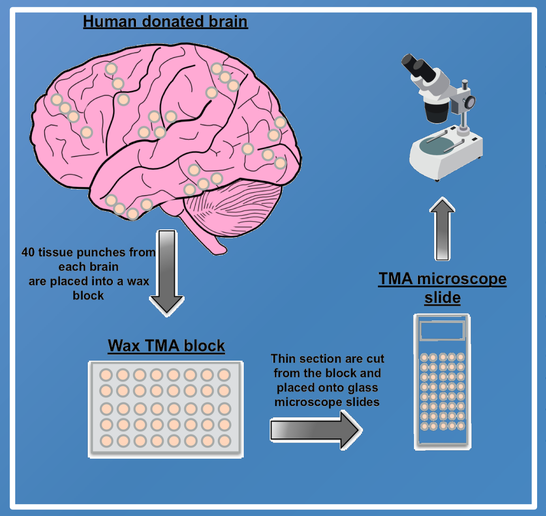

Figure 2 – Flow diagram to represent TMA methodology. 40 tissue samples from various brain regions molded into a wax block and cut into thin sections, to be added to a microscope slide

Results

Result 1 (Figure 3)

- Highest GFAP-IR was seen in the Braak stage IV without dementia was significantly higher than Braak IV with dementia (P=0.019)
- Significantly higher than controls (P=0.004)
- No significant difference in GFAP-IR between Braak IV with dementia with controls and AD or AD and controls

Result 2 (Figure 4)

- No significant difference in AT8-IR or 4G8-IR between Braak IV with dementia or Braak IV without dementia
- Overall Braak IV cases
- significantly higher AT8-IR (P=0.002) and 4G8-IR (P=0.002) compared to controls
- significantly lower AT8-IR (P=0.006) and 4G8-IR (P=0.018) compared to AD

Result 3 (Figure 5)

- No association between MMSE scores and GFAP-IR (P=0.879)
- Significant association between MMSE scores with AT8-IR (P=0.021) and 4G8-IR (P=0.001)

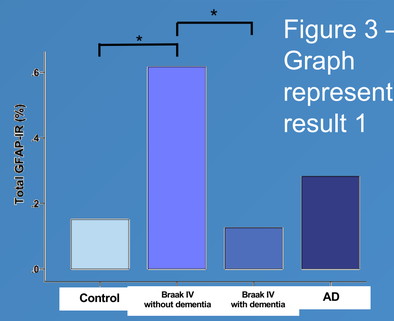

Figure 3 – Graph representing result 1

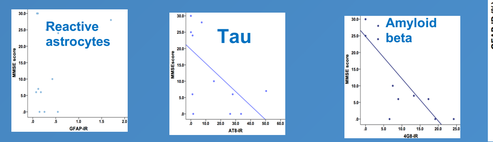

Figure 5 – Graph representing result 3

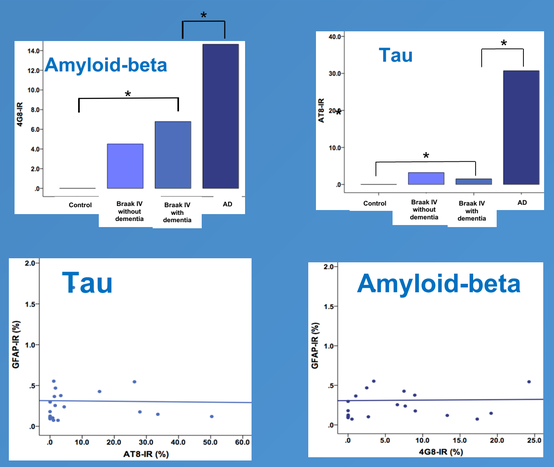

Figure 4 – Graph representing result 2

Discussion

- As a response to the accumulation and development of AD, there is a surge in reactive astrocytes at Braak stage IV when no dementia is present, i.e., the *'tipping point'* . This is followed by a decline in reactive astrocyte activation
- Tau is a strong correlate of cognitive decline (*Riley et al, 2002),* therefore we expected to see a possible increase tau in the Braak IV with dementia. We observed no major difference between cases with and without dementia when measuring tau and Aβ, this suggests another mechanism is inducing the progression of cognitive decline at Braak IV. Evidence from a human tissue study has indicated that **synaptic resistance** may play a role in slowing cognitive decline in the Braak IV cases without dementia (*Bjorkland et al, 2012)*
- The transformation of astrocytes and the loss of normal functioning astrocytes is not linked to cognitive decline as seen in AD, however there was an association between tau and amyloid-beta pathology with decline in cognitive function
- Acknowledgements – Dr Kirsty McAleese (Supervisor)