UNIVERSITY OF CAMBRIDGE

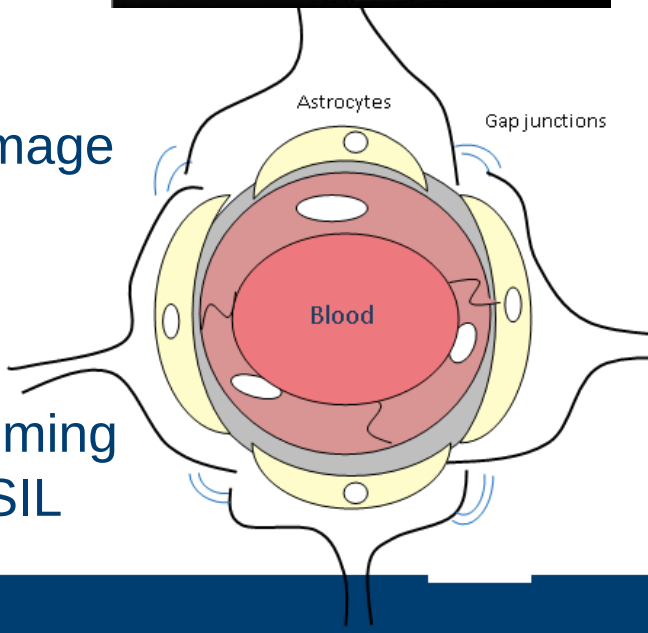
MRC Medical Research Council

Are brain blood vessels leaky in CADASIL? And does this lead to tissue damage?

CADASIL event, 30th June

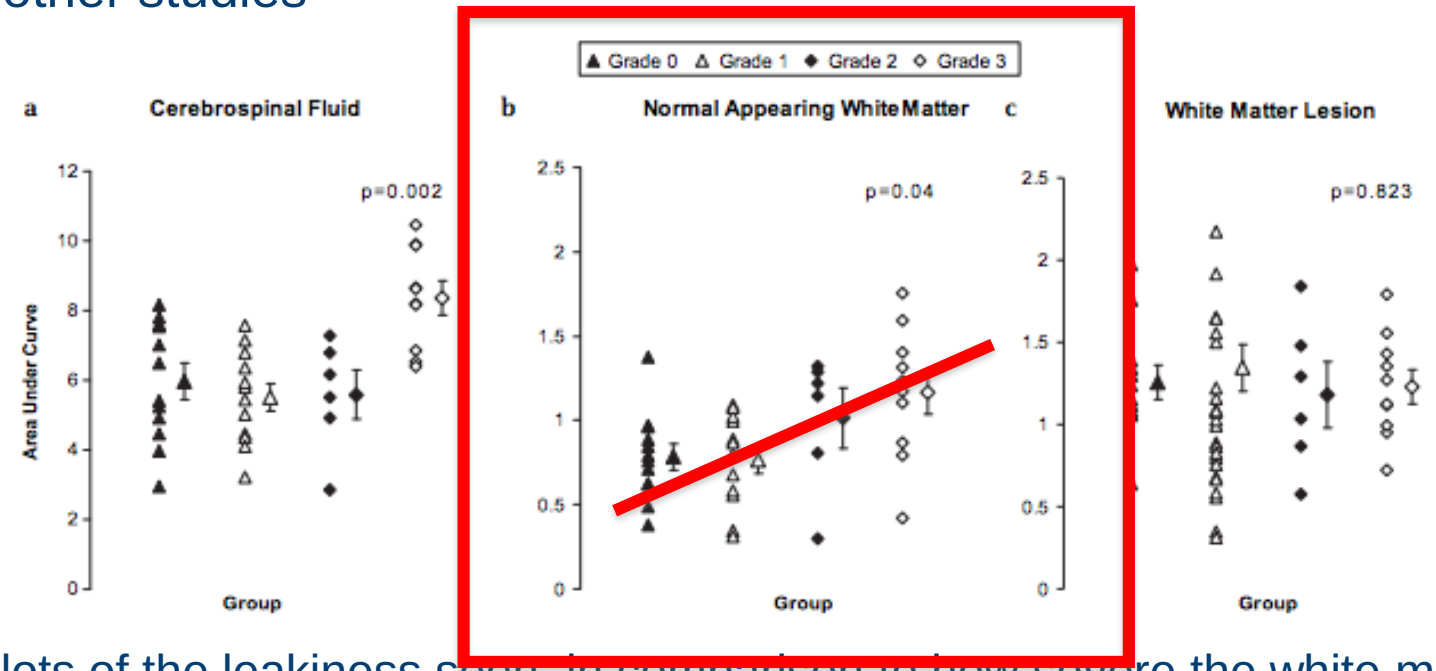
What causes tissue damage in CADASIL?

- Conventionally thought to be low blood flow
- Recent evidence suggests that BBB leakage may play a role
- The BBB lines the brain's blood vessels to keep out various harmful substances carried in the blood
- If the BBB becomes leakier it can allow these substances to pass into the brain and cause damage
- Inflammatory cells are thought to initiate this 'leakiness'
- We want to investigate whether the BBB is becoming leaky in small vessel diseases, including CADASIL



Have other studies shown this leakage?

- Leaky blood vessels have been shown to occur in small vessel disease in other studies

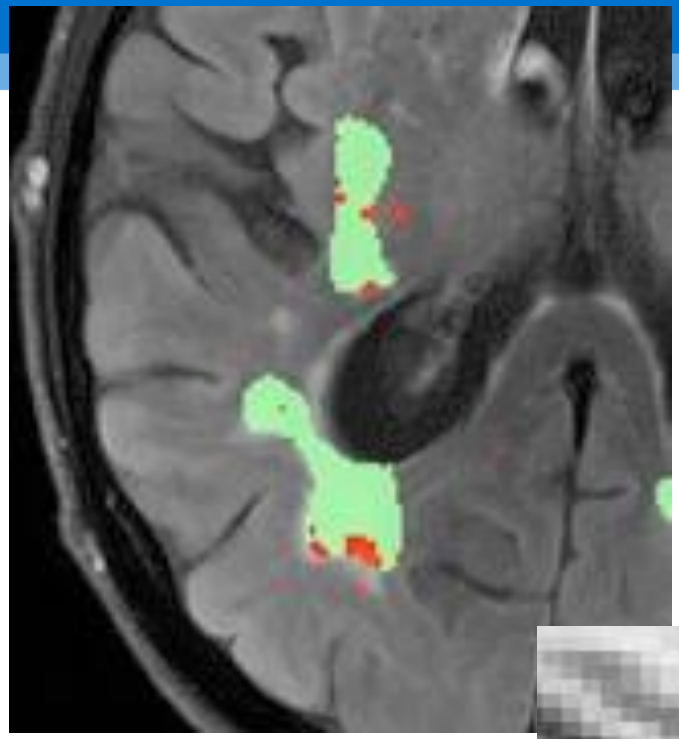


Plots of the leakiness seen, in comparison to how severe the white matter damage is. Higher number of white matter lesions has higher permeability, suggesting that the permeability could be leading to the lesions.

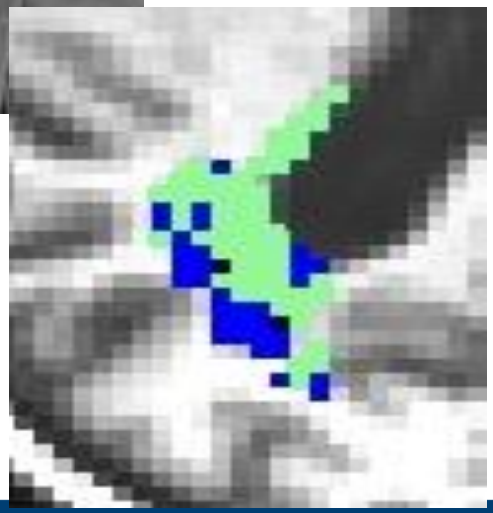
Topakian et al., 2009 BMJ

Has the BBB been seen to be leaky in CADASIL?

- Our pilot data on a small number of subjects suggests that the BBB is leakier and that there is more inflammation in CADASIL
- Leakiness and inflammation are concentrated around the edges of the lesions, suggesting it could be how they ‘grow’



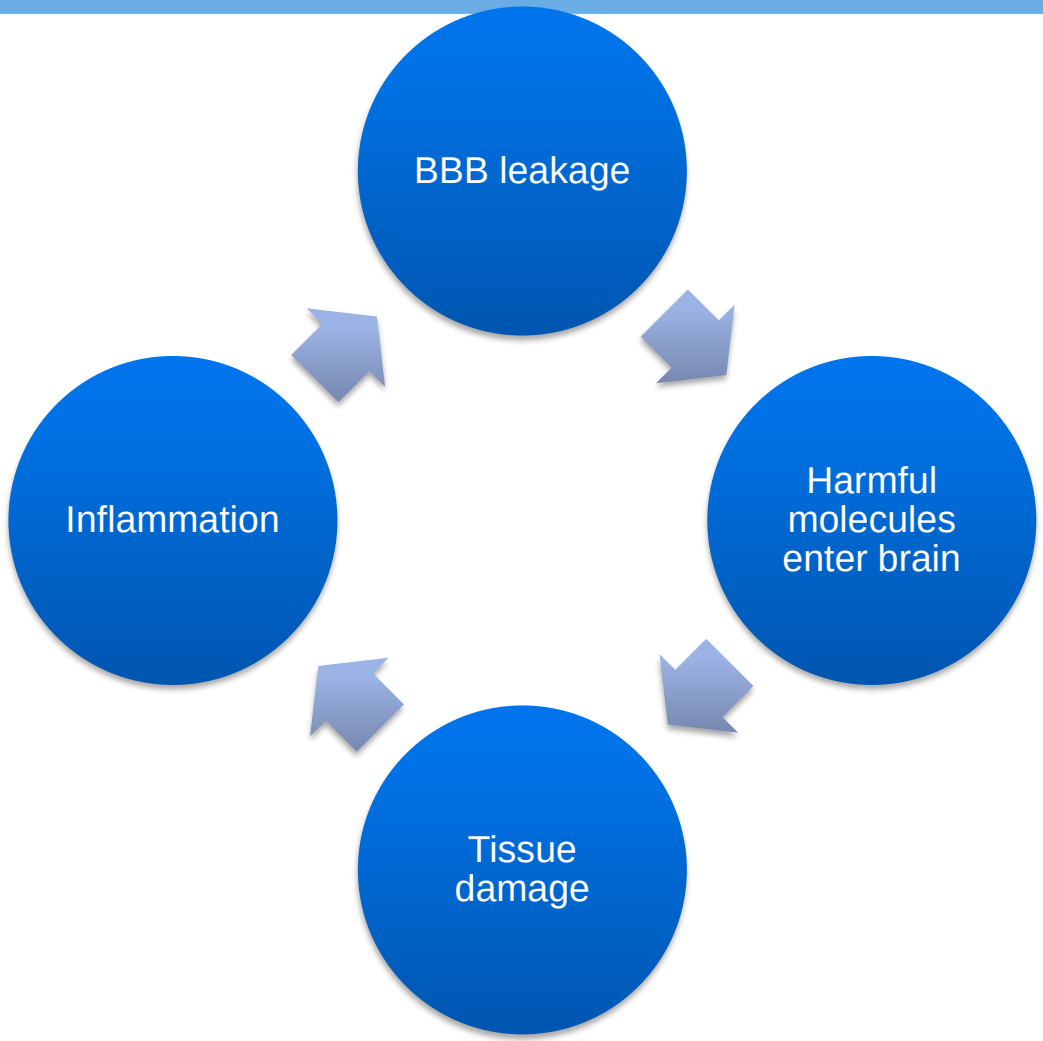
MRI scan for leakiness



PET scan for inflammation

How are we taking this work further?

- We have been given £1.2 million from the MRC to fund this exciting project over the next 3 years!
- New imaging techniques mean we can investigate this leakiness with better resolution than ever before



What is the plan for the project?

- Image BBB leakage and inflammation at baseline using MRI/PET
  - Map where the leakage and inflammation are
  - Measure how much leakage and inflammation is present
- Perform cognitive testing to measure brain function
- Image 1 year later to see if there is now lesions in the regions where leakage/inflammation were seen previously
- Perform cognitive testing again, to see if higher BBB leakage leads to a faster decline in brain function

What happens if the project is successful?

- If we can show that BBB leakage and inflammation are leading to tissue damage in small vessel diseases
- We can then begin to assess whether drugs that block this inflammation reduce the lesions seen