Quantification of White Matter Vasculature in *post mortem* Brains of Demented and Non-Demented Aged Individuals

Madhurima Dey. Supervisor: Prof. Johannes Attems. Institute of Ageing and Health, Newcastle University

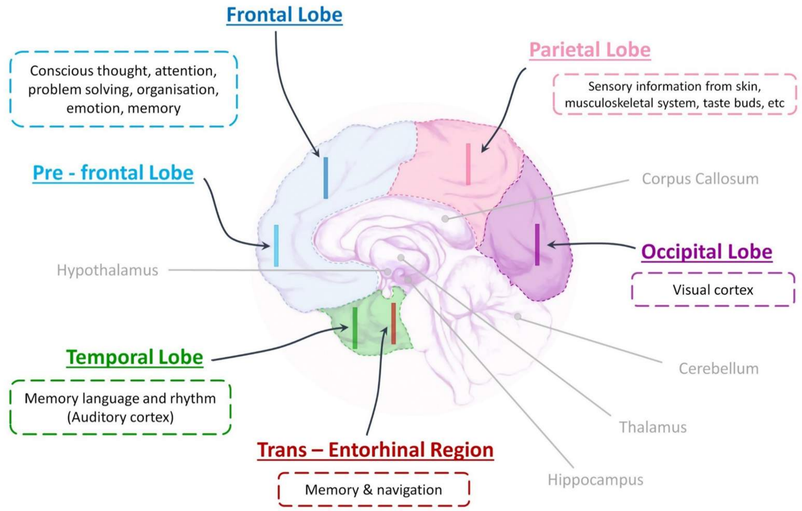
INTRODUCTION

- Alzheimer's disease (AD) is the most common form of neurodegenerative disease, characterised by the accumulation of beta-amyloid (Aß) and hyperphosphorylated tau.
- Cerebral small vessel disease (SVD) is a common co-pathology of AD, which leads to the thickening of the artery wall due to atherosclerosis, lipohyalinosis & arteriolosclerosis. This causes ischaemic damage, thus resulting in the loss of axons and myelin within the white matter (WM).
- This consequent damage is visualised as white matter lesions (WML), which can be seen as white matter hyperintensities (WMH) *in vivo*{1} and under the microscope as pale immunohistochemical staining of the WM and *post mortem*{2} on T2-weighted MRI scans.
- We aimed to quantitatively measure the vessel walls of WM arteries and arterioles of both AD and normally aged non-demented brains and, in conjunction with *post mortem* MRI scores, determine the severity of SVD.
- Currently, most neuropathological studies use a basic, semi-quantitative (SQ) analysis method. However, this cannot detect subtle variations within neuropathological lesions. Quantitative (Q) analysis is objective and more accurate.

METHODS

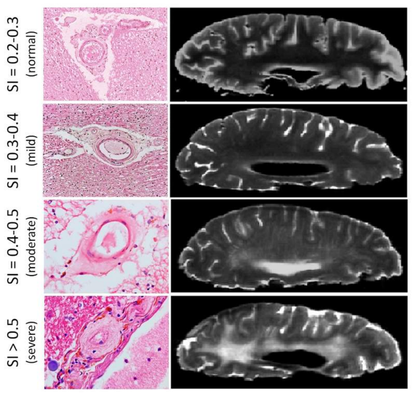
- 38 right brain hemispheres (mean age 84.8 years (± 7.7yrs.) 55.3% female, 63.2% demented) were fixed, then underwent *post mortem* T2 MRI, dissection and Haematoxylin & Eosin (H&E) staining.
- Blinded histology-based analysis was carried out to locate approx. five WM arteries and arterioles per section from pre-frontal, frontal, trans-entorhinal, temporal, parietal & occipital regions of the brain (figure 1).

Schematic to show locations of slides assessed



^ Figure 1: Right hemisphere showing the approx. locations of the slides assessed, along with the corresponding function of that lobe/region, and labels of other key features in the brain.

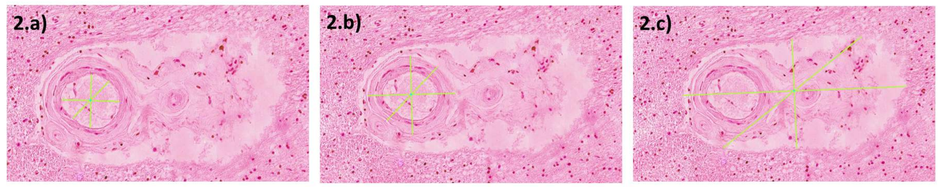
SI measurement & corresponding WMH MRI image



< Figure 3: SI scoring methods for histological slides and MRI images showing the corresponding WMH severity.{2}

Assessment of MRI images are done as part of routine *post mortem* histological assessment according to the ARWMC{5} scale in order to assess WMH.

Quantitative measurement of vessel wall thickness

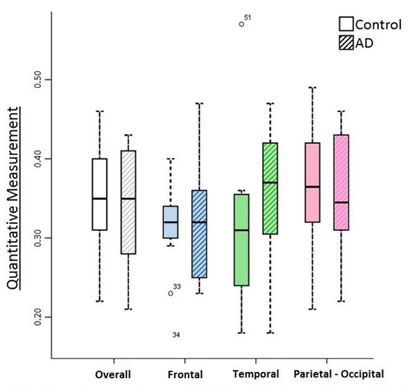


^ Figure 2: Method used to measure the thickness of the vessel wall using VasCalc software {3}.

○ Images were then quantitatively assessed (fig. 2) using specialist software{3} to objectively measure the thickness of the vessel wall using measurements of the internal diameter (a), external diameter (b) and perivascular space of the vessel (c){4}, to determine the Sclerotic Index (SI).

RESULTS

Quantitative Assessment: Control vs. AD



< Figure 4: Quantitative results. Statistical analysis showed no significant difference in any lobes between SI of AD and non-demented control cases

MRI Assessment: Control vs. AD

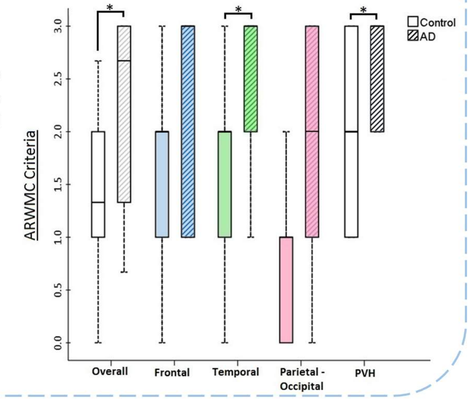


Figure 5: MRI WMH Scores > MRI data was previously recorded as part of routine histological assessment based on the ARWMC scale{5}. These were significantly higher in AD compared to non-demented controls in the overall, PVH and temporal lobe groups

* = P < 0.01

CONCLUSION & DISCUSSION

- The results suggest that, while the amount of SVD appears to be slightly greater in AD cases in comparison to non-demented controls, there is no significant difference between the two groups
- By contrast, we found that the MRI WMH scores were significantly higher in AD compared to non-demented controls, which raises the question whether there are other influencing factors, such as AD associated Aß and tau pathology, which are causing the difference in WMH via alternative mechanisms (e.g., Wallerian like degeneration).
- This study highlights the importance of Q neuropathological assessment of *post mortem* brain sections, as it shows a more profound insight into how the multiple pathologies of the ageing brain interact with a greater degree of accuracy.
- Future directions for this work would be to consider the implications of cerebral amyloid angiopathy, as it incorporates both vascular and AD pathologies.

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m.dey@ncl.ac.uk, 110029731, Physiological Sciences, School of Biomedical Sciences

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