The white matter in Alzheimer’s disease

Dr Kirsty E. McAleese
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Overview

- What is the white matter?
- White matter damage
- Diagnostic relevance?
- Newcastle University study into cause of white matter damage in Alzheimer's disease and normal ageing
White and grey matter

Human brain

Grey matter/cortex

White matter

MRI
White and grey matter

Grey matter/cortex

White matter

Cell bodies
White and grey matter: Brain cell

- Dendrites
- Cell body
- Axon
- Terminal synapse
- Myelin
- Oligodendrocyte

Cortex

White matter

Oligodendrocyte
White and grey matter: tissue

Cortex

White matter

Other brain areas, spinal cord etc...
White matter damage

• Loss of the *myelin* with/without *axonal* loss

• Visualised under microscope or on an MRI scan
White matter damage

Tissue section

Normal white matter

Damaged white matter

MRI scan
White matter damage

- Loss of the myelin with/without axonal loss
- Visualised under microscope or on an MRI scan
- Assumed to represent a vessel disease called **small vessel disease (SVD)**
- WM damage on MRI scan indicates SVD
  - Diagnosis of vascular cognitive impairment/dementia

![Atherosclerosis](image1.png)  ![Arteriolosclerosis](image2.png)
White matter damage in AD

• Studies have shown that WM damage in Alzheimer’s disease (AD) may be caused by a different mechanism

Alzheimer’s disease - Recap
• Most common neurodegenerative disease that causes dementia
• Symptoms include memory impairment, language and executive function deficits
• 2 protein depositions seen under the microscope: Amyloid-β and tau pathology
Amyloid-β pathology
Hyperphosphorylated tau pathology
White matter damage in AD

- Studies have shown that WM damage in Alzheimer’s disease (AD) may be caused by a different mechanism

Alzheimer’s disease
- Most common neurodegenerative disease that causes dementia
- Symptoms include memory impairment, language and executive function deficits
- 2 protein depositions seen under the microscope: \textit{Amyloid-β and tau pathology}
- Death of brain cells – leading to shrinkage of the brain
White matter damage in AD

Non-demented

Alzheimer’s disease

To scale
White matter damage in AD

- Studies have shown that WM damage in Alzheimer’s disease (AD) may be caused by a different mechanism.

- **Degenerative** myelin and axonal loss caused by the deposition of tau and amyloid-β.

- Neuronal loss
White matter damage in AD

Neuronal loss

Neuron and axon

Healthy neuron and axon

Proximal

Distal

Complete loss of the axon

Neuronal dysfunction leads to failure of axonal transport resulting in loss of the axon from the distal end.
White matter damage in AD

Neuronal loss

Amyloid-beta and tau protein

Complete loss of the axon from distal end

Proximal to distal
White matter damage in AD

Neuronal loss
Studies have shown that WM damage in Alzheimer’s disease (AD) may be caused by a different mechanism.

- **Degenerative** myelin and axonal loss caused by the deposition of tau and amyloid-β.
- Neuronal loss
- Wallerian degeneration
Wallerian degeneration

- ‘Self-destruction’ of the axon (and myelin)
- Triggered by blockage of transport up and down the axon
Wallerian degeneration

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Axonal transport dysfunction

Axonal swellings

Axonal transport blockage: release of calpain protease

Destruction of the axon and attached myelin
Diffusion Tensor Imaging (DTI) studies have shown specific WM changes patterns in patients with AD. WM changes are observed in areas connected to the medial temporal lobe (MTL).
White matter damage in AD

- **Tau pathology**
  - Development of tau in AD starts in the MTL
  - Autopsy studies in cases with **no SVD** shown WM damage more severe in areas of high amounts of tau pathology

- Tau pathology for tau
Why is it important to understand what causes white matter damage?

- Overlapping of symptoms between AD and vascular dementia
- MRI evidence of WM damage assumed to represent SVD
- SVD may not be the only causes WM damage – AD?
- Patients may be misdiagnosed as vascular dementia when they may potentially have AD
  - Clinical vs. autopsy diagnosis
  - Affect treatment options
Study conducted at Newcastle University

- It is not clear whether the composition and the cause of WM damage differ between AD and normal ageing

**Aim**

Using *post-mortem* donated brain tissue from the Newcastle Brain Tissue Resource (NBTR)

1. Identify the differences in the composition of WM lesions
2. Establish the cause of WM lesions
What we did

• 55 human *post-mortem* brains: 27 AD, 28 controls

Histological procedures

• Tissue sections cut parietal blocks

• Histological staining

  - LFB
  - Biel
  - Amyloid-β
  - Tau
Tissue assessment

1. WM lesion area
2. Myelin loss
3. Axonal loss
4. Tau and amyloid-β
5. Small vessel disease
Protein measures in frozen tissue

Corresponding frozen coronal slices of parietal tissue: left hemisphere

Wallerian degeneration - **Calpain2**

Hypoperfusion - Myelin-associated glycoprotein (**MAG**) and proteolipid protein (**PLP**)

- **MAG**:PLP

Right hemisphere fixed: neuropathology

WML tissue
**Axonal and myelin loss in WM damage**

**Axonal density**

**AD:** More severe WM damage linked to axonal loss

**Controls:** No axonal loss

![Scatter plot of axonal loss vs. white matter damage](image1)

- **Axonal loss %** vs. **White matter damage (%)**
- \( \rho = -0.648^{**} \)

![Scatter plot of myelin loss vs. white matter damage](image2)

- **Myelin loss** vs. **White matter damage (%)**
- \( \rho = 0.755^{**} \), \( \rho = 0.413^{*} \)

**Myelin loss**

**AD and controls:** More severe WM damage linked to myelin loss
What has caused the WM damage?

**Tau, amyloid-β pathology and small vessel disease**

- Higher amount of myelin loss
- WM damage severity

No link with amyloid-β or SVD
• Calpain2 protein was higher in damaged WM in AD

• Calpain2 was linked to both tau and amyloid-β
Results: biochemical markers of Wallerian degeneration and ischemia in WM lesion tissue

Hypoperfusion – MAG:PLP

- MAG:PLP reduced in controls indicates hypoperfusion
What does this all mean?

- WM damage in AD is different
  - Axon and myelin loss
  - Non-demented – myelin loss

- Cause of WM damage is different between AD and normal ageing
  - AD - Wallerian degeneration mechanism
    - Linked to tau and amyloid-β
    - Non-demented – hypoperfusion likely linked to vessel disease

- Clinically important – WM damage on MRI indicates SVD
  - SVD is not the only cause and may indeed be indicative of AD
  - Accurate diagnosis

- No disputing SVD/vascular influence in AD – not primary cause posterior WM changes
Summary

• The white matter contains axons and myelin that connects all brain cells and different regions of the brain

• WM can become damaged; thought to be caused by small vessels disease - may lead to a diagnosis of vascular dementia

• New studies show that WM damage is different in AD and the AD process itself can lead to WM damage

• Important implications for accurate diagnosis of patients with cognitive impairment or dementia
Thank you

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Newcastle Brain Tissue Resource
http://nbtr.ncl.ac.uk/

Alzheimer’s Research UK

NBTR staff, brain donor and their families