
LUCID

Ageing population – not just a pension problem

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Alzheimer's Research UK The Power to Defeat Dementia

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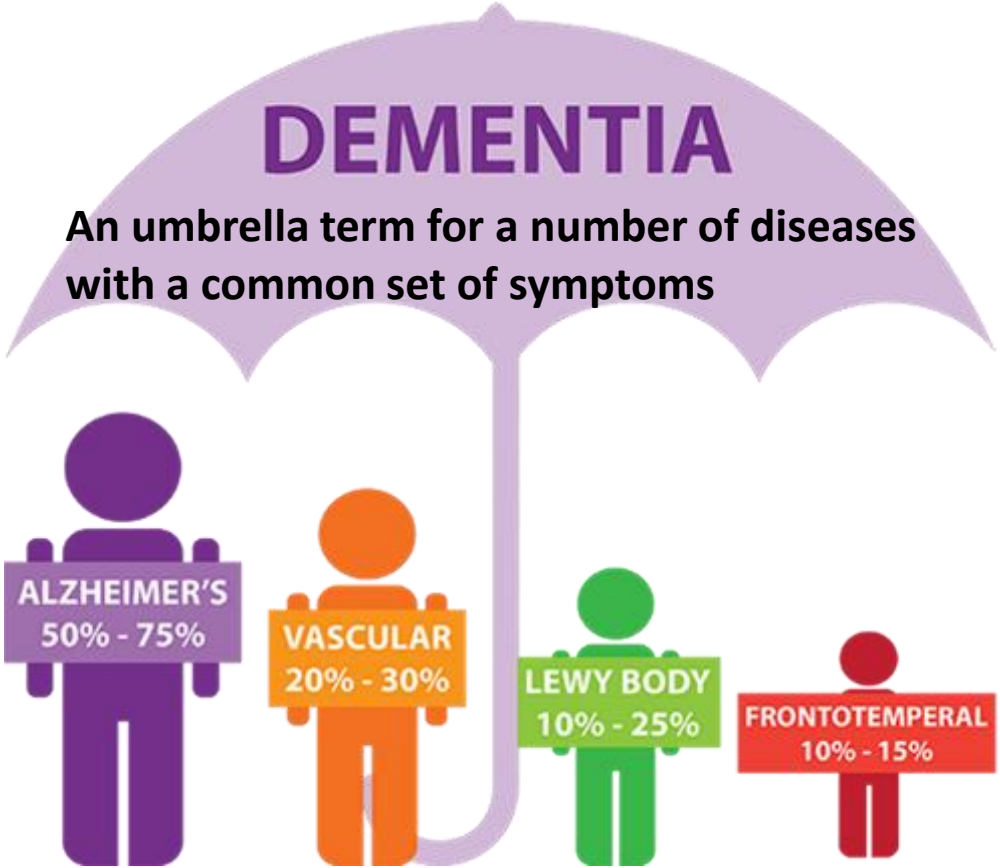
CDBS Centre for Discovery Brain Sciences

CELEBRATING 10 YEARS OF LUCID



- An on-going decline of the brain and its abilities
  - Memory loss
  - Thinking speed
  - Problem solving
  - Language
  - Understanding
  - Judgement
  - Mood

Cognition

The scale of the challenge

850,000 people living with dementia in the UK

90,000 in Scotland

By 2025

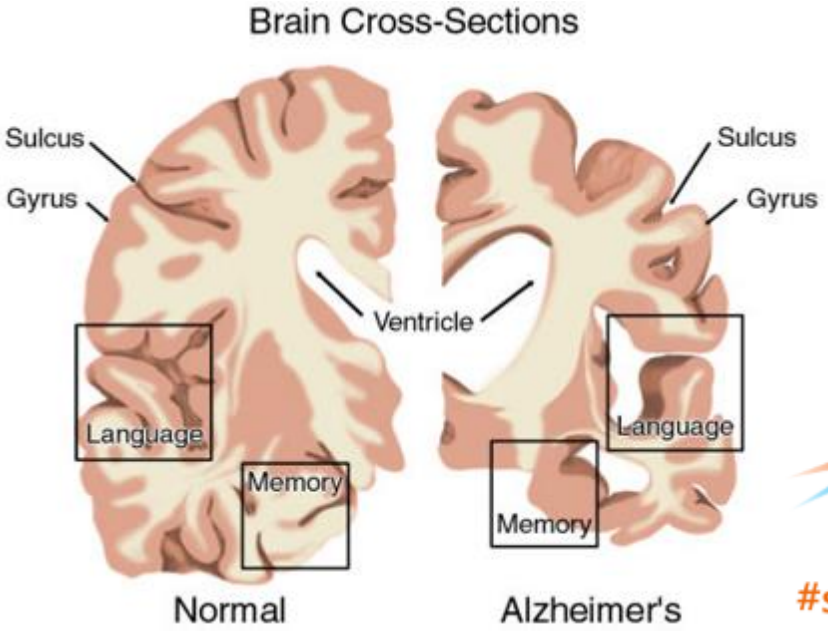
over **one million** people could have dementia in the UK

By 2050

this figure will exceed **2 million**


The cost of dementia in the UK is expected to more than double in the next 25 years, from £26bn to £55bn in 2040.
Alzheimer's Research UK

Dementia is NOT an inevitable part of ageing



Alzheimer's Research UK

#sharetheorange

Shrinkage of the brain by 140g = weight of an orange

Importance of brain blood supply

- The brain's voracious appetite:
  - 2% of body weight
  - 20% of the body's oxygen consumption
  - 25% of the body's glucose consumption
- No storage capacity for glucose and oxygen

400 miles of blood vessels in the brain

Vascular Dementia

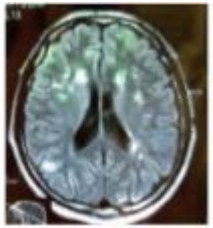
Extensive network of blood vessels within the brain

- Caused by impaired supply of blood to brain cells
- Disruption of blood flow to brain cells means that they do not receive essential energy supplies to function properly which can lead to poor memory

VASCULAR DEMENTIA

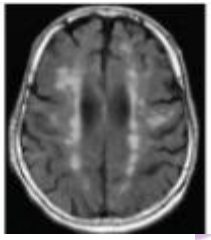
Caused by disease of the blood vessels in brain

Multi infarct dementia



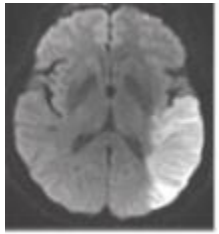
Multiple areas of stroke damage

Cerebral Small Vessel Disease

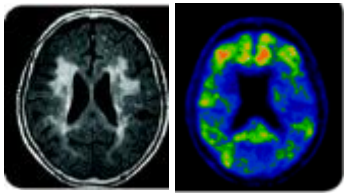


Disease of small vessels (capillaries)

Post stroke dementia



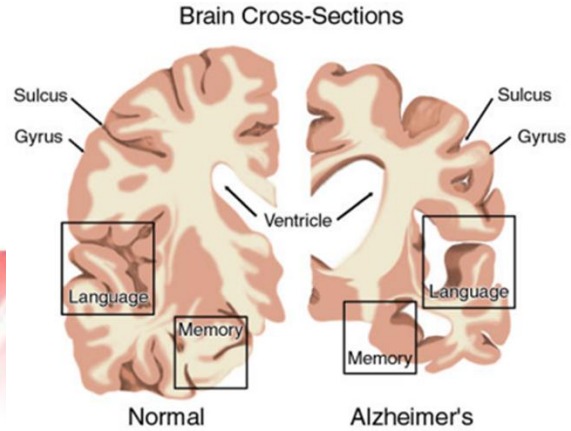
Mixed Dementia



Vascular and Alzheimer's

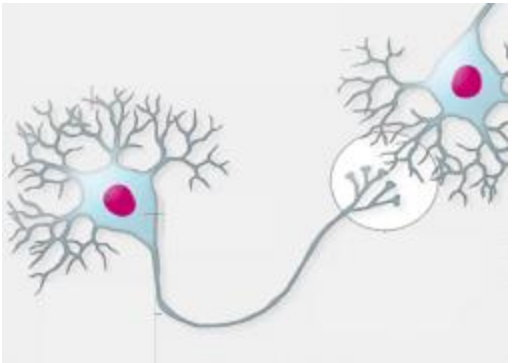
Alzheimer's Disease

- Nerve cells become damaged
- Breakdown in communication
- Memory impairment
- Certain parts of the brain shrink

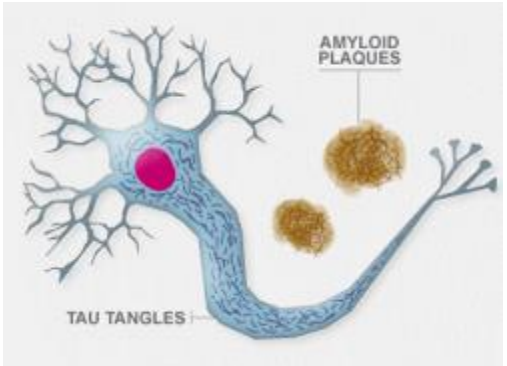


- Build-up of abnormal proteins (**amyloid plaques** and **tangles**)

Normal



Alzheimer's



What causes Alzheimer's? – amyloid cascade

Amyloid

↓

Tangles

↓

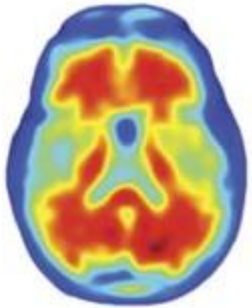
Inflammation

↓

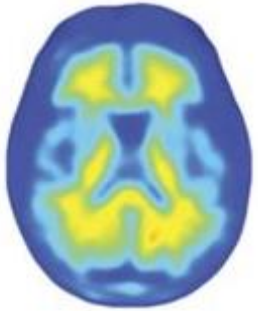
Brain cell death

↓

Dementia



Baseline



1 year of amyloid vaccine

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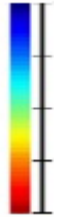
No improvement of symptoms

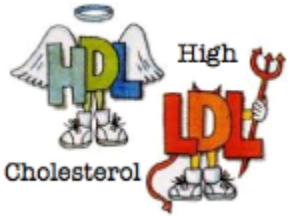


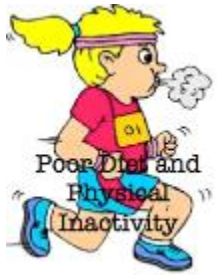
Low amyloid

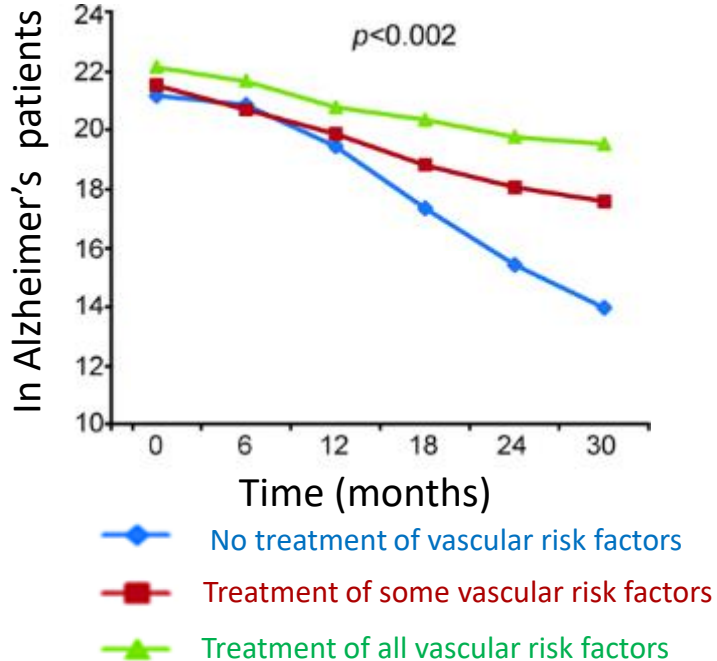
High amyloid

What causes Alzheimer's? – vascular disease

- Vascular risk factors also increase Alzheimer's risk





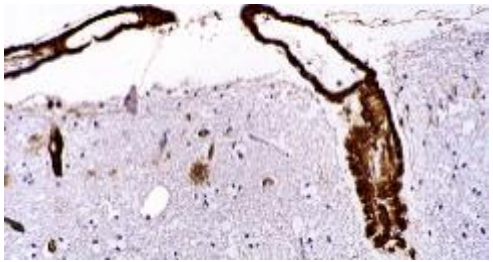


Deschaintre et al 2009, Neurology

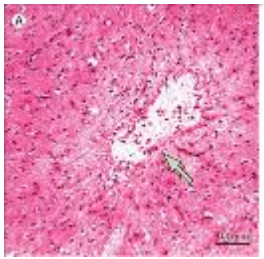
What is good for your heart is good for your head

Vascular damage in Alzheimer's Disease

- At post mortem, most Alzheimer's brains have vascular abnormalities



Cerebral amyloid angiopathy



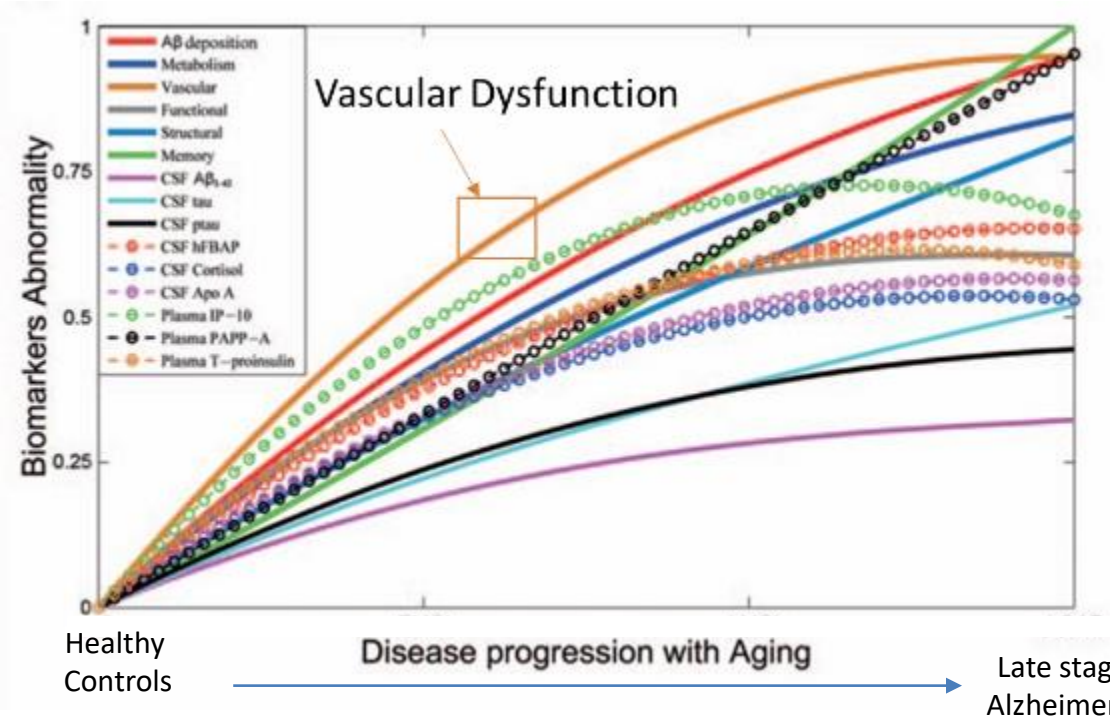
Microinfarct (microscopic stroke)

Abnormal Feature	% Cases
Microvascular degeneration	100
(Cerebral small vessel disease)	
Cerebral amyloid angiopathy	98
Infarct (stroke damage)	36
Micro infarct (microscopic stroke)	31
Microbleed	7

Adapted from Kalaria (2002) Cerebrovasc Dis

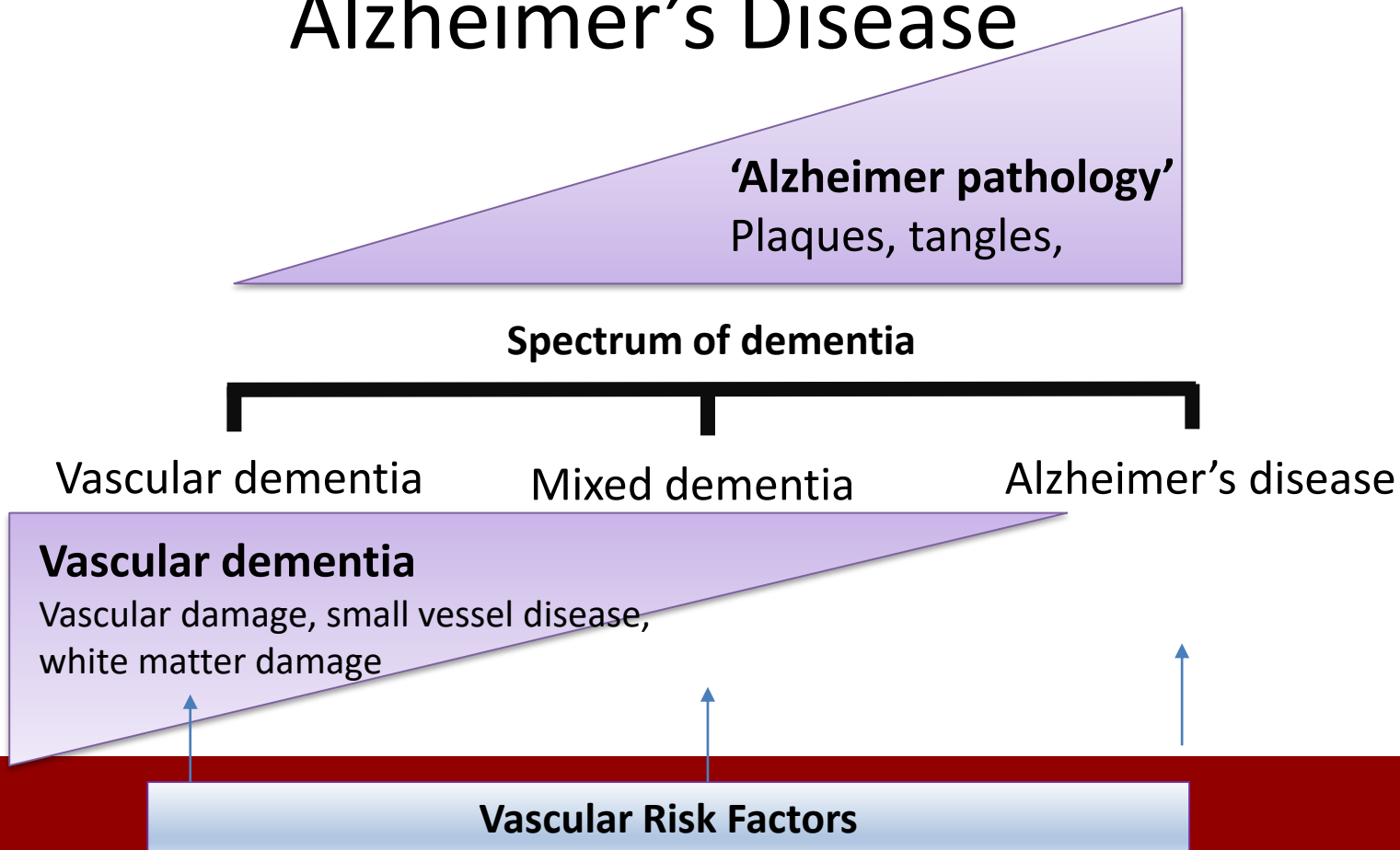
Early vascular changes in Alzheimer's Disease

- Vascular dysfunction is the earliest and most abnormal disease biomarker in Alzheimer's Disease

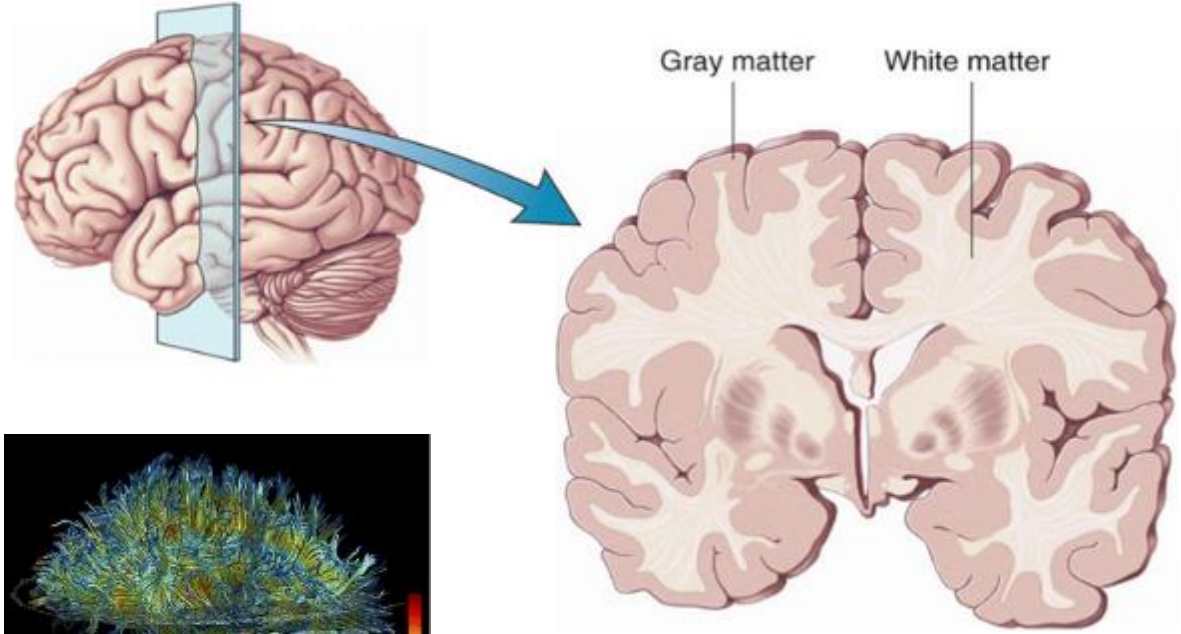


Iturria-Medina et al 2016 Nature Comms

Overlap between Vascular Dementia and Alzheimer's Disease



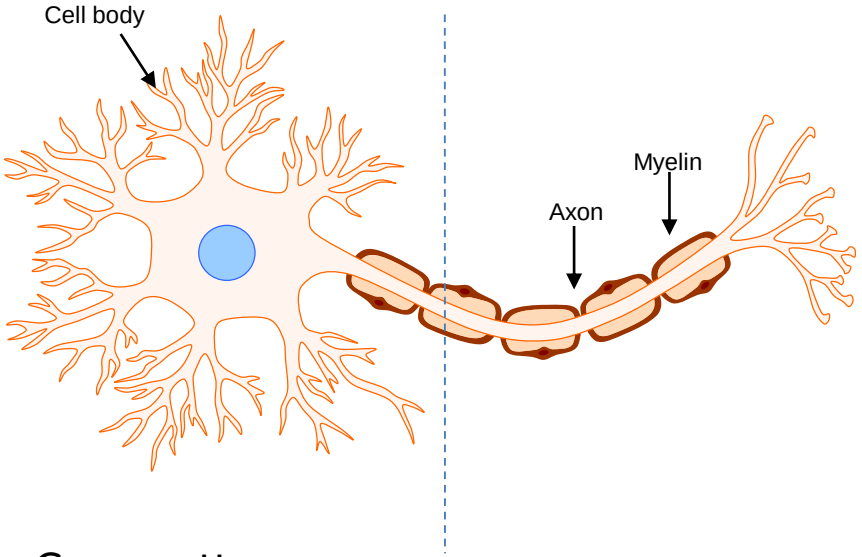
How does vascular disease damage the brain?

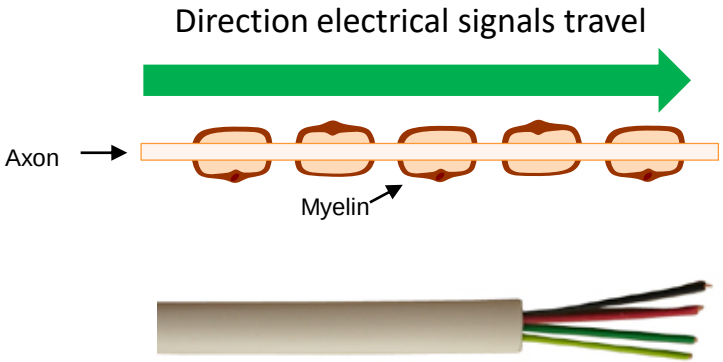


White matter is vulnerable to blood flow reductions

White matter is damaged by vascular disease

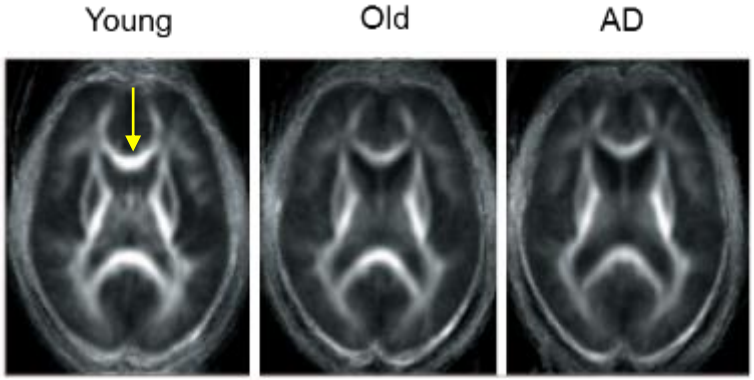
Nerve cell = neuron



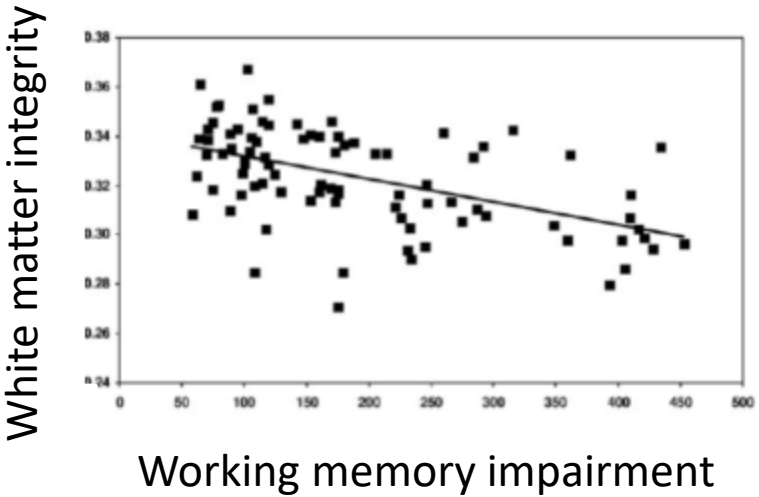


White matter damage and cognitive decline

Diffusion Tensor Imaging



- White matter integrity is disrupted with age, in vascular dementia and Alzheimer's
- Decline in white matter integrity is related to cognitive decline

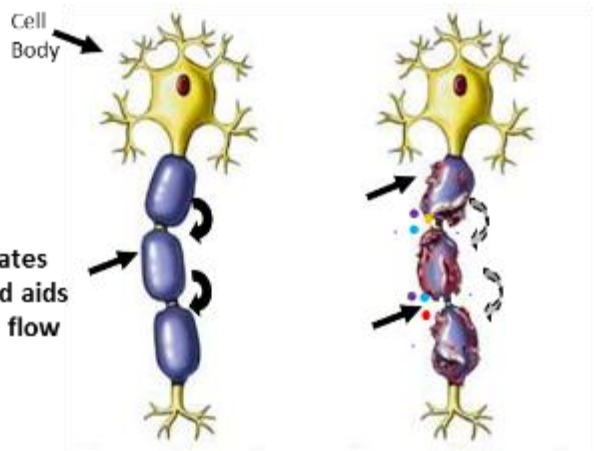


Gootjes et al. 2004; Bastin et al. 2009; Penke et al. 2010

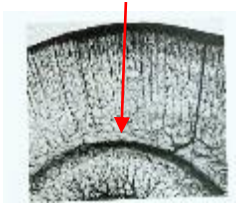
Why is white matter vulnerable to vascular disease?

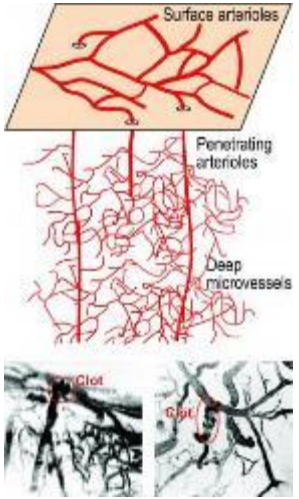
Healthy brain
Normal cognition

Vascular disease
Impaired cognition



White matter

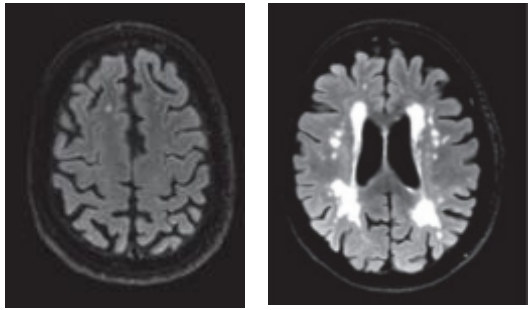


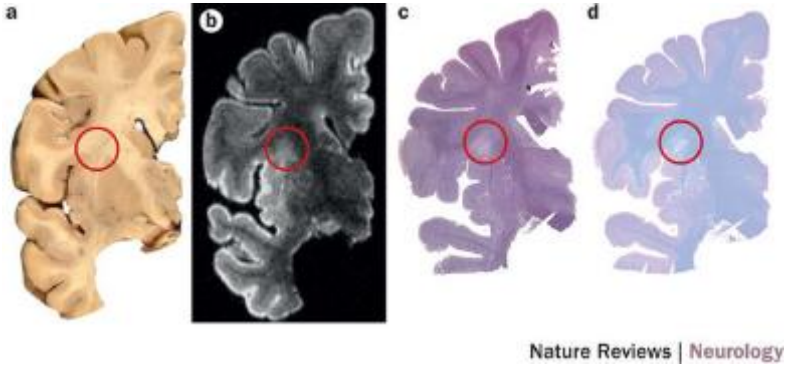


A plumbing issue –
Poor ‘collateral’ supply

Animal models to understand mechanisms of white matter damage

White matter hyperintensities



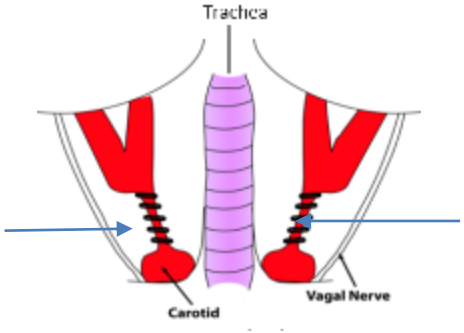


Presumed origin is reduced cerebral blood flow or ‘hypoperfusion’

Animal models can help us address these questions, and test therapies

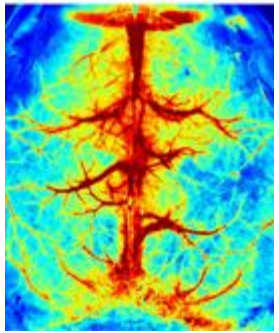
Prins and Scheltens (2015) Nat Rev Neurol

A mouse model for studying blood flow reductions to the brain



Microcoils wrapped around the major blood vessels which supply blood to the brain

Normal blood flow

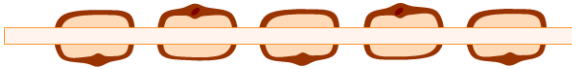


Reduced blood flow

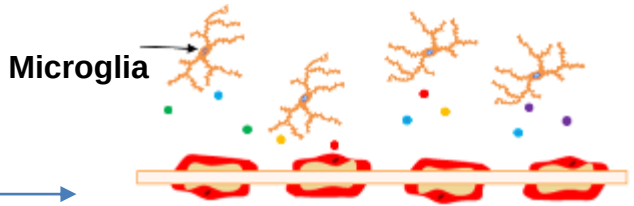
HIGH Blood flow

LOW Blood flow

Healthy – normal blood flow



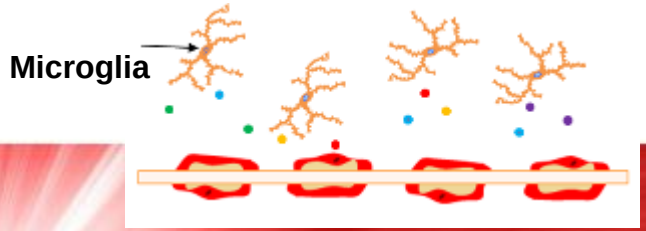
Myelin damage – reduced blood flow

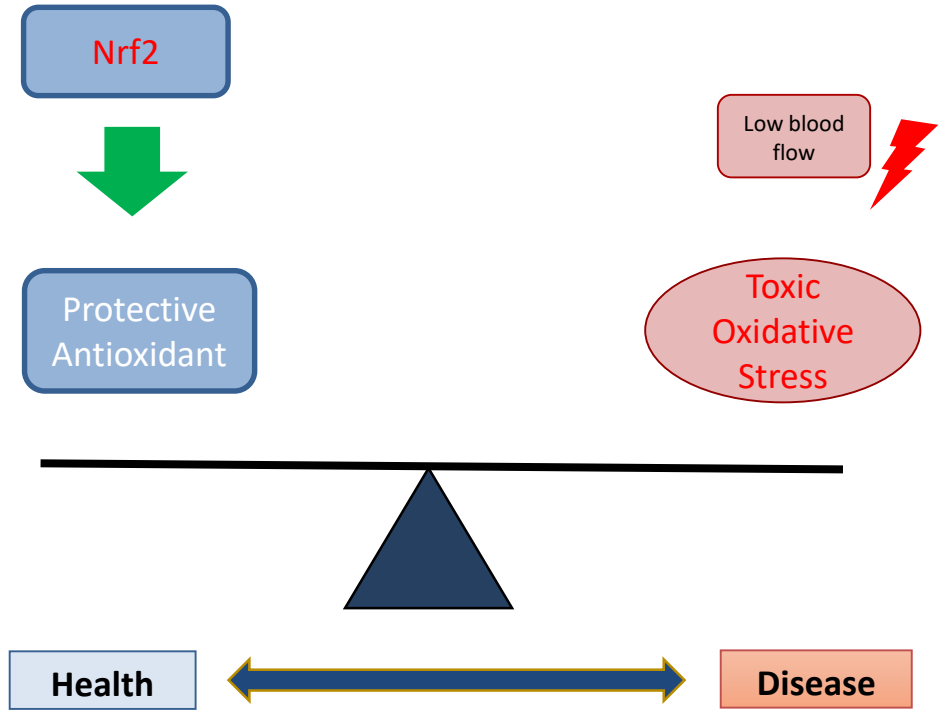


Inflammation and oxidative stress

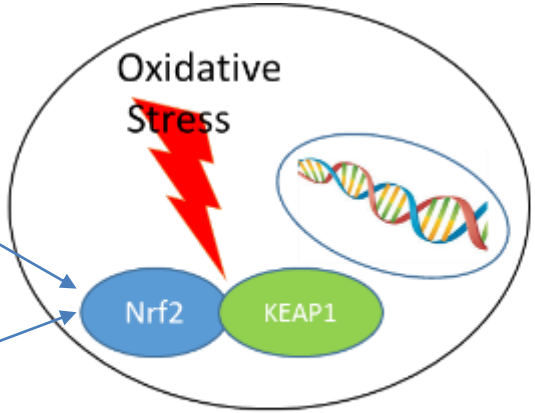
How does white matter become damaged?

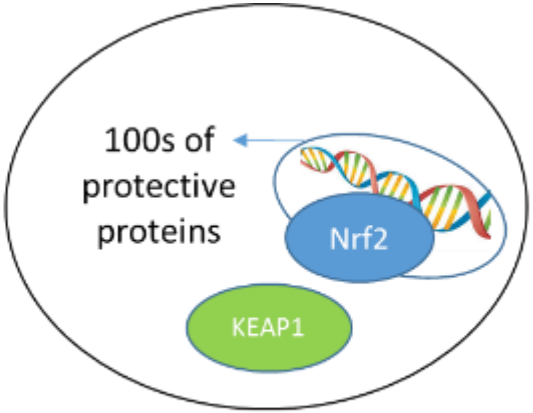
- Reductions in blood flow cause
  - Inflammation
  - Oxidative stress



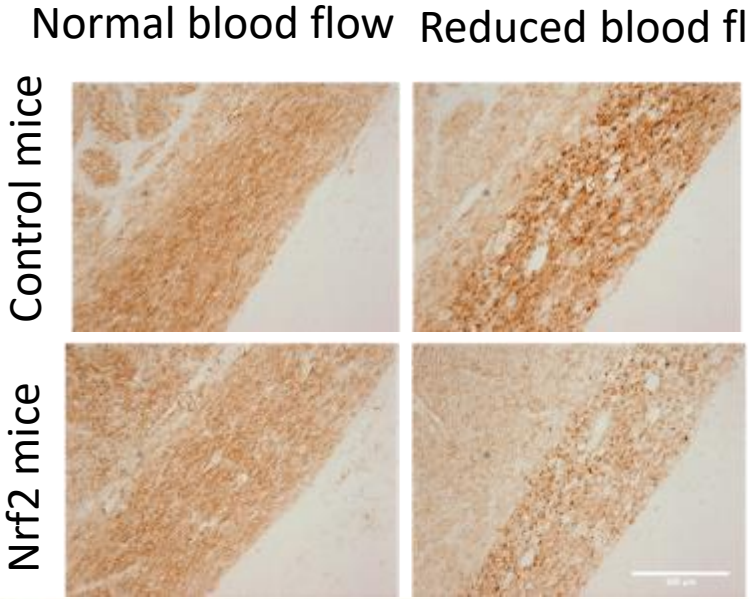


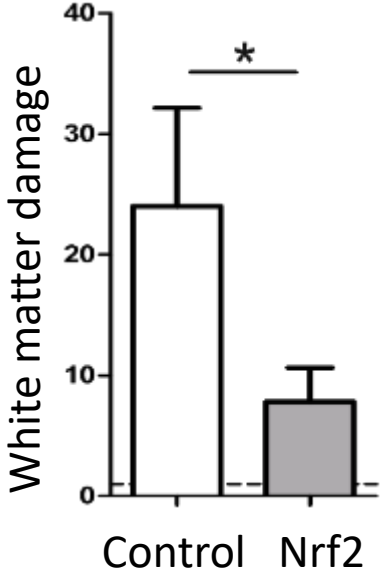
Nrf2 may help combat oxidative stress





Boosting Nrf2 protects white matter

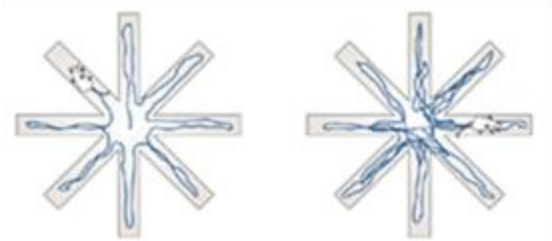




Sigfridsson et al (2018) Scientific Reports

Boosting Nrf2 improves cognition in mice

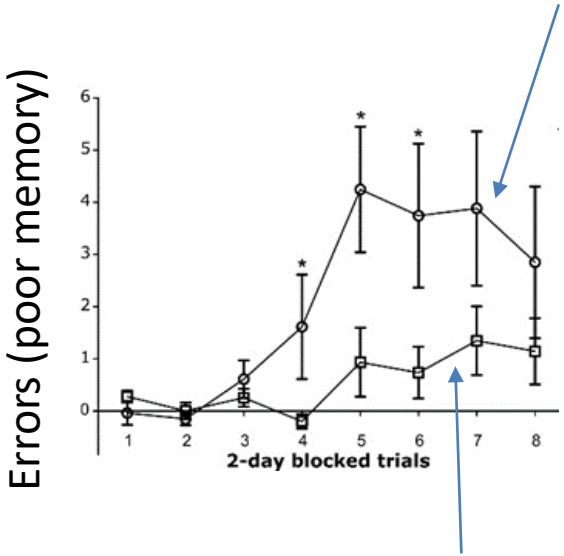
8-arm radial arm maze



Good memory
(few errors)
Normal blood flow

Poor memory
(many errors)
Reduced blood flow

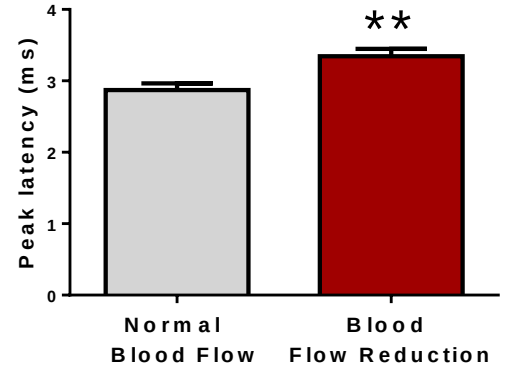
Control mice

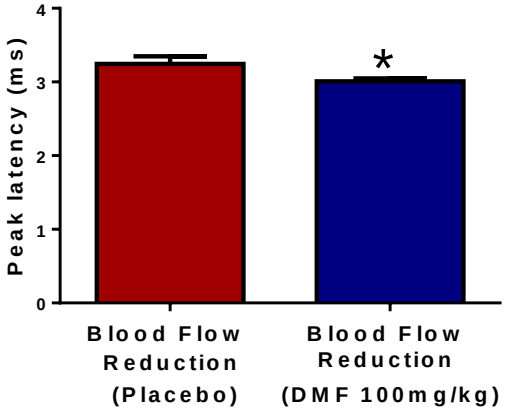


Nrf2 mice

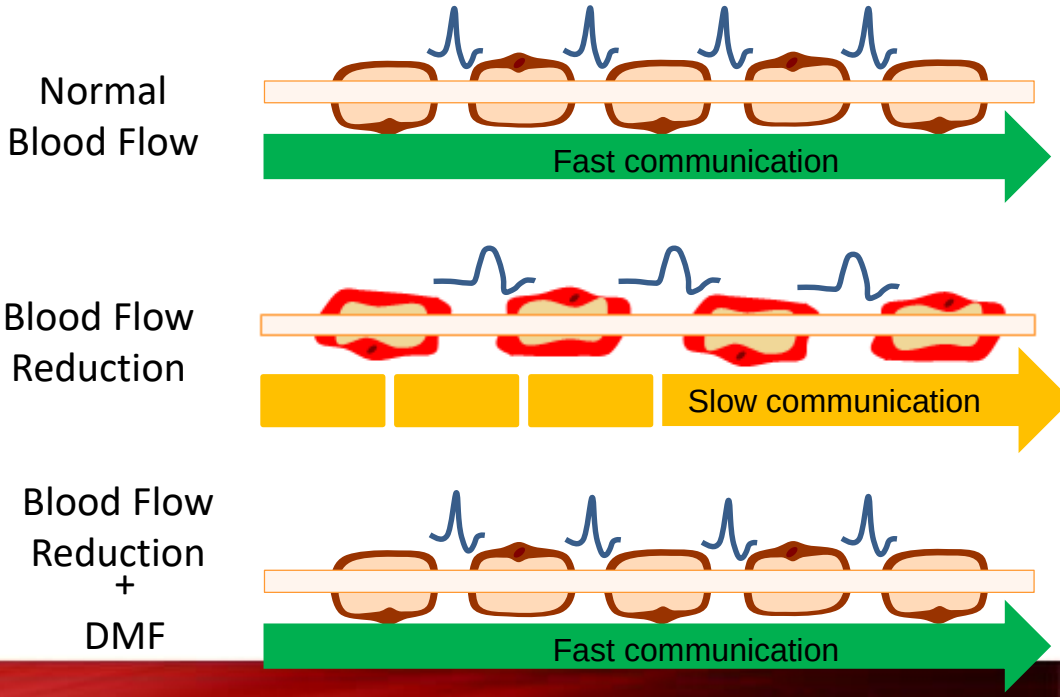
Sigfridsson et al (2018) Scientific Reports

Dimethyl fumarate improves white matter function after blood flow reductions



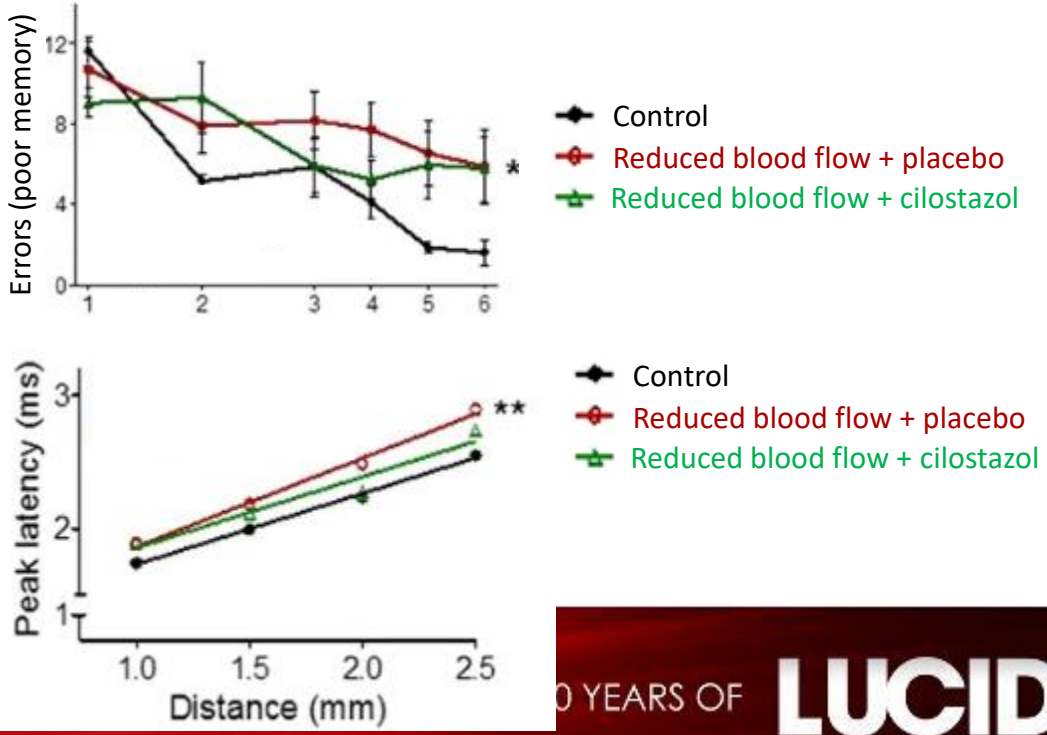


Fowler et al 2018



Cilostazol can improve cognition and white matter function

- Cilostazol
  - Multiple beneficial effects on blood vessels
  - Anti-oxidant
  - Anti-inflammatory



Kitamura et al (2017) Scientific Reports

Clinical trials of cilostazol in small vessel disease patients

- LACI-2 clinical trial
  - Cilostazol (treatment of stroke in Asia-Pacific)
  - Isosorbide Mononitrate (used for heart disease in the UK)
  - Alone or in combination

Cilostazol treatment in clinical trials for Alzheimer's Disease

- Cilostazol augmentation to donepezil treatment in Alzheimer's patients with white matter hyperintensities
  - Glucose metabolism was protected
  - Some evidence of effects on cognition

Lee et al 2019 Neurotherapuetics

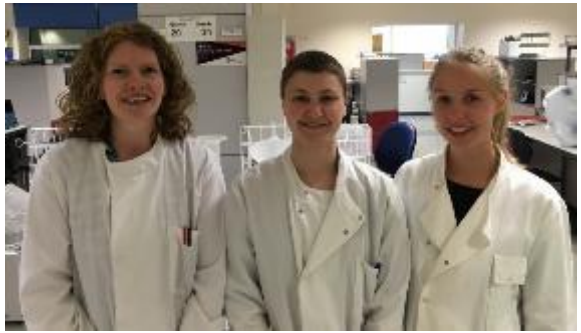
Take home messages

- Dementia is not an inevitable part of ageing but caused by disease processes
- Therapies to target amyloid in Alzheimer's disease have not proven successful
- There is considerable evidence for vascular disease contributing to Alzheimer's Disease
- Vascular Disease disrupts white matter and this is linked to cognitive deficits

Thank you

Fowler Lab

Margaux Aimable
Ellen McIntosh
James Febery
Katherina Nagassima
Lizi Hegarty



Alzheimer's Research UK
The Power to Defeat Dementia

Alzheimer's Society
Leading the fight against dementia

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