The role of arterial pulsatility and white matter microstructure in age-related cognitive decline


Functional Neuroimaging Laboratory
Age-related cognitive decline

- Ageing population (population aged >65 yo expected to double over the next 20 years)
- Loss of independence
- Poorer outcomes for elderly
- Increase risk of late life depression
- Places increased demand on carers
- Increased burden on health care system
Normal Aging: Everyone experiences slight cognitive changes during aging.

Preclinical:
- Silent phase: brain changes without measurable symptoms
- Individual may notice changes, but not detectable on tests
- "A stage where the patient knows, but the doctor doesn’t"

MCI:
- Cognitive changes are of concern to individual and/or family
- One or more cognitive domains impaired significantly
- Preserved activities of daily living

Dementia:
- Cognitive impairment severe enough to interfere with everyday abilities

Mild
- Moderate
- Severe

Cognitive Decline

Time (Years)
Trajectories in cognitive decline with age

Considerable variability in some trajectories

Trajectories in cognitive decline with age

- Variable trajectory (one size does not fit all)
- Some adults maintain high functioning well into later life (Super agers)
- Age-related decline more noticeable for certain functions
- Understanding what drives these differences is important for being able to detect early stages of cognitive decline
White matter and age-related cognitive decline

- Considerable research on the topic
- Partial support for the view that age-related cognitive decline is mediated by changes within cerebral white matter
- Some dispute as to which cognitive functions are influenced by white matter changes (memory vs executive function vs processing speed deficits)
- Strongest findings detected in studies that have measured microstructural properties of white matter vs macrostructural changes
Task switching paradigm

Use of contextual cues to flexibly alternate between task-sets

Single task block
Continued performance of one task in isolation

Mixed task block
Switching between two alternative tasks as indicated by contextual cues

Mixing cost = repeat trials in mixed-task block vs single-task block
Influenced by level of target interference

For review see: Karayanidis, Jamadar, Ruge, Phillips, Heathcote, Forstmann, 2010
Task switching in ageing

Variability in proactive and reactive cognitive control processes across the adult lifespan
Frini Karayanidis *, Lisa R. Whitson, Andrew Heathcote and Patricia T. Michie   Frontiers in Psychology 2011

Task practice differentially modulates task-switching performance across the adult lifespan

- Consistent finding of increased mixing-cost in older adults
- Increased demands placed on working memory
- Greater task ambiguity
- Failure to fully disengage alternative task
Fronto-parietal involvement in task switching

Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. Madden D, Bennett H, and Song A. *Neuropsychol Rev* 2009

Age-related slowing of task switching is associated with decreased integrity of frontoparietal white matter. Gold B, Powell D, Liang X, Jicha G and Smith C. *Neurobiology of aging*

• Demonstrated importance of frontoparietal white matter in task-switching

• However, did not investigate the influence of diffuse white matter changes in task switching and whether these effects were regionally specific or whether they can be just as easily accounted for by gross changes
Current Study

Is the degree in which age related decline in cognitive control related to changes in structural integrity of white matter

Participants
• Healthy older adults
• Mild ischaemic attack

Expt tasks with ERPs
• **Cued-trials task-switching**
• Stop-signal

Functional Measures
• Functional Assessment Questionnaire
• Geriatric Depression Scale
• SF-36
• DASS-42

Neuropsych measures
• WASI, MoCA
• WMS – LM
• Digit Span, choice RT
• CANTAB (IED, SWM, SOC, SSP, PRM)

Imaging
Siemens 3T Verio
• **T1 structural (MPRAGE)**
• Fluid Attenuated Inversion Recovery (FLAIR)
• **Diffusion Weighted Imaging (DWI) sequence**

• **Test**
• **Re-test @ 20-24mo**
## Sample characteristics

- 70 participants
- 35 recruited from HMRI volunteer register
- 35 recruited from neurology clinic

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66.79 (9.54)</td>
<td>43-87 years</td>
</tr>
<tr>
<td>FSIQ</td>
<td>111.64 (14.60)</td>
<td>81-141</td>
</tr>
<tr>
<td>MoCA</td>
<td>25.97 (3.11)</td>
<td>17-30</td>
</tr>
</tbody>
</table>

### Clinical profile

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular risk factors present</td>
<td>39 (56%)</td>
<td>31 (44%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (39%)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>21 (30%)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (16%)</td>
<td></td>
</tr>
<tr>
<td>Multiple vascular risk factors</td>
<td>24 (34%)</td>
<td></td>
</tr>
</tbody>
</table>
## Cognitive domains

### Working memory
- Digit span (WAIS-IV)
- Spatial span (CANTAB)
- Spatial working (CANTAB)

### Episodic memory
- Logical memory (WMS-IV)
- Pattern Recognition memory (CANTAB)

### Executive Function
- Stockings of Cambridge (CANTAB)
- Intra-extra dimensional set shift (CANTAB)

### Processing speed
- Choice RT
- Letter classification task
- Number classification task
Task switching

Cue-target interval = 1000ms
Response-cue interval = 600ms

Outcome measures:
Error mixing-cost
RT mixing-cost
For both neutral and incongruent target types
White matter tractography

• White matter connections estimated using high b-value diffusion weighted MRI
• \( b = 3000 \), 64 directions on Siemens 3T Verio with 32 channel head coil
• Probabilistic whole brain tractography was performed using MRTrix software to derive tractogram
• Tractogram was then filtered into 18 separate white matter pathways using constraint ROI’s derived from a DTI tract atlas from John Hopkins University (JHU).
Measure of WM disruption

- Macroscopic changes
  - White matter hyperintensities
- Microscopic environment
  - Mean FA
  - Mean Diffusivity
  - Axial Diffusivity
  - Radial Diffusivity

### Correlation table

<table>
<thead>
<tr>
<th>Measure</th>
<th>Age</th>
<th>White matter RaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory</td>
<td>-.365***</td>
<td>-.367***</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>-.265*</td>
<td>-.411***</td>
</tr>
<tr>
<td>Executive function</td>
<td>-.430***</td>
<td>-.468***</td>
</tr>
<tr>
<td>Processing speed</td>
<td>-.494***</td>
<td>-.676***</td>
</tr>
</tbody>
</table>

*Both increasing age and white matter disruption associated with poorer performance across multiple cognitive domains*

*p<.05, **p<.01, ***p<.001*
• Correlations with age controlling for white matter radial diffusivity

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<th>Measure</th>
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<th>White matter RaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Working memory</td>
<td>72% attenuated</td>
<td></td>
</tr>
<tr>
<td>Episodic memory</td>
<td>99% attenuated</td>
<td></td>
</tr>
<tr>
<td>Executive function</td>
<td>77% attenuated</td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td>93% attenuated</td>
<td></td>
</tr>
</tbody>
</table>

Nearly all age related variance in episodic memory and processing speed can be accounted for by variability in white matter radial diffusivity.

All correlations with age removed after controlling for variability associated with white matter radial diffusivity.
Correlations with white matter radial diffusivity controlling for age

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<th>Measure</th>
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<tr>
<td>Working memory</td>
<td>71%</td>
<td>attenuated</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>37%</td>
<td>attenuated</td>
</tr>
<tr>
<td>Executive function</td>
<td>62%</td>
<td>attenuated</td>
</tr>
<tr>
<td>Processing speed</td>
<td>35%</td>
<td>attenuated</td>
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Association between white matter radial diffusivity with episodic memory, executive function and processing speed occurs independently of age.

Correlations between white matter RaD and episodic memory, executive function and processing speed remained significant after controlling for variability associated with age.
Working memory

Episodic memory

Executive function

Processing speed

R² values:
- Working memory: 0.1347
- Episodic memory: 0.1686
- Executive function: 0.2189
- Processing speed: 0.4573
Mixing costs increase as a function of white matter microstructure

Error mixing cost with white matter microstructure more obvious with high target interference

RT mixing cost with white matter microstructure more obvious with low target interference
Influence of diffuse vs regional white matter changes on mixing-cost

<table>
<thead>
<tr>
<th>Trial</th>
<th>Overall white matter</th>
<th>IFOL</th>
<th>ILFL</th>
<th>SLFL</th>
</tr>
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<tbody>
<tr>
<td>Error mixing cost (incongruent)</td>
<td>.503***</td>
<td>.520***</td>
<td>.534***</td>
<td>.523***</td>
</tr>
<tr>
<td>Error mixing cost (neutral)</td>
<td>.351**</td>
<td>.350**</td>
<td>.343**</td>
<td>.336**</td>
</tr>
<tr>
<td>RT mixing cost (incongruent)</td>
<td>.290**</td>
<td>.339**</td>
<td>.365**</td>
<td>.341**</td>
</tr>
<tr>
<td>RT mixing cost (neutral)</td>
<td>.415***</td>
<td>.470***</td>
<td>.489***</td>
<td>.466***</td>
</tr>
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IFOL = Inferior fronto-occipital fasciculus – left
ILFL = Inferior longitudinal fasciculus – left
SLFL = Superior longitudinal fasciculus – left

All of the remaining 15 white matter tracts demonstrated weaker correlations compared to overall white matter.
Influence of diffuse vs regional white matter changes on mixing-cost

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Remained significant even after controlling for variability associated with overall white matter.
Large degree of spatial overlap between three white matter tracts

Provides support for previous studies that highlighted the importance of frontoparietal networks in task switching.

Disruption to task specific networks leads to a decrease in efficiency in task switching, as demonstrated by delayed RT, but does not specifically impact accuracy.
Early detection of microstructural white matter changes associated with arterial pulsatility

Todd A.D. Jolly, Grant A. Bateman, Christopher R. Levi, Mark W. Parsons, Patricia T. Michie, Frini Karayanidis*

*Frontiers in Human Neuroscience

This study demonstrated that increased arterial pulsatility is associated with microstructural changes in the white matter.

We postulated that increased arterial pulsatility may increase shear stress to perivascular oligodendrocytes, resulting in demyelination.
We have established...

Age-related decline in many aspects of cognitive functioning are mediated by changes in white matter microstructure.

White matter microstructural changes are associated with a decrease in a number of different cognitive domains.

Cognitive control deficits are associated with disruption to fronto-parietal white matter regions.

White matter microstructural disruption increases as a function of elevated arterial pulsatility.
We did investigate the potential role of arterial pulsatility mediating the relationship between white matter microstructure and cognitive decline.

However, the addition of arterial pulsatility as a covariate had little impact on the strength of the association between white matter microstructure and cognitive function.

This suggests that while arterial pulsatility is related to changes in white matter microstructure, it does not appear to explain the cognitive decline that associated with microstructural disruption within the white matter.
Research Team

Investigators
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Dr Grant Bateman, MRI Unit
A/Prof Peter Schofield, Neuropsychiatry
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Dr Ross Fulham

RHD
Todd Jolly
Patrick Cooper

Clinical Professional Doctorate
Syarifah Wan Ahmadul Badwi

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