Progression of age-related decline in task-switching performance and white matter microstructure: A longitudinal study

Frini Karayanidis, Todd Jolly, Jaime Rennie, Rhoshel Lenroot, Pat Michie, Mark Parsons, Christopher Levi

Functional Neuroimaging Laboratory
School of Psychology
University of Newcastle

ICON-2014 Brisbane
Cognitive changes in healthy ageing vs. dementia

K.R. Daffner / Promoting Successful Cognitive Aging

DOI 10.3233/JAD-2010-1306
Age-related cognitive decline

- Cognitive decline in “healthy older adults” is well-documented
- Large variability across areas of cognition (e.g., Goh et al 2012 Psychol Aging)
- Greater effects on higher order cognitive control processes (i.e., last-in, first-out)
- More prominent structural decline in frontal networks

The present study

In “cognitively intact older” adults, is decline in cognitive control over time associated with changes in microstructure in frontal/parietal WM tracts or diffuse changes across the entire WM?
Proactive and reactive control processes in task-switching paradigms

Use of contextual cues to flexibly alternate between task-sets

- **Proactive control** - advance goal setting and task-set preparation

- **Reactive control** – task implementation in the presence of interference
Task-switching paradigm

- **AR= all-repeat:** Letter – Letter – Letter
- **MR= mixed-repeat:** Letter – Letter – Number – Letter – Number
- **Sw = Switch:** Letter – Letter – Number – Letter – Number - Number

**Mixing Cost =**

**Switch Cost =**
Networks involved in switching-related control

*Ruge, Jamadar, Zimmerman, Karayanidis, HBM, 2013*

*Richter & Yeung, in press*

BA6, Medial Frontal Gyrus;
BA40, IPL;
BA40/7, SPL;
BA7, Precuneus;
BA32, Cingulate Cortex;
BA9/6, Middle Frontal Gyrus;
BA19, Precuneus;
BA9, Middle Frontal Gyrus;
BA7/31, Precuneus;
BA46, Middle Frontal Gyrus;
BA31, Precuneus;
BA39, Middle Temporal gyrus;
BA13, Insula;
BA13/47, Insula;
BA18, Middle Occipital Gyrus;
BA19, Inferior Occipital Gyrus/Fusiform Gyrus
Task-switching and fMRI activation

Jamadar et al. 2010 Neuroimage

A. Informatively - Non-informatively Cued

1. R SFG (24 33 39)
2. Post Cingulate (-4 -61 14)
3. L SPL (-20 -71 48)

Early Cue-Locked (Inf-NonInf) Positivity

RT (Inf - NonInf)

B. Informatively Cued Switch - Repeat

1. L SPL (-28 -51 62)
2. R Precuneus (20 -75 52)
3. L SFG (-16 -9 -59)
4. R MFG (-16 3 59)

Late Cue-Locked (Swt - Rpt) Positivity

RT (Swt - Rpt)
Ageing effects in task-switching

Older adults

- Larger switch cost early in task exposure
- Slower to develop advance preparation to switch
- Sustained mixing cost even after extensive task practice
- Greater engagement of proactive control for switch and repeat trials
- Greater target-driven interference for switch trials

E.g., Karayanidis et al., Frontiers in Psychology 2011; Kray et al., Psychophysiology 2005
Kray et al., Acta Psychologica 2004; Whitson et al., Acta Psychologica 2012
Present study

Characterise change over 2y in healthy older adults

• in WM organisation change
• overall cognitive performance
• specific aspects of task-switching performance

Are changes in cognition associated with deterioration of specific WM tracts or global WM changes?
Fronto-parietal involvement in ageing-related task switching changes

Madden et al., Neuropsychol Rev 2009; Gold et al., Neurobiology of Aging

• Frontoparietal white matter changes linked to age-related differences in task-switching
• However, did not examine whether diffuse white matter differences could account for effect
Role of white matter microstructure in age-related cognitive decline
Jolly, Michie, Bateman, Fulham, Cooper, Levi, Parsons, Rennie, Karayanidis.

**Participants**
- 35 Healthy older adults
- 35 Mild ischaemic attack

**Neuropsych measures**
- WASI, MoCA
- WMS – LM
- Digit Span
- CANTAB (IED, SWM, Stockings, SSP, PRM)

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

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

**Imaging**
- Siemens 3T Verio
- T1 structural (MPRAGE)
- Fluid Attenuated Inversion Recovery (FLAIR)

**Diffusion Weighted Imaging (DWI) sequence**
- **Test**
- Re-test @ 20-24mo
### Measure

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66.79 (9.54)</td>
</tr>
<tr>
<td>FSIQ</td>
<td>111.64 (14.60)</td>
</tr>
<tr>
<td>MoCA</td>
<td>25.97 (3.11)</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
White matter tractography

- Siemens 3T Verio with 32 channel head coil, $b = 3000$, 64 directions
- Probabilistic whole brain tractography using MRTrix software to derive tractogram
- Tractogram was filtered into 18 separate white matter pathways using constraint ROI’s derived from a DTI tract atlas from John Hopkins University (JHU).
Fractional Anisotropy
*directional diffusion*

Mean Diffusivity
*magnitude of diffusion, regardless of direction*

Radial Diffusivity
*Diffusion perpendicular to main fibre orientation*

Axial Diffusivity
*Diffusion along the main fibre orientation*

Hua et al., *Neuroimage* 2008
<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Age</th>
<th>WM 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>

*p<.05, **p<.01, ***p<.001

- Eliminated when partialling WM Rad
- Retained when partialling Age

- Performance in all cognitive domains was associated with both age and all WM measures
- Strongest effects with Radial Diffusivity
Influence of diffuse vs regional white matter on mixing-cost

<table>
<thead>
<tr>
<th>MIXING COST</th>
<th>Total WM</th>
<th>IFOL</th>
<th>ILFL</th>
<th>SLFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error (incongruent)</td>
<td>.503***</td>
<td>.520***</td>
<td>.534***</td>
<td>.523***</td>
</tr>
<tr>
<td>Error (neutral)</td>
<td>.351**</td>
<td>.350**</td>
<td>.343**</td>
<td>.336**</td>
</tr>
<tr>
<td>RT (incongruent)</td>
<td>.290**</td>
<td>.339**</td>
<td>.365**</td>
<td>.341**</td>
</tr>
<tr>
<td>RT (neutral)</td>
<td>.415***</td>
<td>.470***</td>
<td>.489***</td>
<td>.466***</td>
</tr>
</tbody>
</table>

**p<.01, ***p<.001

IFOL = Inferior fronto-occipital fasciculus – left
ILFL = Inferior longitudinal fasciculus – left
SLFL = Superior longitudinal fasciculus – left
IFO: Inferior fronto-occipital fasciculus
direct pathway connecting occipital, posterior temporal, and orbito-frontal areas

ILF: Inferior longitudinal fasciculus
long association fibres running the length of occipital and temporal lobes

SLF: Superior longitudinal fasciculus
long association fibres connecting frontal and parietal lobes
Influence of diffuse vs regional white matter on mixing-cost

<table>
<thead>
<tr>
<th>MIXING COST</th>
<th>Total WM</th>
<th>IFOL</th>
<th>ILFL</th>
<th>SLFL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Error (incongruent)</td>
<td>.503***</td>
<td>.520***</td>
<td>.534***</td>
<td>.523***</td>
</tr>
<tr>
<td>Error (neutral)</td>
<td>.351**</td>
<td>.350**</td>
<td>.343**</td>
<td>.336**</td>
</tr>
<tr>
<td>RT (incongruent)</td>
<td>.290**</td>
<td>.339**</td>
<td>.365**</td>
<td>.341**</td>
</tr>
<tr>
<td>RT (neutral)</td>
<td>.415***</td>
<td>.470***</td>
<td>.489***</td>
<td>.466***</td>
</tr>
</tbody>
</table>

**p<.01, ***p<.001

IFOL = Inferior fronto-occipital fasciculus – left
ILFL = Inferior longitudinal fasciculus – left
SLFL = Superior longitudinal fasciculus – left

RT mixing cost effects remained significant when controlling for total WM
Role of white matter microstructure in age-related cognitive decline

Jolly, Michie, Bateman, Fulham, Cooper, Levi, Parsons, Rennie, Karayanidis.

Conclusions

• Age-related decline in task switching performance is mediated by changes in white matter microstructure
• Stronger associations between RaD in IFO, ILF, SLF pathways and mixing cost
• RaD variability in older samples is consistent with demyelination changes
• These WM changes
  – Mediate relationship between age and task-switching performance
  – Remain significant even when controlling for total WML volume
  – Are associated with variability in intracranial arterial pulsatility, especially in the presence of cardiovascular risk factors (*Jolly et al, Frontiers Hum Neurosci* 2013)
Is the rate of age-related decline of cognitive control ability related to changes in structural integrity of white matter
Karayanidis, Jolly, Rennie, Michie, Bateman, Fulham, Cooper, Levi, Parsons

Participants
- 20 Healthy older adults
- 8 Mild ischaemic attack

Neuropsych measures
- WASI, MoCA
- WMS – LM
- Digit Span
- CANTAB (IED, sWM, Stockings, SSP, PRM)

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

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

Imaging
- Siemens 3T Verio
- T1 structural (MPRAGE)
- Fluid Attenuated Inversion Recovery (FLAIR)
- Diffusion Weighted Imaging (DWI) sequence
- Test
- Re-test @ 20-24mo
Participants

<table>
<thead>
<tr>
<th></th>
<th>Full Sample</th>
<th>Time 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>70</td>
<td>28</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Age</td>
<td>65.7 +/- 9.3 y</td>
<td>65.4 +/- 8.9</td>
</tr>
<tr>
<td>MoCA</td>
<td>25.97 (3.11)</td>
<td>27.0 +/- 2.5</td>
</tr>
<tr>
<td>FA WMTotal</td>
<td>0.398 +/- 0.02</td>
<td>0.399 +/- 0.02</td>
</tr>
<tr>
<td>RaD WMTotal</td>
<td>0.451 +/- 0.03</td>
<td>0.448 +/- 0.03</td>
</tr>
</tbody>
</table>
Brain volumes

Cortical GM Volume
(t(27)=3.06, p<.005)

Cortical WM Volume

Subcortical GM Volume

Total GM Volume
(t(27)=2 p<.005)
Whole brain DTI measures

**FA Total**

Baseline: ~0.400
Retest: ~0.400

**MD Total**

Baseline: ~0.575
Retest: ~0.580

_t(27) = -2.75, p = .01_

**RaD Total**

Baseline: ~0.455
Retest: ~0.450

_t(27) = -3.37, p = .002_

**AxD Total**

Baseline: ~0.830
Retest: ~0.840

_t(27) = -2.21, p = .036_
### Pathway-specific DTI measures

#### Changes from Baseline to Retest

<table>
<thead>
<tr>
<th></th>
<th>FA</th>
<th>MD</th>
<th>Ax</th>
<th>RaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATR</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATR</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCFma</td>
<td></td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCFmi</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CST</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CST</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CgCin</td>
<td>L</td>
<td>0.015</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>CgCin</td>
<td>R</td>
<td></td>
<td>0.048</td>
<td></td>
</tr>
<tr>
<td>CgHi</td>
<td>L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CgHi</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFO</td>
<td>L</td>
<td>0.001</td>
<td>0.002</td>
<td>0.005</td>
</tr>
<tr>
<td>IFO</td>
<td>R</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>ILF</td>
<td>L</td>
<td>0.005</td>
<td>0.012</td>
<td>0.029</td>
</tr>
<tr>
<td>ILF</td>
<td>R</td>
<td>0.002</td>
<td>0.001</td>
<td>0.021</td>
</tr>
<tr>
<td>SLF</td>
<td>L</td>
<td>0.011</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>SLF</td>
<td>R</td>
<td>0.015</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>UNC</td>
<td>L</td>
<td>0.024</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>UNC</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>0.010</td>
<td>0.002</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Wakana et al., Radiology 2005*
Radial Diffusivity

IFO - L
p = 0.005

ILF - L
p = 0.029

IFO - R
p = 0.001

ILF - R
p = 0.021
Task-switching paradigm

Mixing Cost =
AR= all-repeat: Letter – Letter – Letter

Switch Cost =
Sw = Switch

Error

Reaction time
Task-switching: *Informative Cues (prepared)*

1. Greater mixing cost
2. Greater switch cost
3. Greater congruence cost
Correlations between cost and WM RaD measure

<table>
<thead>
<tr>
<th>Error Cost</th>
<th>Baseline</th>
<th>Retest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mixing</td>
<td></td>
</tr>
<tr>
<td>RaD</td>
<td>Incongr</td>
<td></td>
</tr>
<tr>
<td>TotalWM</td>
<td>Switch</td>
<td></td>
</tr>
<tr>
<td>IFO-L</td>
<td>.457**</td>
<td>.468**</td>
</tr>
<tr>
<td>IOF-R</td>
<td>.503**</td>
<td>.435*</td>
</tr>
<tr>
<td>ILF-L</td>
<td>.475**</td>
<td>.435*</td>
</tr>
<tr>
<td>ILF-R</td>
<td>.531**</td>
<td></td>
</tr>
<tr>
<td>SLF-L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLF-R</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** p<.01; all remain significant when controlling for total WM FA or age
## Correlations between mixing cost and WM RaD measure

<table>
<thead>
<tr>
<th>Error Cost</th>
<th>Baseline</th>
<th>Retest</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>RaD</td>
<td>Mixing</td>
<td>Mixing</td>
<td>Mixing</td>
</tr>
<tr>
<td>TotalWM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFO-L</td>
<td>0.457**</td>
<td>0.468**</td>
<td>-</td>
</tr>
<tr>
<td>IOF-R</td>
<td>0.503**</td>
<td>0.435*</td>
<td>-</td>
</tr>
<tr>
<td>ILF-L</td>
<td>0.475**</td>
<td>0.435*</td>
<td>-</td>
</tr>
<tr>
<td>ILF-R</td>
<td>0.531**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SLF-L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLF-R</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** p<.01; all remain significant when controlling for total WM FA or age
Baseline to Re-test

Error Mixing Cost

MoCA

worse at retest

r = 0.672
p < 0.001

IFO RaD

worse at retest

r > 0.985
p < 0.001

ILF RaD

worse at retest

r > 0.965
p < 0.001
WM RaD with MoCA / Mixing Cost

**BASELINE**

- **Left**
- **Right**

<table>
<thead>
<tr>
<th>% Error Mixing Cost</th>
<th>MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.457-0.531</td>
<td>-0.234-0.325</td>
</tr>
<tr>
<td>p = 0.011-.003</td>
<td>p &gt; 0.05</td>
</tr>
</tbody>
</table>

**IFO & ILF Rad**

**IFO & ILF RaD**

**RETEST**

- **Left**
- **Right**

<table>
<thead>
<tr>
<th>% Error Mixing Cost</th>
<th>MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.365-.435</td>
<td>-0.353-.497</td>
</tr>
<tr>
<td>p = 0.036-.009</td>
<td>p = 0.033-.004</td>
</tr>
</tbody>
</table>

**IFO & ILF Rad**

**IFO & ILF RaD**
WM RaD with MoCA / Mixing Cost

![Graph 1: Change Mixing Cost vs IFO & IFL Rad](image1.png)

![Graph 2: Change in MoCA vs IFO & ILF RaD](image2.png)

p > .10
Summary

Over 24 months:

- Significant decline in global functioning measures (MoCA), but not in IQ / Memory / WM

- Under prepared task conditions (Informative cues) and with incongruent stimuli, baseline to retest showed
  - Reduced sustained control (mixing cost)
  - Reduced proactive control (switch cost for informative cues)
  - Reduced reactive control (congruence cost for informative cues)

  All affecting primarily response accuracy.

- Substantial variability in size of change across participants
Summary

Over 24 months:

- Reduced WM organisation in pathways connecting occipito-temporal-frontal and parieto-frontal areas
  - Effects larger for RaD consistent with myelination changes
  - Measure very consistent within individuals across time (baseline to retest)
Summary

At each test time:

• RaD in these long anterior-posterior tract consistently correlated with error mixing cost and less so with MoCA

BUT:

No correlation between change in MixCost/MoCA and change in WM RaD

• Obvious culprit – sample size?

• Alternative more sensitive behavioural measures – latent parameters to differentiate between drift rate (Madden) and threshold (Ratcliff) changes?
Acknowledgements

Todd Jolly
Patrick Cooper
Jaime Rennie
Rhoshel Lenroot
Christopher Levi
Mark Parsons
Pat Michie
Correlations between cost and WM FA measure

<table>
<thead>
<tr>
<th>Error Cost</th>
<th>Baseline</th>
<th>Retest</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FA</td>
<td>Mixing</td>
<td>Incongr</td>
<td>Switch</td>
<td>Mixing</td>
</tr>
<tr>
<td>TotalWM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFO-L</td>
<td>-.513**</td>
<td></td>
<td></td>
<td>-.497**</td>
</tr>
<tr>
<td>IOF-R</td>
<td>-.489**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILF-L</td>
<td>-.500**</td>
<td></td>
<td></td>
<td>-.472**</td>
</tr>
<tr>
<td>ILF-R</td>
<td>-.575**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLF-L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLF-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** p<.01; all remain significant when controlling for total WM FA or age

Stronger pattern consistent with RaD;