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TRANSLATIONAL NEUROSCIENCE AND MENTAL HEALTH

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

T.Jolly, P.Michie, G.Bateman R.Fulham P.Cooper, C.Levi,
M.Parsons & F.Karayanidis.

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

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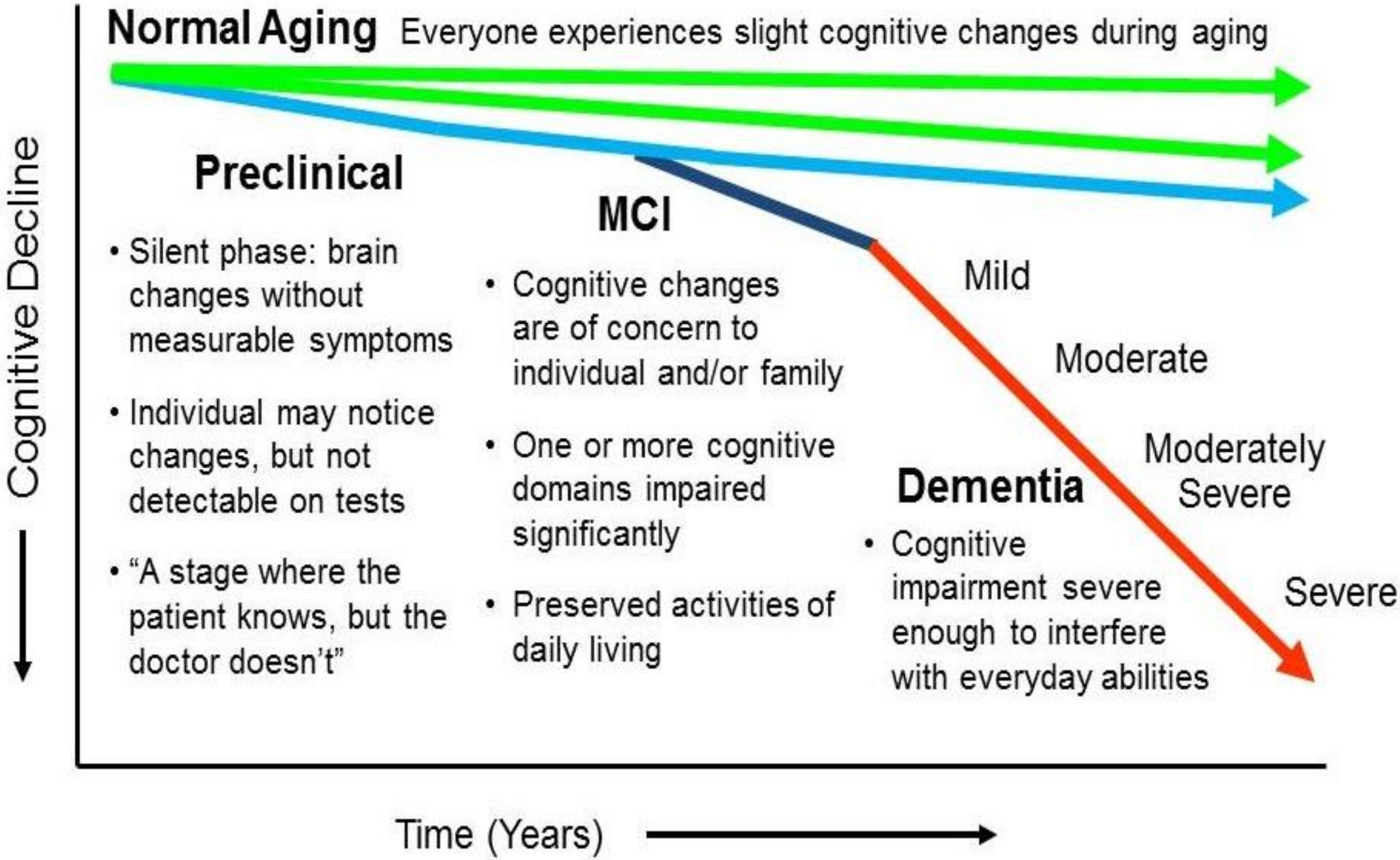
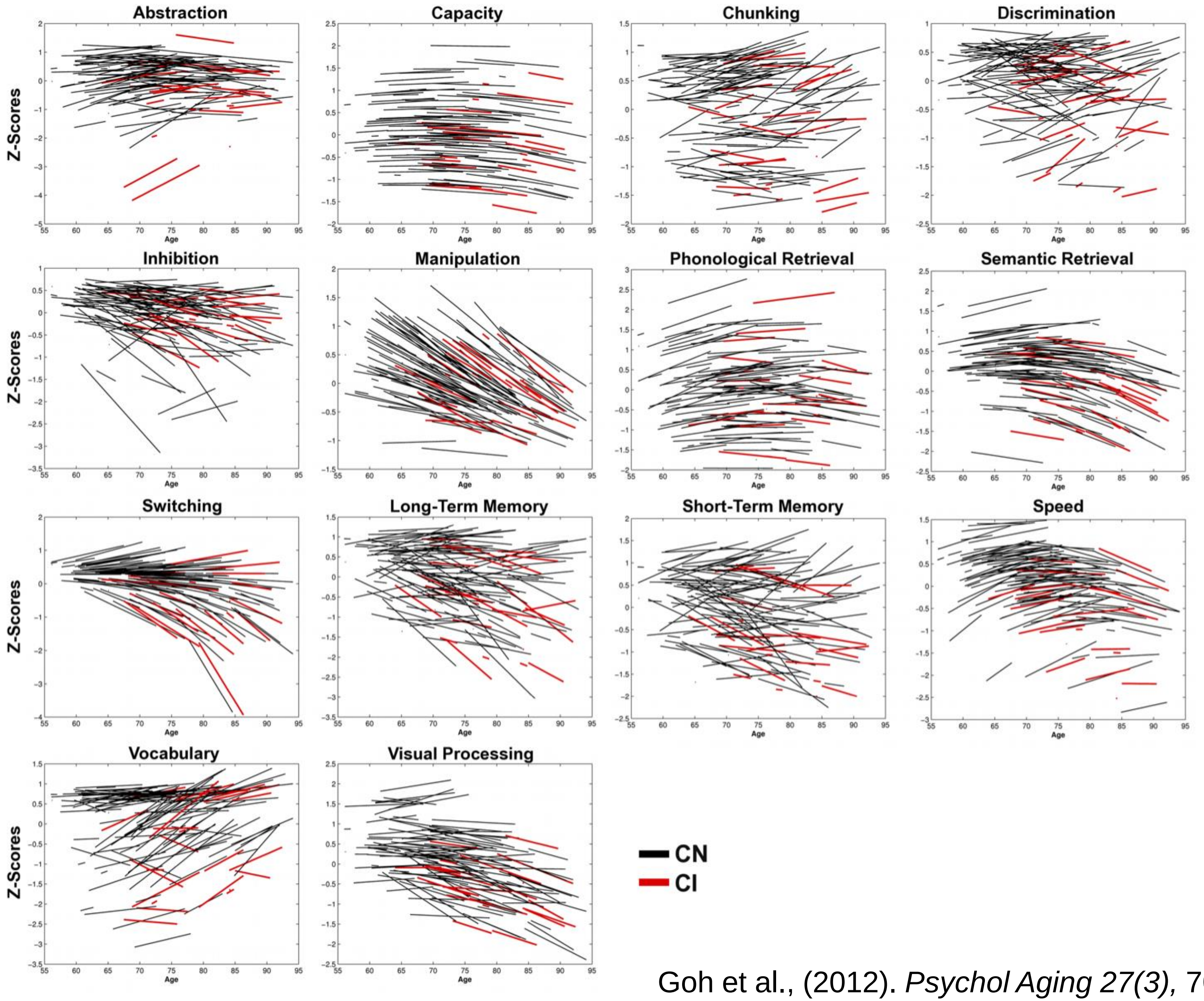
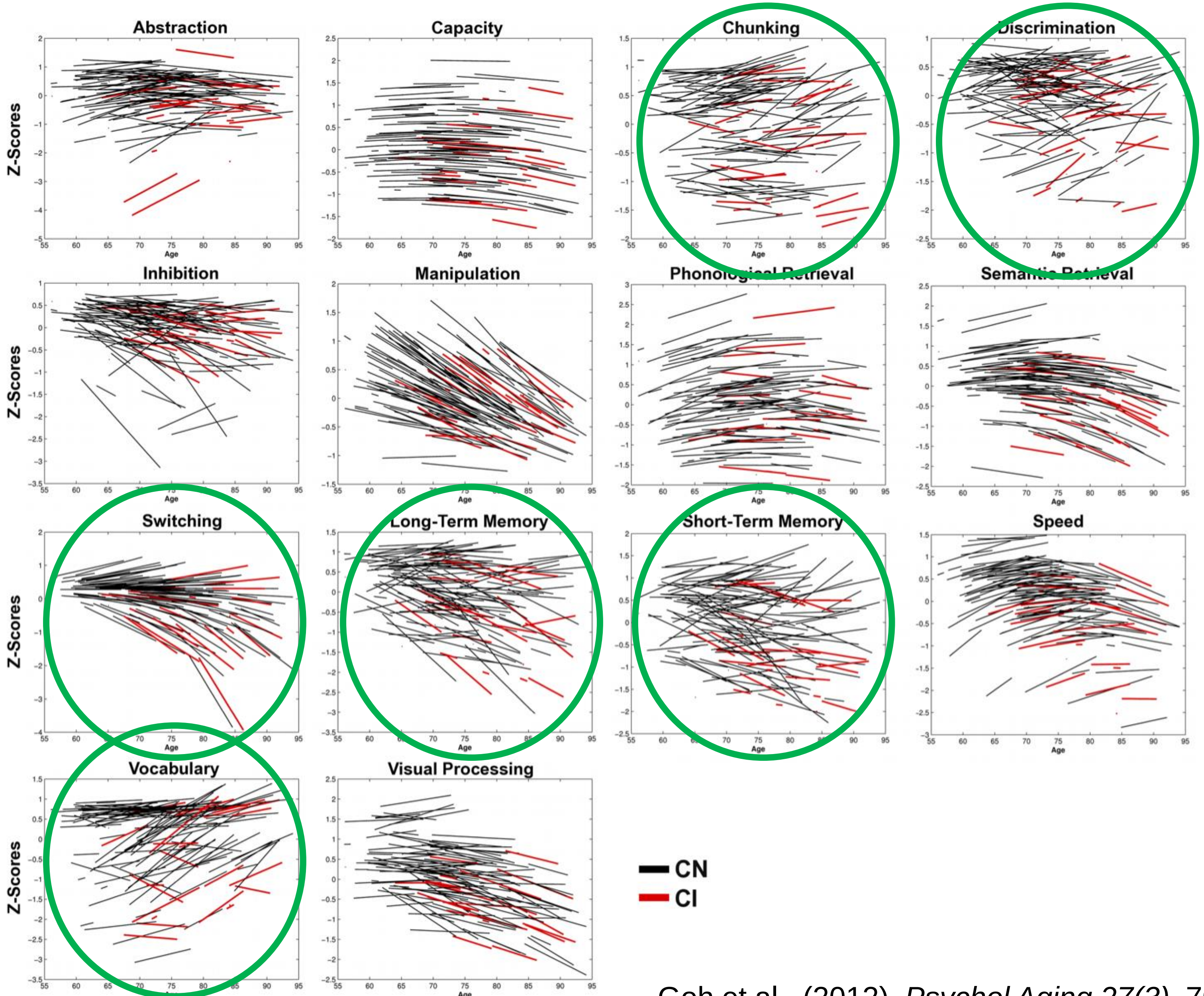

Normal Aging Everyone experiences slight cognitive changes during aging
Preclinical
• Silent phase: brain changes without measurable symptoms
• Individual may notice changes, but not detectable on tests
• "A stage where the patient knows, but the doctor doesn't"
MCI
• Cognitive changes are of concern to individual and/or family
• One or more cognitive domains impaired significantly
• Preserved activities of daily living
Mild
Moderate
Moderately Severe
Severe
Dementia
• Cognitive impairment severe enough to interfere with everyday abilities
Cognitive Decline
Time (Years)

Trajectories in cognitive decline with age



Goh et al., (2012). *Psychol Aging 27(3),* 707-719

Considerable variability in some trajectories



Goh et al., (2012). *Psychol Aging 27(3),* 707-719

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

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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

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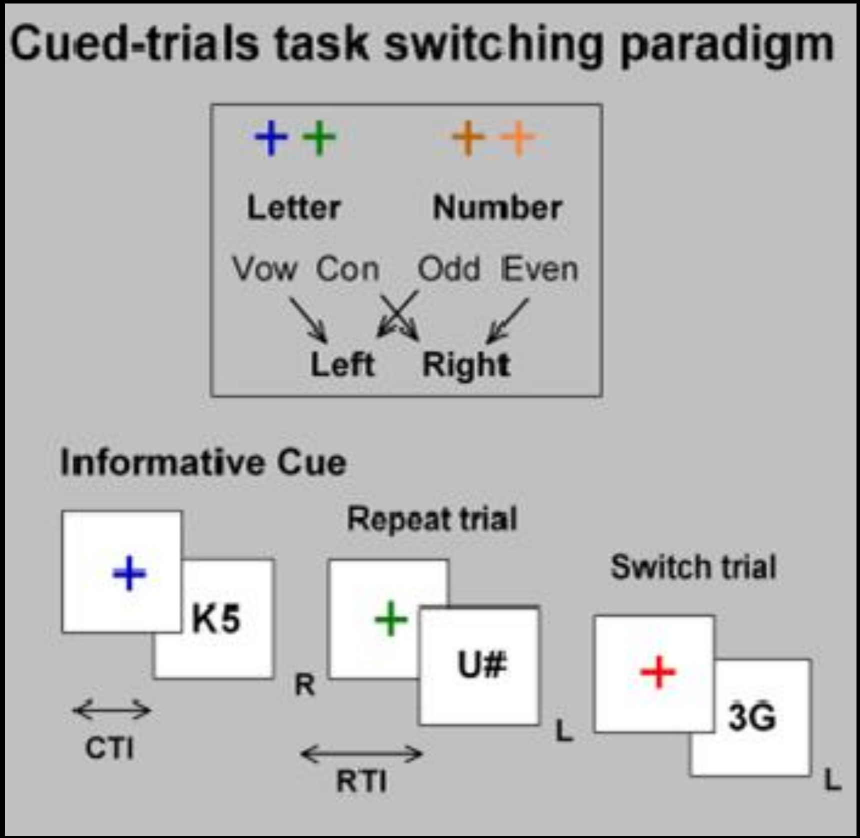
Task switching paradigm

For review see:
Karayanidis, Jamadar, Ruge, Phillips, Heathcote, Forstmann, 2010

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

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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
Lisa R. Whitson, Frini Karayanidis *, Patricia T. Michie *Acta Psychologica 139 (2012) 124-136*

- Consistent finding of increased mixing-cost in older adults

-Increased demands placed on working memory

-Greater task ambiguity

-Failure to fully disengage alternative task

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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

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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

Imaging

Siemens 3T Verio

- **T1 structural (MPRAGE)**
- Fluid Attenuated Inversion Recovery (FLAIR)
- **Diffusion Weighted Imaging (DWI) sequence**

Neuropsych measures

- WASI, MoCA
- **WMS – LM**
- **Digit Span, choice RT**
- **CANTAB (IED, SWM, SOC, SSP, PRM)**

Functional Measures

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

- **Test**
- **Re-test** @ 20-24mo

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Sample characteristics

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

Measure	**Mean (SD)**	**Range**
Age (yrs)	66.79 (9.54)	43-87 years
FSIQ	111.64 (14.60)	81-141
MoCA	25.97 (3.11)	17-30
Clinical profile	**Yes**	**No**
Vascular risk factors present	39 (56%)	31 (44%)
Hypertension	27 (39%)	
Hypercholesterolemia	21 (30%)	
Atrial fibrillation	11 (16%)	
Multiple vascular risk factors	24 (34%)	

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

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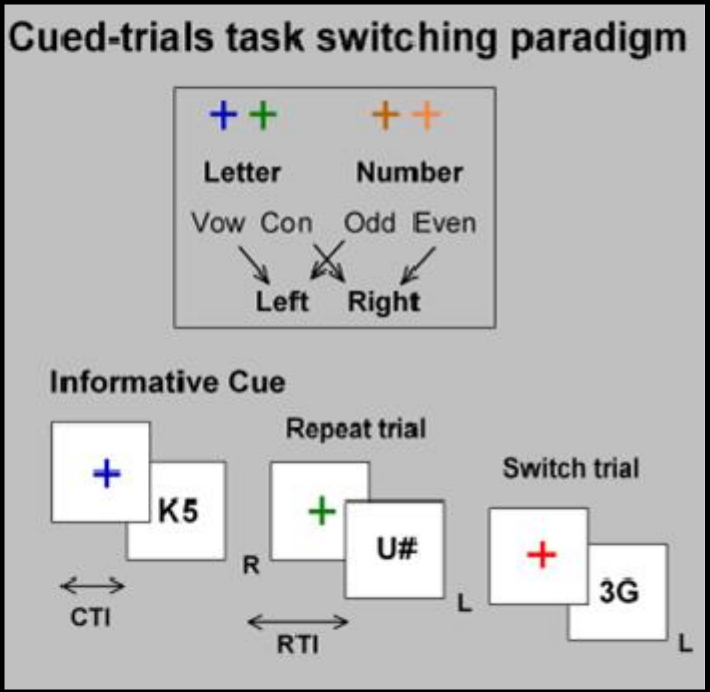
Task switching

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



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

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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).

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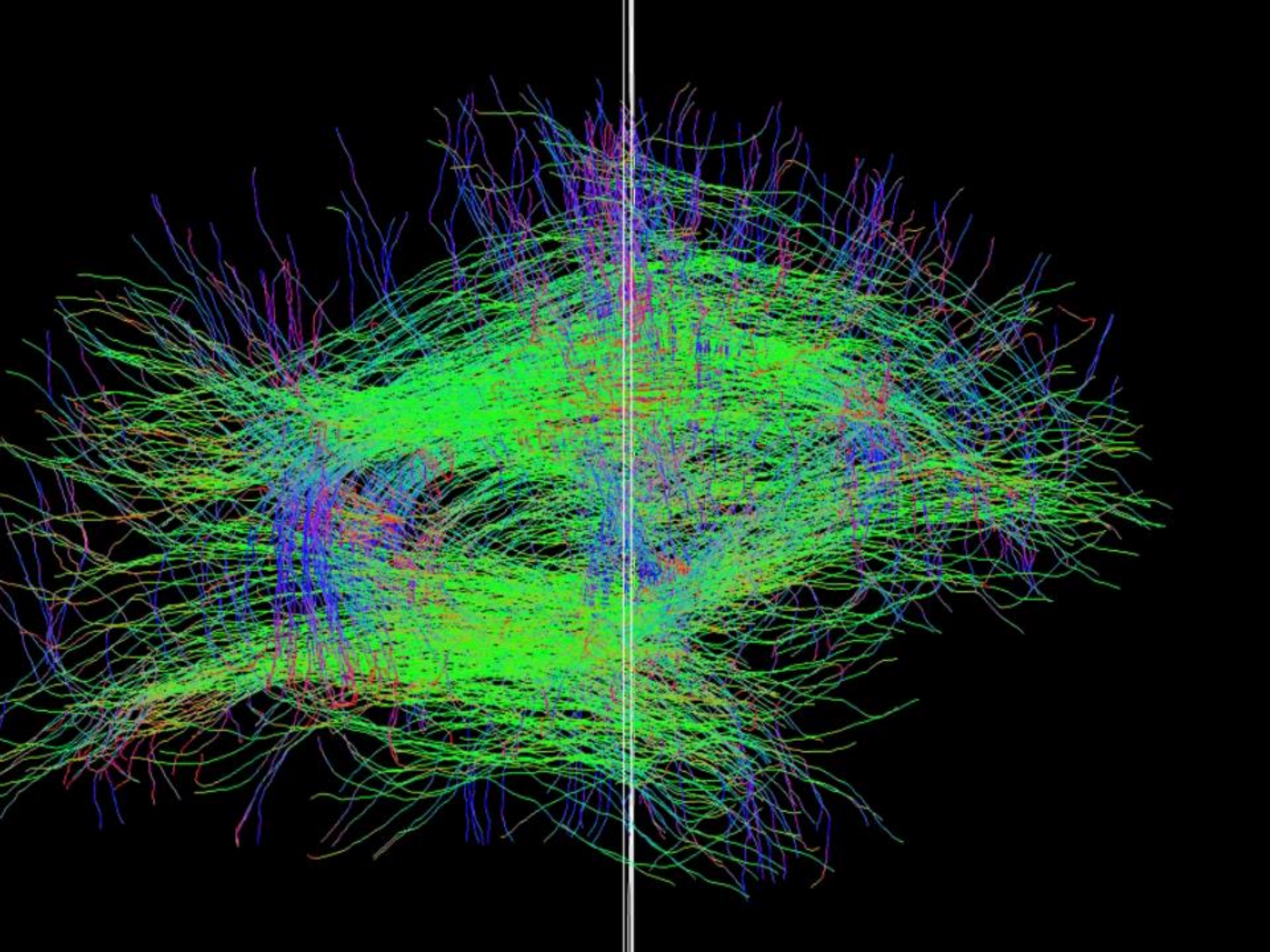
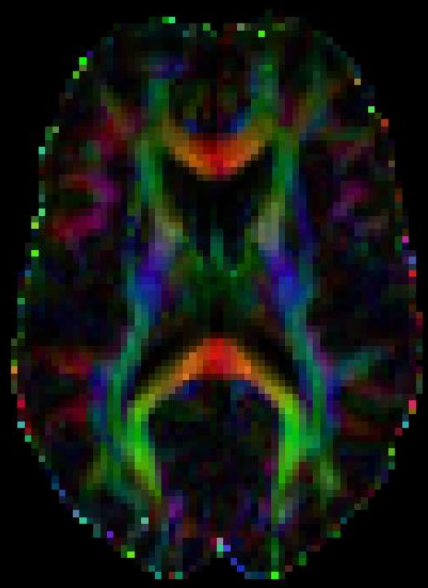
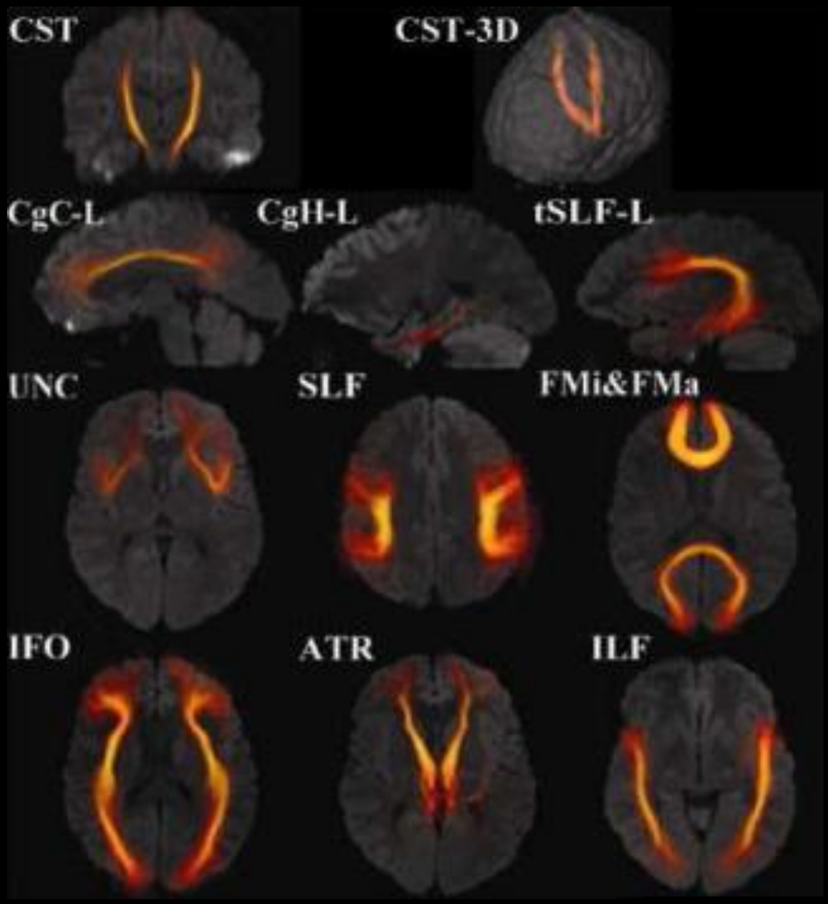


Measure of WM disruption

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





Hua et al., (2008). *Neuroimage, 39(1),* 336-347.

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- Correlation table

Measure		
	Age	White matter RaD
Working memory	-.365***	-.367***
Episodic memory	-.265*	-.411***
Executive function	-.430***	-.468***
Processing speed	-.494***	-.676***

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

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

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- Correlations with age controlling for white matter radial diffusivity

Measure		
	Age	White matter RaD
Working memory	72% attenuated	
Episodic memory	99% attenuated	
Executive function	77% attenuated	
Processing speed	93% attenuated	

- 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

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Correlations with white matter radial diffusivity controlling for age

Measure		
	Age	White matter RaD
Working memory		71% attenuated
Episodic memory		37% attenuated
Executive function		62% attenuated
Processing speed		35% attenuated

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

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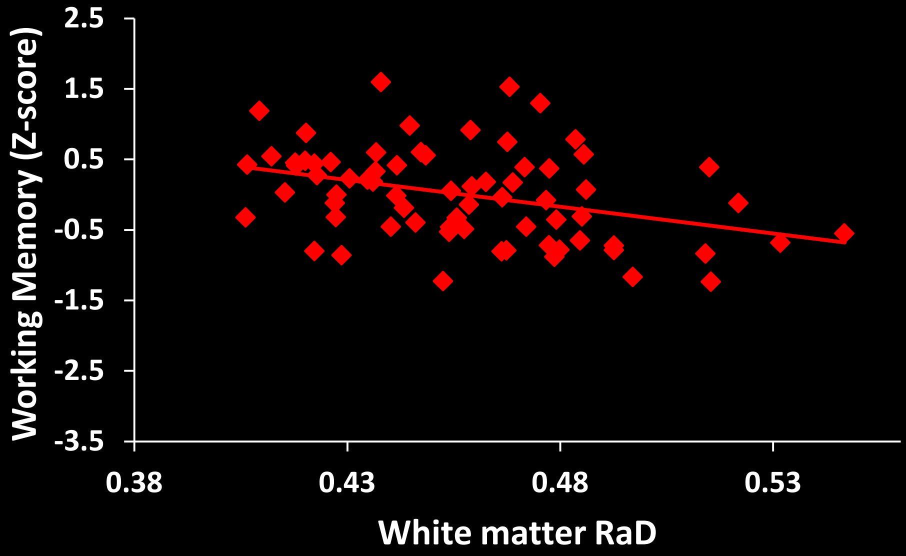
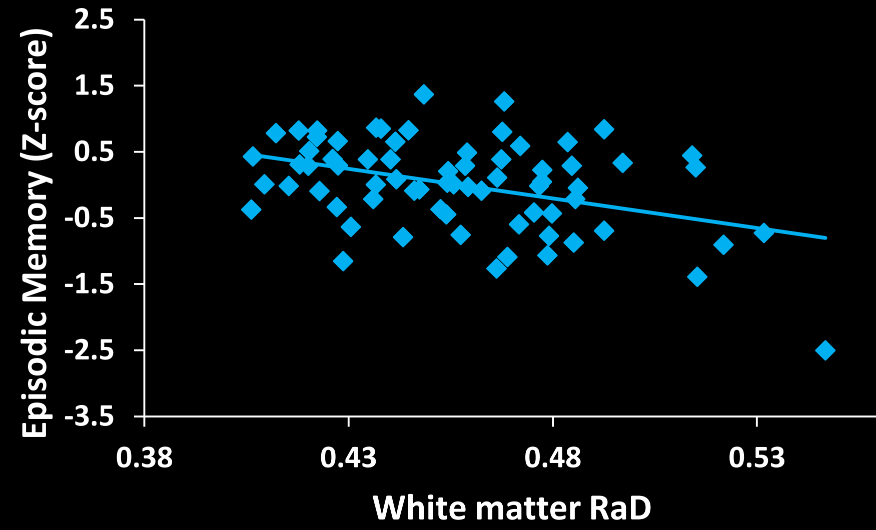
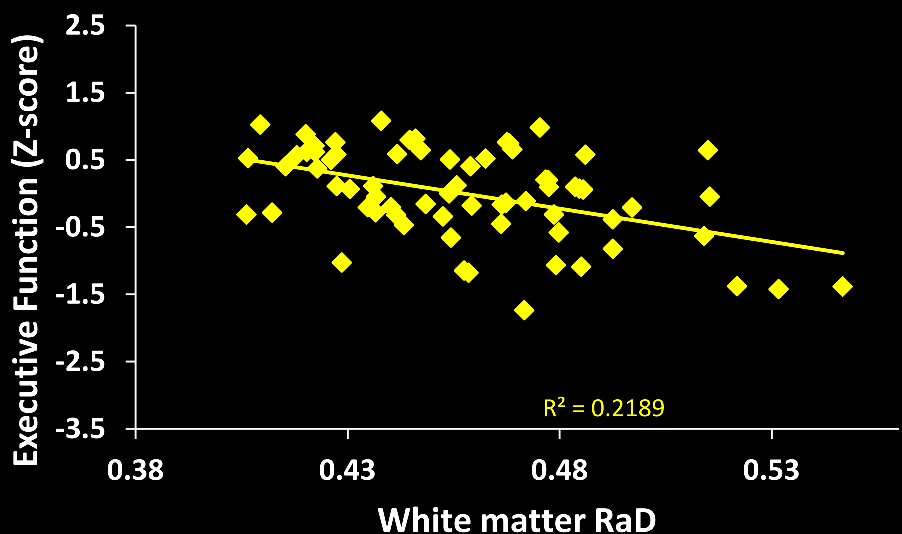
Working memory



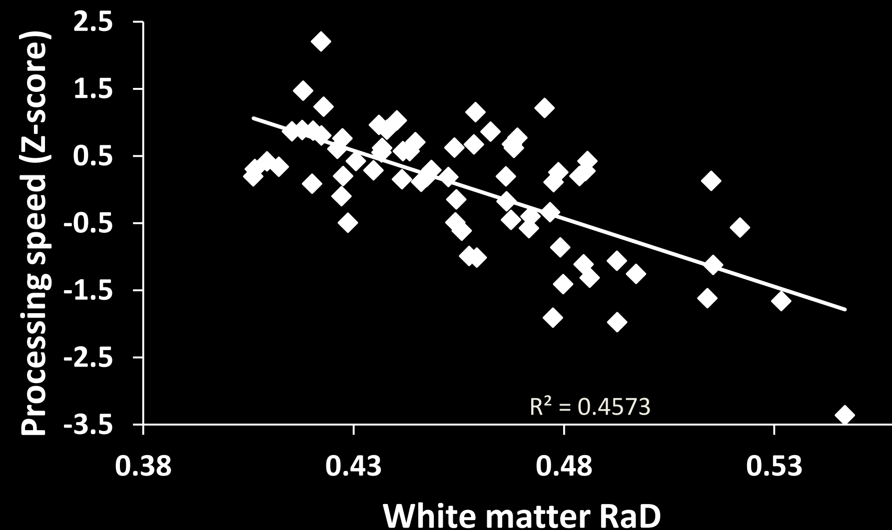
Episodic memory



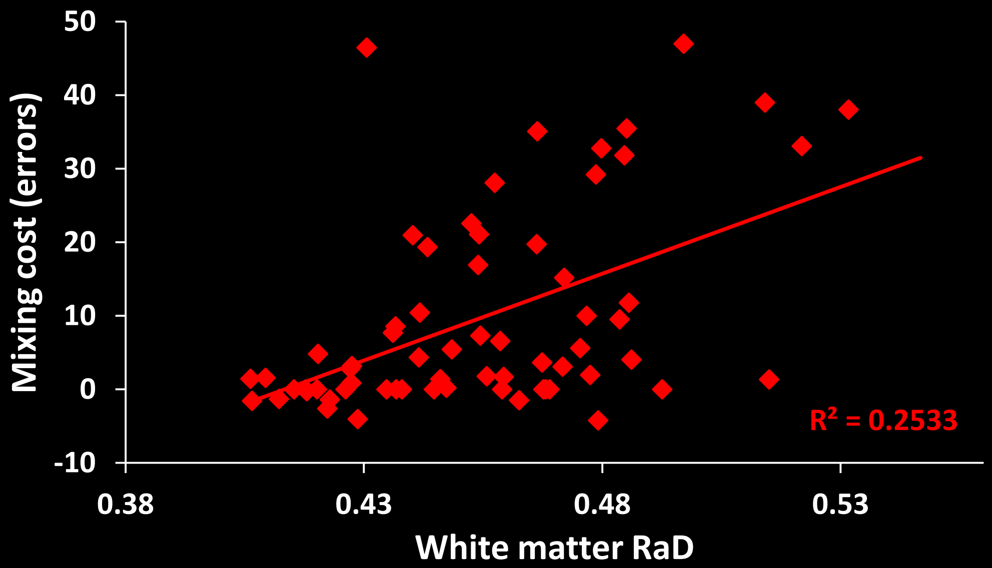
Executive function



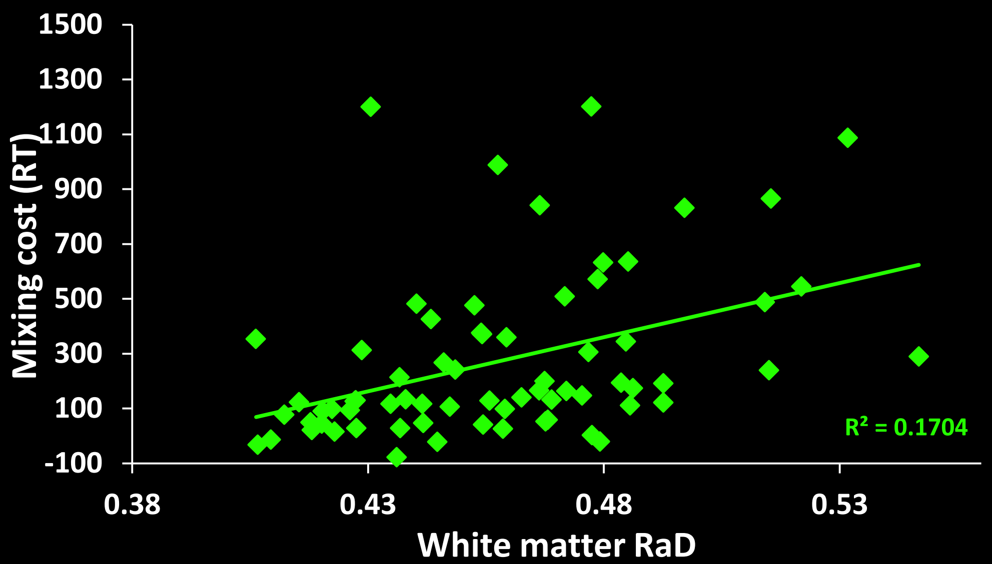
Processing speed



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

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Influence of diffuse vs regional white matter changes on mixing-cost

Trial				
	Overall white matter	**IFOL**	**ILFL**	**SLFL**
Error mixing cost (incongruent)	.503***	.520***	.534***	.523***
Error mixing cost (neutral)	.351**	.350**	.343**	.336**
RT mixing cost (incongruent)	.290**	.339**	.365**	.341**
RT mixing cost (neutral)	.415***	.470***	.489***	.466***

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.

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Influence of diffuse vs regional white matter changes on mixing-cost

Trial				
	Overall white matter	IFOL	ILFL	SLFL
Error mixing cost (incongruent)	.503***	.520***	.534***	.523***
Error mixing cost (neutral)	.351**	.350**	.343**	.336**
RT mixing cost (incongruent)	.290**	.339**	.365**	.341**
RT mixing cost (neutral)	.415***	.470***	.489***	.466***

Remained significant even after controlling for variability associated with overall white matter

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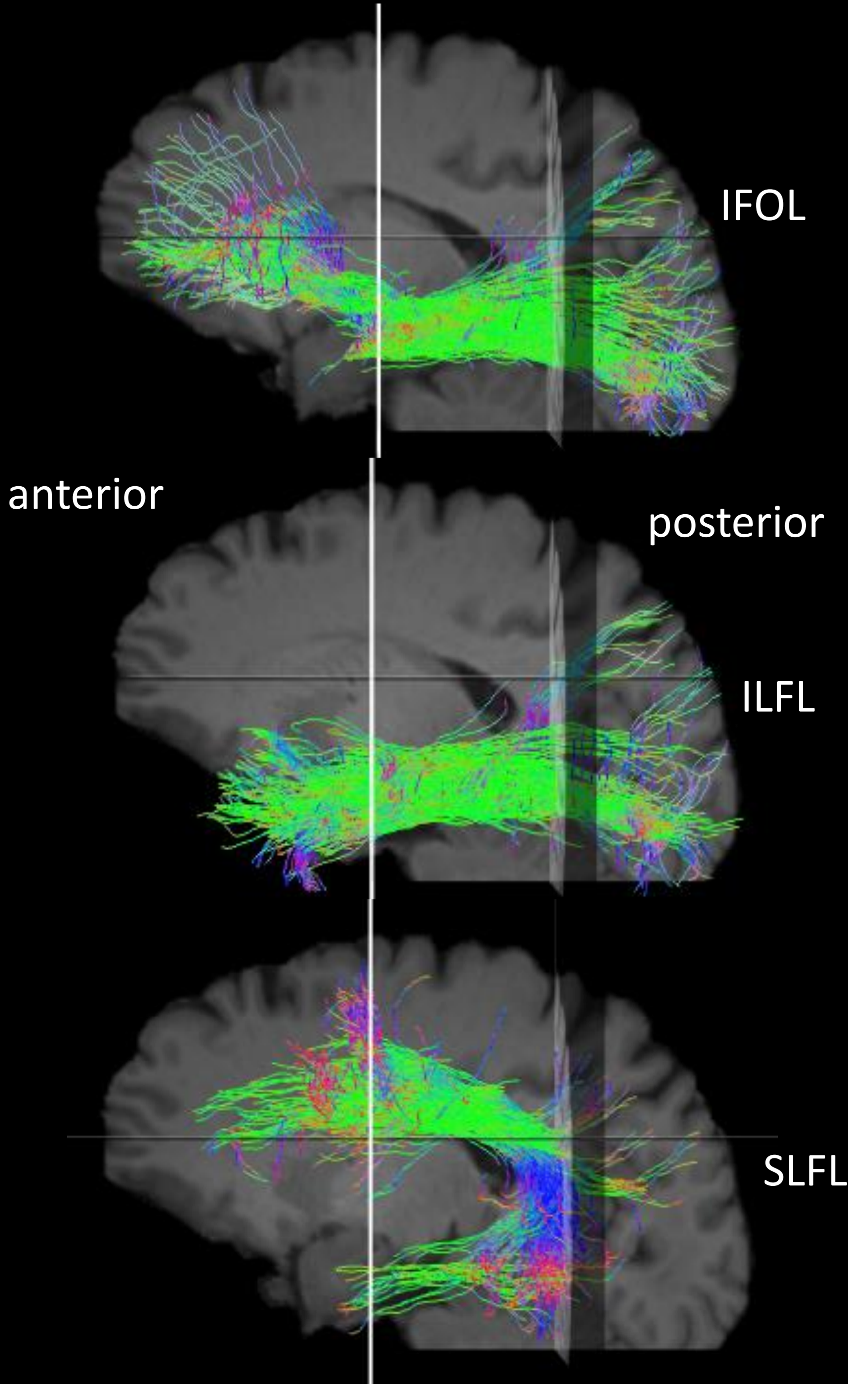

Large degree of spatial overlap between three white matter tracts

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

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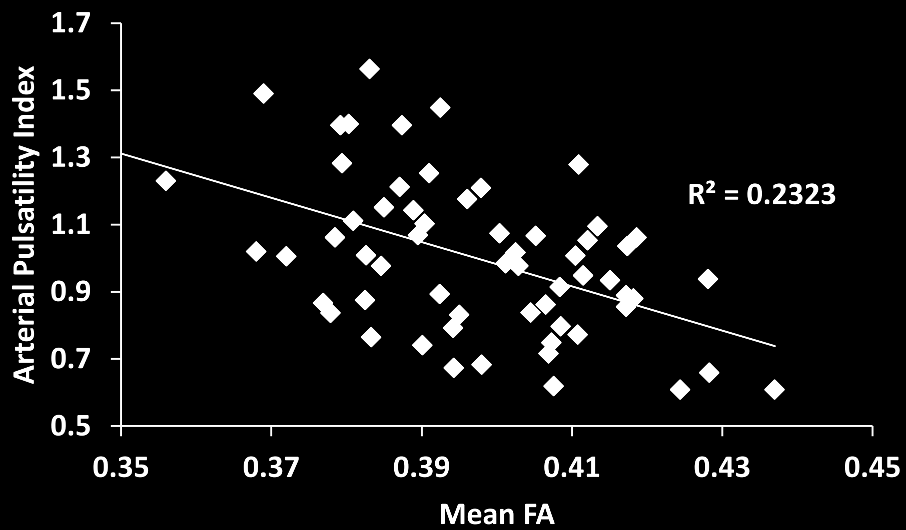
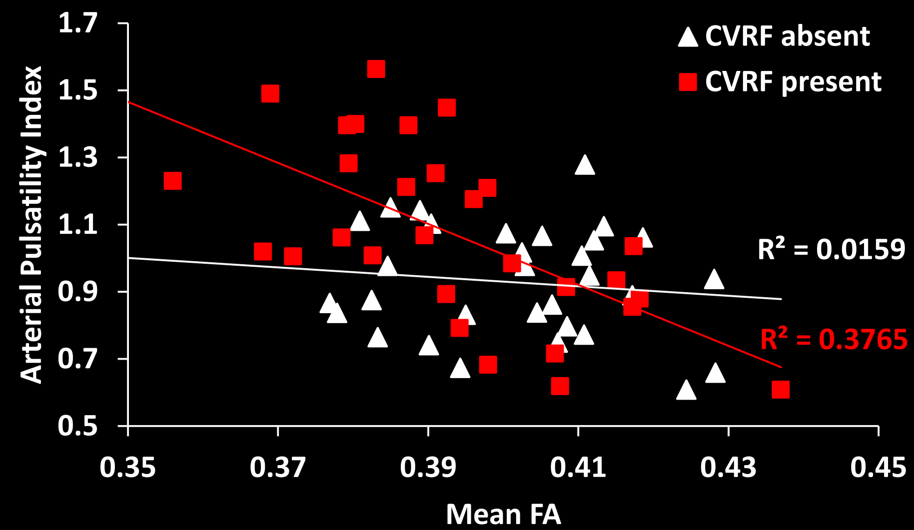
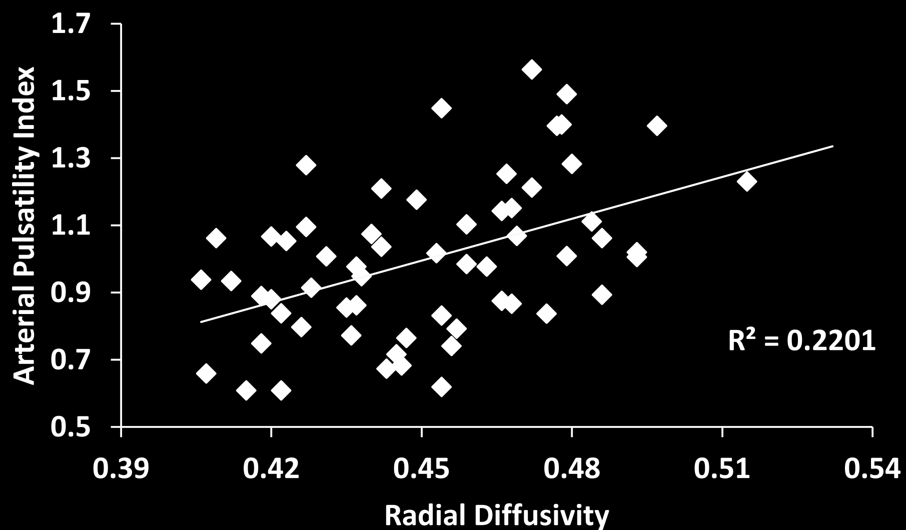
Early detection of microstructural white matter changes associated with arterial pulsatility

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

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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.

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Research Team

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Investigators

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Clinical Professional Doctorate

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Undergraduate students

Jaime Rennie

Programming

Tony Kemp

In-house software (EEGDisplay)

Dr Ross Fulham

This project is funded by Hunter Medical Research Institute (HMRI) Project Award to FK as well as APA Scholarship and HMRI RHD Top-Up Award to TJ

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HMRI Hunter Medical Research Institute