Building a better model of white matter changes in aging:

The myelodegenerative hypothesis and cognition

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Introduction

The myelodegenerative hypothesis states that age-related declines in white matter are due to changes in myelination. These myelin changes, in turn, engender cognitive decline, and eventually dementia (Bartzokis et al., 2005).

Two problems arise from this view:

1) This claim is based upon studies using DTI metrics such as radial diffusivity (RD), which measures the diffusion of water and should increase as myelin degrades. This inference is poor because RD reflects only one aspect of
2) ignores the critical role of white matter in engendering *preserved* cognition.

We addresses this problem by

1) comparing RD to the magnetization transfer ratio (MTR), which measures the myelin-bound proton pool, and represents information normally invisible to conventional MRI or DWI, and
2) Applying models sensitive to age-related declines, as well as cognitions demonstrating age-related preservation.

Therefore, we test the claims of the myelodegenerative hypothesis to determine

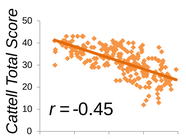
1) if they capture the same underlying physiological characteristic, MTR and RD should show similar voxelwise morphology
2) these white matter metrics should predict both age-related decline as well as age-related preservation of cognitive function.

Behavioural Measures

We used 4 cognitive tasks, two which showed age-related decline, and 2 which showed preserved cognition.

Fluid Intelligence

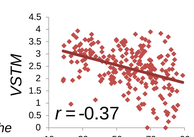
The Cattell Culture Fair asks subjects to match colored patches to a template, in order to



Which square fits?

Working Memory

The Visual Short Term Memory task demands subjects remember color identity over short (1s)



Report the color in the marked location.

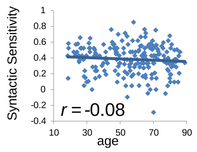
In contrast, many functions are *preserved* across the lifespan, such as the *syntactic* and *semantic* sensitivity to realistic sentences (Tyler et al., 2011).

Syntax

John knew that *BORING COLLEAGUES*

- Preferred Continuation (Dominant, DOM): *WERE* approaching his office.
- Least Preferred Continuation (Subordinate, SUB): *WAS* damaging his career.

the difference in the acceptability response to SUB and DOM sentences is a measure of *Syntactic* or *Sensitivity* which shows no age-related decline:



Semantics

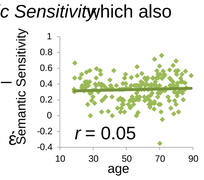
Similarly constructed sentences provide a reliable measure of *Semantic Sensitivity*, which also remains preserved.

e.g.,

(DOM)

vs.

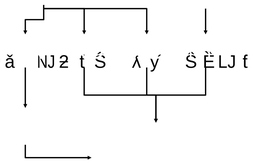
(SUB)

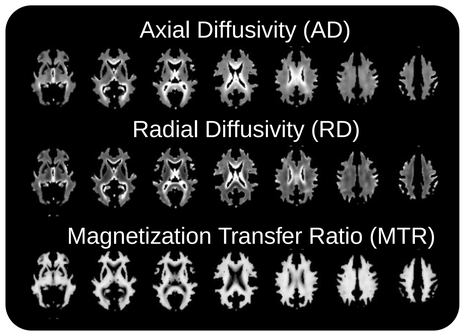


Imaging Methods

Preprocessing

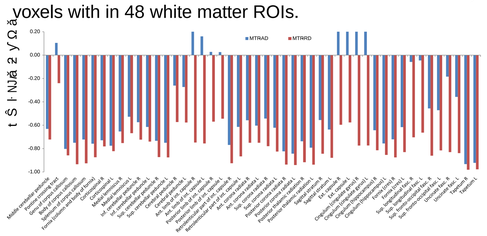
All images processed using tract-based spatial statistics (TBSS) in order to put data within a common stereotaxic space.



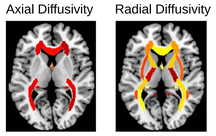


Similarity Analysis

Similarity between RD & MTR measures and dissimilarity between MTR & AD should reflect myelination. We therefore conducted a voxelwise analysis of the correlation between voxels with in 48 white matter ROIs.



Similarity between MTR and:



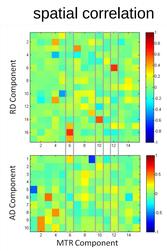
Supporting our first hypothesis, voxelwise correlations are greater between MTR and RD than MTR and AD, suggesting that these two independent imaging modalities measure a similar underlying characteristic.

ICA and Model Estimation

We used a data-driven approach to finding patterns of structural variation

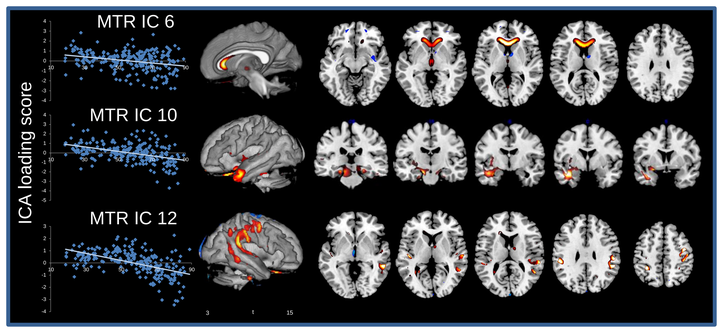
Ideal patterns of MTR would show a corresponding pattern of variance in RD but not AD components

ICA performed using the GIFT Source-based morphometry toolbox (Calhoun et al., 2001)



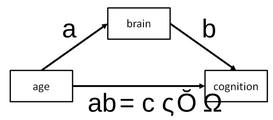
Grey boxes outline 3 components which show a significantly greater spatial correlation between an MTR-RD component pair than other MTR-AD component pair.

These components are more fully described below:



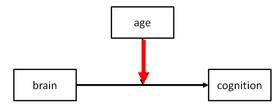
Results

Mediation models represent an ideal means of testing causal mechanisms accounting for age-related *decline* (e.g., Cattell, Visual Short Term Memory).



Such models necessitate significant *a*, *b*, and *ab* terms, the latter of which indicates an attenuation of the age cognition relationship once brain is taken into account.

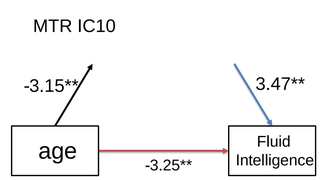
Moderation models represent an ideal means of testing why some cognitive functions are *preserved* (e.g., Syntactic and Semantic Sensitivity).

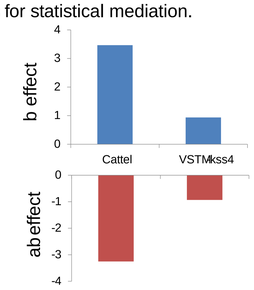


Such models necessitate an overall model fit (R²), as well as a significant age x brain interaction (red arrow).

explaining decline

Of the three myelin-related components, an MTR component localized to parietal regions acts as a significant mediator of subject scores of fluid intelligence (Cattell), satisfying all 3 conditions for statistical mediation.



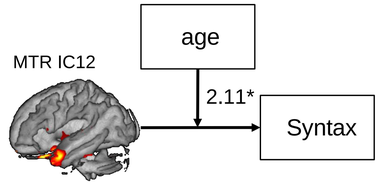


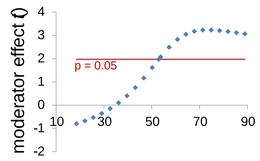
Mediation Effects in Behavioral Measures Demonstrating Age-related Decline

Independent Component	Behavioral Measure	ab effect (t)	b effect (t)
IC6	Cattell	-1.30	1.36
	VSTMkss4	-1.06	1.10
IC10	Cattell	-3.25	3.46
	VSTMkss4	-0.93	0.93
IC12	Cattell	-0.84	-1.03
	VSTMkss4	0.12	0.12

explaining preservation

In contrast, moderation models demonstrate that an MTR component localized to the anterior temporal lobe became a significant predictor of syntactic sensitivity only at later ages (>52)





Moderation Effects in Behavioral Measures Demonstrating Age-related Preservation

Independent Component	Behavioral Measure	Model fit (R)	MTR X AGE (t
IC6	Syntax	.08	.09
	Semantic	.13	-1.52
IC10	Syntax	.10	.50
	Semantic	.11	-1.20
IC12	Syntax	.23 (0.008)	-2.11
	Semantic	.15	1.01

Conclusions

- MTR strongly predicts RD greater than AD, supporting the idea that these metrics track a common physiological characteristic.
- White matter changes in parietal regions predict age-related cognitive decline,
- While white matter changes in anterior temporal regions evidence evolving mechanisms that support preservation of cognitive function.

References

- Bartzokis G, et al. 2004. Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "disconnection" in aging and Alzheimer's disease. Neurobiol Aging 25:843-851
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