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 (Bartozik 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 myelination.
2. Focusing exclusively on white matter’s role in explaining cognition ignores the critical role of white matter in explaining preserved cognition.

We address 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 and as well as age-related preservation of cognitive function.

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**Imaging Methods**

Preprocessing

- All images processed using tract-based spatial statistics (TBSS) in order to put data within a common anatomic 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 m: 48 white matter RDs.

**ICA and Model Estimation**

We used a data-driven approach to finding patterns of spatial 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)

**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.

Explaining decline

- Of the three myelin 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.

Explaining preservation

- In contrast, mediation models demonstrate that an MTR component localized to the anterior temporal lobe became a significant predictor of syntactic sensitivity only at later ages (>50).

**Conclusions**

- MTR strongly predicts RD greater than AD, supporting the idea that these metrics track a common physiological characteristic.
- While 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.

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**References**


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**Tables and Figures**

- [Tables and figures related to the study's findings and methodologies are included here.]

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**Visual Aids**

- [Diagrams and figures related to the study's findings and methodologies are included here.]

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**Supplementary Material**

- [Supplementary material related to the study's findings and methodologies are included here.]

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**Supplementary Text**

- [Additional text and explanations related to the study's findings and methodologies are included here.]

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