THE EFFECT OF HEALTHY AGING ON MULTIPLE MEASURES OF WHITE MATTER INTEGRITY

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INTRODUCTION

DIFFUSION TENSOR IMAGING (DTI): Structural imaging technique that measures water diffusion, or movement, as a proxy for white matter integrity (WMI) (Basser et al., 1994)

DTI research in healthy aging had primarily focused on the average amount (mean diffusivity, MD) and directional coherence (fractional anisotropy, FA) of water movement

- Higher MD and lower FA in older versus younger adults (Salat et al., 2005; Sullivan & Pfefferbaum, 2006)
- Largest age differences in frontal white matter (e.g., genu of the corpus callosum, anterior corona radiata) (Hedden & Gabrieli, 2005; Pfefferbaum et al., 2005)

Recent studies that assessed water movement parallel (axial diffusivity, λ1) and perpendicular (radial diffusivities, λ2 and λ3) to the primary diffusion direction revealed two patterns associated with the age-related FA decrease

- Increase in axial and radial diffusivities (Sullivan et al., 2006, 2008)
- Increase in radial diffusivities only (Bhagat & Beaulieu, 2004; Madden et al., 2008)

Both patterns were attributed to similar neural bases of diffusion (i.e. axonal shrinkage and demyelination)

Results from other studies indicate that these patterns may be more complex and vary by brain region (e.g., Stadlbauer et al., 2008; Vernooij et al., 2008)

AIM: To identify patterns of age differences in multiple WMI measures and propose neural bases underlying each pattern of diffusion

METHOD

PARTICIPANTS

- 14 young adults (18.9 ± 0.7 years; 9 female)
- 14 old adults (67.6 ± 3.1 years; 10 female)

DTI METHODS

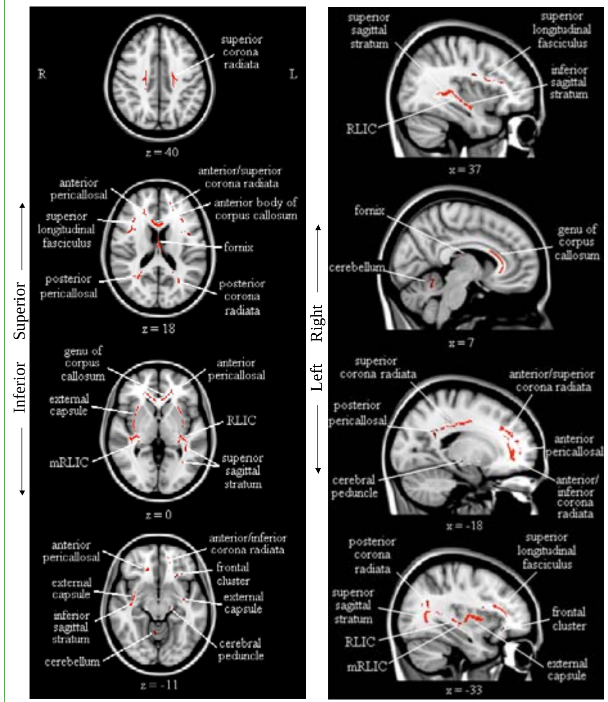
- 3T Siemens Trio
- Two EPI sequences acquired per participant
  - Diffusion weighted gradients b=0 and b=1000 s/mm^2 applied in 35 orthogonal directions
  - 55 axial interleaved slices
  - 2.5 mm^3 spatial resolution; FOV=240x240 mm
  - TR/TE=7700/100ms
- Data processed with FMRIB’s diffusion toolbox (Behrens, 2003; Smith et al., 2004)
  - Runs were concatenated in time
  - BET binary brain mask: limited tensor fitting to brain space
  - Eddycorrect: corrected eddy current and movement distortion
  - DTIfit: independently fit diffusion tensors to each voxel
- WMI maps (FA, MD, λ1, λ2, λ3) were derived from the diffusion tensor

DTI ANALYSES

- Between-group t-test for FA
  - Tract-Based Spatial Statistics and Randomise (cluster threshold = 3, $p < .05$) (Smith et al., 2006) for skeleton-wise comparisons
  - Clusters labeled with reference to JHU ICBM-DTI-81 White Matter atlas
- Between-group t-tests for non-FA diffusivity measures
  - Values extracted from significant FA clusters
  - Bonferroni corrected for 28 comparisons per WMI measure ($p < .0018$)

AGE GROUP DIFFERENCES IN WMI

DIFFERENCES IN FA: Significant clusters (RED) indicate where Young > Old



DIFFERENCES IN DIFFUSIVITY: Significantly greater values in young (Y > O) or old (O > Y), in left ([lt]) or right ([rt]) hemisphere only

REGION	FA	MD	λ1	λ2 & λ3 (avg.)
Genu of corpus callosum [a, b]	Y > O	O > Y	O > Y	O > Y
External capsule [a]	Y > O	O > Y	O > Y	O > Y
Fornix [a, c]	Y > O	O > Y	O > Y	O > Y
Superior sagittal stratum	Y > O	O > Y [rt]		O > Y
Superior longitudinal fasciculus [a, d]	Y > O	O > Y		O > Y
Medial RLIC	Y > O			O > Y
Frontal cluster [lt]	Y > O			O > Y
Posterior pericallosal [c]	Y > O			O > Y
Anterior/inferior corona radiata [lt, e]	Y > O			O > Y
Cerebellum [rt]	Y > O			O > Y
Posterior corona radiata	Y > O			O > Y [lt, †]
Inferior sagittal stratum	Y > O			O > Y [rt, †]
Retrolenticular part of internal capsule (RLIC)	Y > O		Y > O [rt]	O > Y
Anterior/superior corona radiata	Y > O		Y > O	O > Y
Anterior pericallosal	Y > O		Y > O	O > Y [rt]
Cerebral peduncle [lt]	Y > O		Y > O	O > Y
Superior corona radiata	Y > O		Y > O [lt]	O > Y

Note. Replicated earlier findings from [a] Sullivan et al., 2008; [b]Sullivan et al., 2006; [c]Vernooij et al., 2008; [d]Madden et al., 2008; and [e]Bhagat & Beaulieu, 2004. † = Marginally significant ($p < .002$)

DISCUSSION

THREE PATTERNS of age differences in diffusivity were associated with the age-related decrease in FA

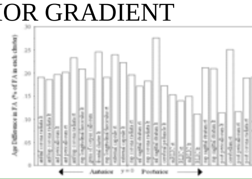
- The first two patterns, but not the third one, have been reported previously

PATTERNS VARIED BY BRAIN REGION, which may reflect differential aging of underlying neural substrates that affect diffusion

PATTERN	PROPOSED NEURAL BASIS	RELATION TO PRESENT RESULTS
↑ axial and radial diffusivity	Global increase in intra/extra cellular fluid from a combination of decreased packing density, thinning myelin, decreased axon diameter, and/or inflammation (e.g., Sullivan et al., 2008)	▪ Genu has many small diameter fibers susceptible to demyelination and shrinkage that may lead to decreased packing density in aging (Pfefferbaum et al., 2000) ▪ External capsule and fornix subject to partial volume effects from adjacent CSF and gray matter
↑ radial diffusivity only	Decreased myelination and possibly axonal loss or damage that only increased diffusion perpendicular to the primary diffusion direction (e.g., Bhagat & Beaulieu, 2004; Madden et al., 2008)	▪ Most clusters contain long range anterior-to-posterior association tracts - inferior fronto-occipital fasciculus in superior and inferior sagittal stratum and anterior/inferior corona radiata - superior longitudinal fasciculus - uncinate fasciculus in frontal cluster ▪ Susceptible to demyelination in aging (Yakovlev & Lecours, 1967)
↓ axial and ↑ radial diffusivity	Decreased coherence of fiber orientation that decreases fluid parallel to and increases fluid perpendicular to the primary diffusion direction	▪ All clusters contain projection tracts that pass though regions with many crossing fibers (i.e., inferior-superior tracts that pass through long range anterior-posterior tracts) that may decreased coherence of diffusion in the primary direction - thalamic radiations in RLIC, anterior/superior and superior corona radiata, and anterior pericallosum - corticospinal tract in superior corona radiata and cerebral peduncle ▪ Subject to age-related axonal shrinkage (Stadlbauer et al, 2008; Zhou et al, 1997)

ANTERIOR-POSTERIOR GRADIENT

- Age differences in FA were seen throughout the brain
- However, the magnitude of the age difference was greater in anterior ($y > 0$) versus posterior ($y < 0$) clusters ($p < .05$)



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