



DTI-based Measures of White Matter Integrity Predict Cognitive Performance in Healthy Aging

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BACKGROUND

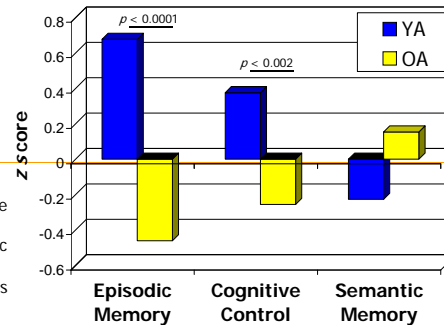
- Most prior research on the neurobiology of age-related cognitive decline has focused on structural and functional changes in cortical gray matter structures.
- New studies, however, suggest that decreased white matter integrity is also associated with advanced age.
 - Histological studies indicate a reduced number and density of myelinated fibers in old brains.^{1,3}
 - MRI-based studies show that white matter volume reductions in aging are more widespread and of greater magnitude than gray matter changes.^{4,5}
 - Further, studies using diffusion tensor imaging (DTI) show reduced levels of fractional anisotropy, particularly in anterior white matter.⁶⁻⁹
- Little is known, however, about the functional correlates of these striking white matter changes.

Diffusion Imaging Basics

- Fractional anisotropy (FA) is a measure of the relative ease with which water moves in tissues.
- Physical barriers, such as cell bodies, axons, and myelin, restrict water diffusion. If movement is restricted to a single direction, such as along dense bundles of axonal projections, the FA in that tissue is high.
- While the precise microstructural correlates of FA remain unknown, DTI is capable of detecting changes in white matter that occur in aging and disease, providing a marker of white matter integrity.

COGNITIVE TESTING

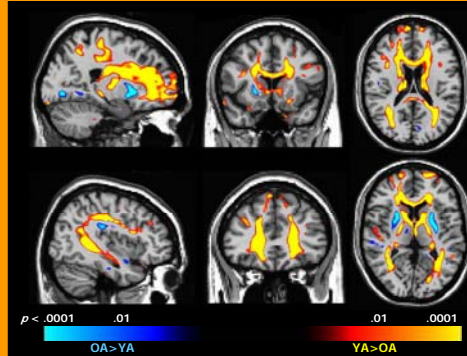
- All participants performed a series of cognitive tasks to assess:
 - Episodic memory (delayed recall of word lists and stories)
 - Semantic memory (Boston Naming, WAIS Vocabulary)
 - Cognitive control processes (Stroop, letter fluency, digit span)
- We calculated standardized composite scores for each measure (z scores)
- YA performed significantly better than OA on tests of episodic memory ($p < .0001$) and cognitive control ($p < .002$)
- OA performed better than YA on semantic memory tasks, but this difference did not reach significance ($p = 0.16$)



CONCLUSIONS

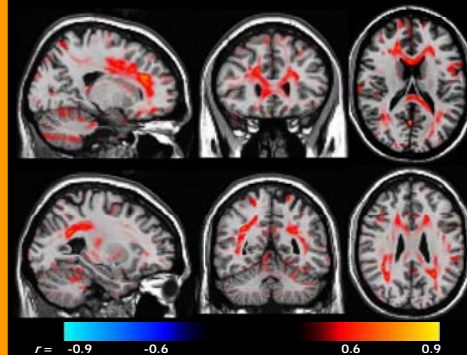
- Consistent with previous studies,⁷⁻⁹ the present results confirm that white matter in anterior regions of the brain, such as the frontal lobe and anterior corpus callosum, is particularly vulnerable to the effects of aging, although other regions show reduced FA as well.
- Further, decreased integrity of anterior white matter appears to underlie reduced cognitive control in aging.
 - Our data complement a recent fiber tracking study that showed correlations between anterior callosal integrity and performance on the Stroop task.⁶
 - While age-related impairments in cognitive control processes are commonly attributed to reduced frontal lobe activity, the present results underscore the importance of also considering the underlying white matter.
- Reduced white matter integrity in frontal regions may result in a disconnection syndrome,^{1,9} leading to inefficient or inappropriate engagement of cognitive control processes.
- In contrast, in more posterior white matter regions, such as those underlying the superior temporal gyrus and posterior parietal lobe, FA was more closely related to episodic memory function.
 - This pattern supports the view that temporo-parietal communication is essential for episodic memory processes.¹²
 - Lesions of the fornix and temporal stem in monkeys produce deafferentation of the hippocampus that results in dense amnesia.¹³
 - The present findings suggest that the effects of advanced age on the integrity of temporal lobe connections may lead to a similar disconnection between MTL structures and association areas, albeit with far subtler effects on episodic memory.

FA IS REDUCED IN OA



- FA values were predominantly lower in OA compared to YA ($p < 0.001$).
- This reduction was greatest in anterior regions, such as the genu and anterior body of the corpus callosum, and in the white matter underlying the superior and medial frontal gyri and orbitofrontal cortex.
- Reduced FA was also noted in the white matter underlying the middle and superior temporal gyri, temporal stem, and temporoparietal junction.

FA CORRELATES WITH COGNITIVE PERFORMANCE IN OA



- We calculated correlations between each composite score and FA across the entire brain on a voxel-wise basis (threshold: $p < .01$).
- FA in regions of white matter underlying PFC correlated positively with performance on cognitive control tasks.
- FA in more posterior regions, underlying the temporal and parietal lobes, correlated with performance on episodic memory tasks.
- Correlations were found in similar regions in YA, but were of lesser magnitude in YA, likely due to a smaller sample of cognitive data for YA.
- Performance on semantic memory tasks did not correlate strongly with FA in either OA or YA.
- Several regions showing significant correlations were confirmed by manually delineating specific ROIs.

METHODS

Participants

Group	N	Age*	Edu*	MMSE*
YA	36	21.9 ± 2.6 (18–28)	15 ± 2.0 (12–18)	29.2 ± 1.0 (27–30)
OA	39	70.3 ± 7.2 (61–86)	17 ± 3.0 (14–23)	29.2 ± 1.2 (27–30)

* Scores are mean ± SD (range)

Image Acquisition

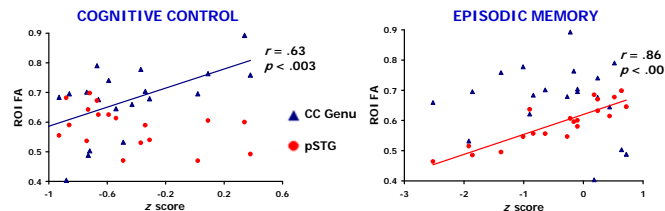
- High resolution DTI scan: 1.5 T Sonata system; TR=9.1, TE=68, slice thickness=2mm isotropic, 60 slices, FOV 256X256, 8 directions with b value=700 s/mm², and 1 low b image with b value=0

Image Analysis

- Data were processed using tools from the FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>) and FSL (<http://www.fmrib.ox.ac.uk/fsl>) packages.
- DTI data were motion and eddy current corrected, spatially normalized to MNI space, and smoothed with a 4mm kernel.
- Diffusion tensor and FA metrics were derived as previously described.^{10,11}
- Voxel-wise independent sample *t* tests ($p < 0.001$) compared FA for YA and OA across the entire brain.

ROI-BASED ANALYSES IN OA

- Cognitive Control z scores correlated with FA in anterior corpus callosum ($p < .003$), but not temporal stem ($p > .4$).
- Episodic Memory z scores correlated with FA underlying posterior superior temporal gyrus (pSTG; $p < 0.001$), but not anterior corpus callosum ($p > .3$).
- Correlations remained significant even after covarying for age-effects ($p < .01$).



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