# Age-Related Differences in White Matter Tract Microstructure Are Associated with Cognitive Performance from Childhood to Adulthood

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**Background:** Age-related differences in white matter tract microstructure have been well established across the life span. In the present cross-sectional study, we examined whether these differences are associated with neurocognitive performance from childhood to late adulthood.

**Methods:** Diffusion tensor imaging was performed in 296 healthy subjects aged 8 to 68 years (mean = 29.6, SD = 14.6). The corpus callosum, two projection tracts, and five association tracts were traced using probabilistic tractography. A neurocognitive test battery was used to assess speed of processing, attention, spatial working memory, verbal functioning, visual learning, and executive functioning. Linear mediation models were used to examine whether differences in white matter tract fractional anisotropy (FA) were associated with neurocognitive performance, independent of the effect of age.

**Results:** From childhood to early adulthood, higher FA of the cingulum bundle and inferior frontooccipital fasciculus (IFOF) was associated with higher executive functioning and global cognitive functioning, respectively, independent of the effect of age. When adjusting for speed of processing, FA of the IFOF was no longer associated with performance in the other cognitive domains with the exception of visual learning. From early adulthood to late adulthood, white matter tract FA was not associated with cognitive performance independent of the age effect.

**Conclusions:** The cingulum bundle may play a critical role in protracted maturation of executive functioning. The IFOF may play a key role in maturation of visual learning and may act as a central "hub" in global cognitive maturation by subserving maturation of processing speed.

**Key Words:** Aging, cognition, development, diffusion tensor imaging, executive functioning, white matter

Brain white matter (WM) tracts are critical to coordinated activity among brain regions. Diffusion tensor imaging (DTI) studies have demonstrated tract-specific differences in WM microstructure across the life span–for example, substantially lower fractional anisotropy (FA), a putative measure of neural fiber coherence, diameter, and myelination (1,2), in childhood than early adulthood and higher FA in early adulthood than late adulthood (3–5). Investigating the neurocognitive correlates of these age-related differences in WM microstructure may provide insights relevant to the onset and course of neurocognitive disorders in adolescence and adulthood.

To date, published DTI studies have not included both children and older adults to examine the relationships between WM tract microstructure and cognitive performance across the life span. In a previous study and meta-analysis, we identified robust age-related FA differences across adolescence, particularly in the superior longitudinal fasciculus (SLF), which were associated with verbal working memory and verbal fluency independent of the effect of age (6). Other DTI studies have observed further associations between WM microstructure and cognitive performance from childhood to adulthood, independent of the effect of age, in the SLF (7–10), splenium of the corpus callosum (CC) (7,11), genu of CC (7,12), and the inferior frontooccipital fasciculus (IFOF)/inferior longitudinal fasciculus (ILF) (8). Similarly, from adulthood to old age, DTI studies have found associations between WM microstructure and cognitive performance, independent of the effect of age, in the SLF (13), splenium of CC (14,15), genu of CC (15,16), IFOF (14,17), ILF (13,14,18), and cingulum (13). The relationships between WM tract microstructure and cognition observed across adulthood do not necessarily correspond to the relationships observed across adolescence.

Most previous work included relatively small samples sizes that did not evaluate children and older adults collectively. Thus, these samples were limited in their ability to detect trends that are comparable to the age-related WM differences reported in more general DTI studies across the life span (3–5). Another limitation has been the use of voxelwise analyses (8,12,13), regions of interest (11,16), or atlas-based masks (4,10), as opposed to a priori defined and anatomically valid, individually traced WM tracts. In addition, most studies included one or few neurocognitive tests and/or few WM tracts, limiting their ability to examine the specificity of WM tracts to different neurocognitive domains.

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In the current study, we used probabilistic tractography (19) to identify nine anatomically valid WM tracts in the brain and examined their relationship to age and neurocognitive performance across multiple domains from childhood to late adulthood. Importantly, this allowed us to investigate the neurocognitive correlates of the major WM tracts in relation to their unique aging patterns. We hypothesized that 1) WM tract FA and neurocognitive performance would show pronounced differences between childhood and early adulthood and thereafter moderate differences between early adulthood and late adulthood and 2) differences in WM tract FA would be associated with neurocognitive performance from childhood to late adulthood, independent of the effect of age. As a secondary aim, we compared different modeling approaches of age-related WM differences and examined the effect of using different models on the relationships between age, WM tract FA, and cognition. To our knowledge, this is the first DTI study to report on these relationships across multiple cognitive domains from childhood to late adulthood.

## Methods and Materials

### Participants

Two-hundred and ninety-six healthy individuals (52% male) between the ages of 8.1 and 68.1 years (mean 29.6 ± 14.6; median 25.9) were recruited through local advertisements and by word of mouth. Written informed consent was obtained from participants or from a parent or guardian if the participant was a minor; all minors provided assent. Participants had no history of a DSM-IV Axis I major mood or psychotic disorder as assessed by structured diagnostic interview (20,21). Other exclusion criteria included 1) intellectual or learning disability, 2) medications with known adverse cognitive effects, 3) magnetic resonance imaging contraindications, 4) pregnancy, and 5) significant medical illness that could affect brain structure. Mean IQ as estimated from the Wide Range Achievement Test 3 (WRAT-3)-reading subtest was 103 ± 11.5 (data missing for 2 subjects) (22). Handedness was determined using the Edinburgh Handedness Inventory (23); median laterality quotient was .74 (range −1 to 1). Please see Table 1 for demographic characteristics. This study was approved by the Institutional Review Board of the North Shore–Long Island Jewish Health System.

### DTI Acquisition and Preprocessing

All subjects received a DTI exam at the North Shore University Medical Center, Manhasset, New York, on a GE Signa HDx 3.0 T system (General Electric, Milwaukee, Wisconsin). The sequence included volumes with diffusion gradients applied along 31 nonparallel directions (b = 1000 s/mm$^2$) and five volumes without diffusion weighting (repetition time = 14 seconds, echo time = minimum, matrix = 128 × 128, field of view = 240 mm). Each volume consisted of 51 contiguous 2.5-mm axial slices acquired parallel to the anterior-posterior commissural line using a ramp sampled, double spin-echo, single shot echo-planar imaging method.

All scans were reviewed by a radiologist, and all images were visually inspected to ensure that no gross abnormalities were evident. Image processing was conducted using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; Oxford, United Kingdom; http://fsl.fmrib.ox.ac.uk/fsl). Eddy-current induced distortions and head-motion displacements were corrected through affine registration of the 31 diffusion volumes to the first b0 volume using FSL's Linear Registration Tool (25). The b-vector table (i.e., gradient directions) for each participant was then adjusted according to the rotation parameters of this linear correction. Nonbrain tissue was removed using FSL's Brain Extraction Tool. FA, radial diffusivity (RD), and axial diffusivity (AD) (1,2) were then calculated at each voxel of the brain by fitting a diffusion tensor model to the raw diffusion data using weighted least squares in FSL's Diffusion Toolbox. FA was chosen as the primary measure for analysis because it has been the most widely used measure in relevant studies and thereby provides optimal between-study comparability.

### Tractography

The probable trajectories of two interhemispheric tracts (splenium and genu of CC), two projection tracts (corticospinal tract [CST] and anterior thalamic radiation [ATR]), and five bilateral association tracts (IFOF, ILF, SLF, cingulum, and uncinate fasciculus) were traced as follows. Within-voxel probability density functions of the principal diffusion direction were estimated using Markov Chain Monte Carlo sampling in FSL's BEDPOSTX tool (19). A spatial probability density function was then estimated across voxels based on these local probability density functions using FSL's PROBTRACKX tool (19), in which 5000 samples were taken for each input voxel with a .2 curvature threshold, .5-mm step length, and 2000 steps per sample. The procedure was conducted in 304 study eligible individuals but failed in 8 of those individuals, yielding a total sample size of 296. For each tract, seed masks, waypoints, termination and exclusion masks were defined on the MNI152 T1 1-mm template (see Methods in Supplement 1). Masks were normalized to each subjects' diffusion space using FSL's Linear Registration Tool (25), applying the affine parameters obtained by coregistering the first b0 volume to the MNI152 T1 1-mm template. The resulting tracts were thresholded at a normalized probability value (see Methods in Supplement 1 and Figure 1) and visually inspected to confirm successful tracing in each individual. Mean FA, RD, and AD of each tract were then extracted for analysis.

### Neurocognitive Assessments

A subgroup of participants ($n$ = 219–256) was administered the following battery of neurocognitive tests: Brief Assessment of Cognition in Schizophrenia, Trail Making Test, Continuous Performance Test–identical pairs, Wechsler Memory Scale (3rd ed.)-spatial span, Controlled Oral Word Association Test, Animal Naming Test, UMd Letter-Number Span Task, Hopkins Verbal Learning Test (revised), Brief Visuospatial Memory Test (revised), Neuropsychological Assessment Battery-mazes, and Wisconsin Card Sorting Test (26,27). For statistical analysis, we composed the following neurocognitive domains based on conceptual overlap between the tests and domain reliability as assessed with Cronbach's alpha: speed of processing, attention, spatial working memory, verbal functioning, visual learning, and executive functioning (see Methods in Supplement 1). Raw scores were converted to $Z$ scores such that higher values were indicative of better performance across all tests. Neurocognitive data were only included when administered within 6 months of magnetic resonance imaging scanning (thus excluding 12 subjects).

### Statistical Analysis

Outliers in tract FA values and neurocognitive $Z$ scores, defined as exceeding 3 standard deviations from the mean, were substituted by the next lowest or highest value within 3 SD. This

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