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

Supplementary Information

Neurocognitive Domains

Speed of Processing: Brief Assessment of Cognition in Schizophrenia - symbol coding (*n* = 228), Trail Making Test - part A (*n* = 255); Cronbach's alpha = 0.68.

Attention: Continuous Performance Test - identical pairs, average of d' 2, 3 and 4 (*n* = 220).

Spatial Working Memory: Wechsler Memory Scale 3rd ed. - spatial span (*n* = 228).

Verbal Functioning: Controlled Oral Word Association Test – total words (*n* = 255), Animal Naming Test (*n* = 256), UMd Letter-Number Span Task (*n* = 228), Hopkins Verbal Learning Test rev. – immediate recall, total correct words (*n* = 228); Cronbach's alpha = 0.69.

Visual Learning: Brief Visuospatial Memory Test rev. - total recall (*n* = 227).

Executive Functioning: Neuropsychological Assessment Battery - mazes subtest (*n* = 228), Wisconsin Card Sorting Test - categories completed & percent errors (*n* = 222 & *n* = 219), Trail Making Test - part B (*n* = 255); Cronbach's alpha = 0.75.

Placement of Seed Masks, Way-Points, Termination and Exclusion Masks for Probabilistic Tractography

Genu of Corpus Callosum: A seed mask of the midsagittal section of the genu was derived from the ICBM-DTI-81 white matter (WM) atlas, provided in FSL (1). An exclusion mask was drawn posterior to the seed mask, excluding fibers tracing posterior to the seed. The resulting tracts of each subject were thresholded at a normalized probability value of 0.005.

Splenium of Corpus Callosum: A seed mask of the midsagittal section of the splenium was derived from the ICBM-DTI-81 WM atlas, provided in FSL (1). An exclusion mask was placed anterior to the seed mask, excluding fibers tracing anterior to the seed. The resulting tracts of each subject were thresholded at a normalized probability value of 0.005.

Corticospinal Tract: A seed mask of precentral gyrus WM was derived from the HarvardOxford subcortical atlas, provided in FSL (2), and a second seed mask was manually drawn in the pons. The resulting tracts of each subject were thresholded at a normalized probability value of 0.01.

Anterior Thalamic Radiation: A seed mask of the thalamus was derived from the HarvardOxford subcortical atlas, provided in FSL (2), and then manually edited according to the MNI152 T1 brain to exclude the medial and lateral geniculate nuclei. A way-point of prefrontal WM was derived from the HarvardOxford atlas, provided in FSL (2), which was also used as a termination mask (i.e. fibers were terminated when they reached prefrontal WM). A second way-point was manually drawn in the anterior limb of the internal capsule (ALIC), on 3 coronal slices in the anterior section of the ALIC. An exclusion mask of occipital, temporal, parietal, and sensory-motor (including supplementary motor) gray matter (GM) was derived from the HarvardOxford cortical atlas, provided in FSL (2). This exclusion mask was manually expanded to exclude fibers tracing into the brainstem or the contra-lateral hemisphere. The resulting tracts of each subject were thresholded at a normalized probability value of 0.005.

Inferior Longitudinal Fasciculus (ILF): Occipital and temporal seed masks were derived from the HarvardOxford atlas, provided in FSL (2), based on the trajectory of the ILF in the Johns Hopkins University (JHU) tractography atlas, provided in FSL (3). The occipital seed mask comprised the occipital fusiform WM, occipital pole WM, temporal occipital fusiform WM, cuneus WM, inferior lateral occipital WM, lingual WM, and intracalcarine WM. The temporal seed mask comprised the temporal pole WM, anterior temporal fusiform WM, and anterior middle temporal WM. An exclusion mask was drawn anterior to the temporal pole. The resulting tracts of each subject were thresholded at a normalized probability value of 0.01.

Inferior Fronto-Occipital Fasciculus (IFOF): Frontal and occipital seed masks were derived from the HarvardOxford atlas, provided in FSL (2), based on the trajectory of the IFOF in the JHU tractography atlas, provided in FSL (3). The frontal seed comprised the frontal pole WM, inferior frontal gyrus (pars triangularis) WM, medial frontal WM, and orbito-frontal WM; the superior section of the frontal pole was removed as it is not included in the main trajectory of the IFOF (3). The occipital seed mask comprised the inferior division of the lateral occipital WM, supracalcarine WM, fusiform occipital WM, and lingual WM. A way-point was manually drawn in the anterior section of the temporal stem, including the external capsule and WM medial to the insular cortex, according to the trajectory of the IFOF in the JHU tractography atlas, provided in FSL (3). An exclusion mask was drawn in each contra-lateral hemisphere. The GM of the seed regions was also defined as a termination mask. The resulting tracts of each subject were thresholded at a normalized probability value of 0.01.

Superior Longitudinal Fasciculus (SLF): A seed mask was manually drawn in the frontal part of the SLF (just anterior to the precentral gyrus) based on the trajectory of the SLF in the JHU tractography atlas, provided in FSL (3). A way-point was manually drawn in the frontal

section of the SLF just posterior to the seed mask, and a second way-point comprising WM of the middle temporal gyrus (MTG) was derived from the HarvardOxford atlas, provided in FSL (2). A termination mask was drawn anterior to the seed mask and inferior to the MTG WM, and combined with MTG GM as derived from the HarvardOxford atlas, provided in FSL (2). The resulting tracts of each subject were thresholded at a normalized probability value of 0.01.

Cingulum: A seed mask of the anterior cingulum was manually drawn on 3 coronal slices just anterior to the genu of corpus callosum. A second seed mask was manually drawn on 3 coronal slices just posterior to the splenium of the corpus callosum. An exclusion mask was drawn anterior to the cingulate cortex, inferior to the level of the hippocampus and in each contra-lateral hemisphere. The resulting tracts of each subject were thresholded at a normalized probability value of 0.05.

Uncinate Fasciculus (UF): Frontal and temporal seed masks were derived from the HarvardOxford atlas, provided in FSL (2), based on the trajectory of the UF in the JHU tractography atlas, provided in FSL (3). The frontal seed mask comprised the frontal pole WM, frontal medial WM, subcallosal WM, and orbito-frontal WM; only WM below the level of the anterior cingulate cortex was included. The temporal seed mask comprised the temporal pole WM. An exclusion mask was drawn posterior to the planum polare. The resulting tracts of each subject were thresholded at a normalized probability value of 0.05.

Table S1. Age at Peak Performance for 6 Cognitive Domains as Assessed with LOESS, Poisson and Quadratic Models.

	LOESS	**Poisson**	**Quadratic**
	Peak Age (95% CI)	**Peak Age** (95% CI)	**Peak Age** (95% CI)
Speed of Processing	24.04 (21.3 - 26.8)	28.34 (0.9 - 55.8)	32.97 (7.0 - 58.9)
Attention	27.71 (8.5 - 46.9)	35.78 (6.8 - 64.8)	39.44 (9.5 - 69.4)
Spatial WM	20.37 (10.5 - 30.3)	23.91 (0.0 - 48.8)	26.40 (0.0 - 54.0)
Verbal Functioning	49.74 (17.1 - 82.4)	35.79 (5.2 - 66.4)	39.44 (11.9 - 66.9)
Visual Learning	8.13 (0.9 - 15.4)	14.55 (0.0 - 43.8)	8.13 (0.0 - 36.6)
Executive Functioning	20.37 (10.5 - 30.3)	23.37 (0.0 - 50.7)	26.02 (1.7 - 50.4)

CI, confidence interval; LOESS, local regression; WM, working memory.

Table S2. Mediation Models of Associations Between Age, Radial and Axial Diffusivity, And Cognitive Performance from Childhood into Early Adulthood.[1]

	Radial Diffusivity			**Axial Diffusivity**			
	β	*t*-value	*p*-value	β	*t*-value	*p*-value	*n*
Cingulum							
Global cognitive functioning:[2]							109
Age 1[a]	**0.300**	**3.25**	**0.002**	0.300	3.25	0.002	
Age 2[b]	**0.177**	**1.84**	**0.068**	0.291	3.16	0.002	
RD/AD[c]	**-0.312**	**-3.25**	**0.002**	-0.134	-1.46	0.148	
Executive functioning:							115
Age 1[a]	**0.229**	**2.50**	**0.014**	0.229	2.50	0.014	
Age 2[b]	**0.129**	**1.33**	**0.185**	0.228	2.48	0.015	
RD/AD[c]	**-0.259**	**-2.68**	**0.008**	-0.023	-0.25	0.807	
IFOF							
Global cognitive functioning:[2]							81
Age 1[a]	**0.500**	**5.13**	**<0.001**	0.500	5.13	<0.001	
Age 2[b]	**0.411**	**4.08**	**<0.001**	0.516	5.12	<0.001	

	Radial Diffusivity			Axial Diffusivity			
	β	*t*-value	*p*-value	β	*t*-value	*p*-value	*n*
RD/AD[c]	**-0.253**	**-2.51**	**0.014**	0.068	0.67	0.503	
Speed of processing:							93
Age 1[a]	**0.658**	**8.34**	**<0.001**	0.658	8.34	<0.001	
Age 2[b]	**0.597**	**7.20**	**<0.001**	0.663	8.26	<0.001	
RD/AD[c]	**-0.174**	**-2.10**	**0.039**	0.028	0.35	0.726	
Attention:							88
Age 1[a]	**0.607**	**7.08**	**<0.001**	0.607	7.08	<0.001	
Age 2[b]	**0.534**	**5.91**	**<0.001**	0.602	6.86	<0.001	
RD/AD[c]	**-0.198**	**-2.19**	**0.031**	-0.028	-0.32	0.752	
Spatial working memory:							93
Age 1[a]	0.262	2.59	0.011	0.262	2.59	0.011	
Age 2[b]	0.216	2.00	0.048	0.276	2.70	0.008	
RD/AD[c]	-0.128	-1.18	0.240	0.096	0.94	0.352	
Verbal functioning:							92
Age 1[a]	0.427	4.481	<0.001	0.427	4.48	<0.001	
Age 2[b]	0.365	3.59	0.001	0.434	4.47	<0.001	
RD/AD[c]	-0.169	-1.66	0.100	0.041	0.42	0.674	
Visual learning:							92
Age 1[a]	**0.221**	**2.15**	**0.034**	0.221	2.15	0.034	
Age 2[b]	**0.125**	**1.17**	**0.244**	0.222	2.12	0.037	
RD/AD[c]	**-0.270**	**-2.52**	**0.013**	0.005	0.05	0.959	
Executive functioning:							87
Age 1[a]	0.396	3.97	<0.001	0.396	3.97	<0.001	
Age 2[b]	0.355	3.40	0.001	0.428	4.29	<0.001	
RD/AD[c]	-0.133	-1.28	0.205	0.184	1.85	0.069	

AD, axial diffusivity; IFOF, inferior fronto-occipital fasciculus; RD, radial diffusivity.

[1] Mediation analyses were performed using hierarchical linear regression (age first entered as independent variable and test performance as dependent variable, and then white matter tract RD or AD added as second independent variable) before and after the age peak of each tract, which was derived from a local regression model. Mediation analyses for radial and axial diffusivity were only performed for the white matter tracts and cognitive domains that were significant in the mediation analyses of fractional anisotropy.

[2] The global cognitive score comprised the average z-score of all individual tests. Higher scores indicated better performance across all cognitive domains.

[a] Not adjusted for RD/AD.

[b] Adjusted for RD/AD.

[c] Adjusted for age.

Table S3A. Mediation Models of Associations Between Age, White Matter Tract FA and Cognitive Performance from Childhood into Early Adulthood.[1]

	Executive Functioning			Speed of Processing			Attention			Spatial Working Memory			Verbal Functioning			Visual Learning		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
Cingulum		*n* = 115			*n* = 121			*n* = 116			*n* = 121			*n* = 120			*n* = 120	
Age 1[a]	**0.229**	**2.50**	**0.01**	0.464	5.71	0.00	0.601	8.02	0.00	0.056	0.61	0.54	0.349	4.04	0.00	-0.14	-1.52	0.13
Age 2[b]	**0.157**	**1.65**	**0.10**	0.430	4.94	0.00	0.555	6.96	0.00	0.018	0.18	0.85	0.308	3.34	0.00	-0.23	-2.42	0.02
FA[c]	**0.217**	**2.28**	**0.03**	0.092	1.062	0.29	0.128	1.60	0.11	0.105	1.07	0.29	0.114	1.24	0.22	0.256	2.68	0.01
IFOF		*n* = 81			*n* = 93			*n* = 88			*n* = 93			*n* = 92			*n* = 92	
Age 1[a]	**0.500**	**5.13**	**0.00**	**0.658**	**8.34**	**0.00**	**0.607**	**7.08**	**0.00**	**0.262**	**2.59**	**0.01**	**0.427**	**4.48**	**0.00**	**0.221**	**2.15**	**0.03**
Age 2[b]	**0.420**	**4.36**	**0.00**	**0.599**	**7.35**	**0.00**	**0.547**	**6.19**	**0.00**	**0.194**	**1.85**	**0.07**	**0.356**	**3.60**	**0.00**	**0.129**	**1.23**	**0.22**
FA[c]	**0.293**	**3.04**	**0.00**	**0.186**	**2.29**	**0.02**	**0.190**	**2.15**	**0.04**	**0.209**	**1.99**	**<0.05**	**0.216**	**2.18**	**0.03**	**0.287**	**2.73**	**0.01**
SLF		*n* = 102			*n* = 108			*n* = 103			*n* = 108			*n* = 107			*n* = 107	
Age 1[a]	0.297	3.11	0.00	0.538	6.58	0.00	0.598	7.50	0.00	0.176	1.84	0.07	0.444	5.07	0.00	0.059	0.61	0.55
Age 2[b]	0.256	2.64	0.01	0.494	5.89	0.00	0.579	7.00	0.00	0.162	1.62	0.11	0.420	4.61	0.00	0.000	-0.00	0.99
FA[c]	0.180	1.86	0.07	0.163	1.94	0.06	0.071	0.86	0.39	0.052	0.52	0.60	0.085	0.93	0.35	0.213	2.13	0.04
ILF		*n* = 95			*n* = 101			*n* = 96			*n* = 101			*n* = 100			*n* = 100	
Age 1[a]	0.316	3.22	0.00	**0.610**	**7.65**	**0.00**	0.637	8.01	0.00	0.182	1.84	0.07	0.467	5.22	0.00	0.147	1.47	0.15
Age 2[b]	0.262	2.53	0.01	**0.533**	**6.38**	**0.00**	0.600	7.09	0.00	0.124	1.18	0.24	0.428	4.46	0.00	0.066	0.62	0.54
FA[c]	0.158	1.51	0.13	**0.208**	**2.49**	**0.02**	0.106	1.25	0.21	0.156	1.47	0.14	0.106	1.11	0.27	0.217	2.05	0.04
CST		*n* = 86			*n* = 93			*n* = 88			*n* = 93			*n* = 92			*n* = 92	
Age 1[a]	0.396	3.97	0.00	0.658	8.34	0.00	0.607	7.08	0.00	0.262	2.59	0.01	0.427	4.48	0.00	0.221	2.15	0.03
Age 2[b]	0.376	3.65	0.00	0.652	7.90	0.00	0.583	6.50	0.00	0.210	2.02	0.05	0.378	3.87	0.00	0.186	1.74	0.09
FA[c]	0.078	0.76	0.45	0.022	0.27	0.79	0.079	0.88	0.38	0.186	1.79	0.08	0.182	1.86	0.07	0.128	1.20	0.23

	Executive Functioning			Speed of Processing			Attention			Spatial Working Memory			Verbal Functioning			Visual Learning		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
CC genu		*n* = 82			*n* = 88			*n* = 83			*n* = 88			*n* = 87			*n* = 87	
Age 1[a]	0.490	5.02	0.00	0.694	8.93	0.00	**0.711**	**9.10**	**0.00**	0.280	2.71	0.01	0.520	5.61	0.00	**0.293**	**2.83**	**0.01**
Age 2[b]	0.462	4.71	0.00	0.662	8.41	0.00	**0.665**	**8.53**	**0.00**	0.260	2.45	0.02	0.500	5.24	0.00	**0.226**	**2.22**	**0.29**
FA[c]	0.161	1.64	0.11	0.142	1.80	0.08	**0.195**	**2.50**	**0.02**	0.091	0.85	0.40	0.086	0.90	0.37	**0.300**	**2.94**	**0.00**
CC splenium		*n* = 75			*n* = 81			*n* = 76			*n* = 81			*n* = 80			*n* = 80	
Age 1[a]	0.540	5.48	0.00	0.685	8.36	0.00	0.702	8.47	0.00	0.296	2.76	0.01	0.539	5.66	0.00	0.386	3.69	0.00
Age 2[b]	0.507	4.96	0.00	0.674	7.80	0.00	0.662	7.70	0.00	0.286	2.52	0.01	0.550	5.45	0.00	0.363	3.30	0.00
FA[c]	0.121	1.18	0.24	0.035	0.41	0.68	0.131	1.53	0.13	0.035	0.31	0.76	-0.03	-0.34	0.74	0.076	0.69	0.49

CC, corpus callosum; CST, corticospinal tract; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus.

[1] Mediation analyses were performed using hierarchical linear regression (age first entered as independent variable and test performance as dependent variable, and then white matter tract FA added as second independent variable), before and after the age peak of each tract, which was derived from a local regression model.

[a] Not adjusted for FA.

[b] Adjusted for FA.

[c] Adjusted for age.

Table S3B. Mediation Models of Associations Between Age, White Matter Tract FA and Cognitive Performance from Early Adulthood into Late Adulthood.[1]

	Executive Functioning			Speed of Processing			Attention			Spatial Working Memory			Verbal Functioning			Visual Learning		
	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*	β	*t*	*p*
IFOF		*n* = 121			*n* = 122			*n* = 120			*n* = 123			*n* = 123			*n* = 123	
Age 1[a]	-0.197	-2.19	0.03	-0.232	-2.62	0.01	-0.152	-1.66	0.10	-0.163	-1.82	0.07	-0.048	-0.53	0.60	-0.186	-2.08	0.04
Age 2[b]	-0.179	-1.89	0.06	-0.246	-2.63	0.01	-0.173	-1.80	0.07	-0.165	-1.74	0.09	-0.058	-0.60	0.55	-0.197	-2.09	0.04
FA[c]	0.057	0.60	0.55	-0.045	-0.48	0.63	-0.068	-0.71	0.47	-0.005	-0.06	0.96	-0.029	-0.31	0.76	-0.035	-0.37	-0.71
ILF		*n* = 113			*n* = 114			*n* = 112			*n* = 115			*n* = 115			*n* = 115	
Age 1[a]	-0.199	-2.14	0.03	-0.206	-2.22	0.03	-0.134	-1.41	0.16	-0.179	-1.94	0.06	0.005	0.05	0.96	-0.137	-1.47	0.15
Age 2[b]	-0.185	-1.96	0.05	-0.195	-2.08	0.04	-0.118	-1.23	0.22	-0.142	-1.55	0.13	0.026	0.28	0.78	-0.136	-1.43	0.16
FA[c]	0.087	0.92	0.34	0.061	0.65	0.52	-0.090	0.94	0.35	0.225	2.45	0.02	0.128	1.35	0.18	0.007	0.08	0.94
CC genu		*n* = 126			*n* = 127			*n* = 125			*n* = 128			*n* = 128			*n* = 128	
Age 1[a]	-0.181	-2.05	0.04	-0.242	-2.79	0.01	-0.085	-0.95	0.35	-0.172	-1.97	0.05	-0.007	-0.08	0.94	-0.206	-2.36	0.02
Age 2[b]	-0.186	-1.99	0.05	-0.242	-2.64	0.01	-0.113	-1.20	0.24	-0.158	-1.71	0.09	-0.030	-0.32	0.75	-0.208	-2.25	0.03
FA[c]	-0.015	-0.16	0.88	-0.001	-0.01	0.99	-0.090	-0.95	0.34	0.044	0.48	0.63	-0.074	-0.79	0.43	-0.005	-0.06	0.96
ATR		*n* = 218			*n* = 227			*n* = 220			*n* = 228			*n* = 227			*n* = 227	
Age 1[a]	-0.162	-2.41	0.02	-0.023	-0.34	0.73	0.292	4.51	0.00	-0.135	-2.04	0.04	0.163	2.48	0.01	-0.422	-6.97	0.00
Age 2[b]	-0.154	-2.24	0.03	-0.025	-0.36	0.72	0.292	4.43	0.00	-0.131	-1.95	0.05	0.158	2.36	0.02	-0.412	-6.71	0.00
FA[c]	0.043	0.63	0.53	-0.010	-0.15	0.88	0.001	0.01	0.99	0.022	0.33	0.75	-0.028	-0.42	0.68	0.052	0.85	0.40

ATR, anterior thalamic radiation; CC, corpus callosum; FA, fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus.

[1] Mediation analyses were performed using hierarchical linear regression (age first entered as independent variable and test performance as dependent variable, and then white matter tract FA added as second independent variable), before and after the age peak of each tract, which was derived from a local regression model.

[a] Not adjusted for FA.

[b] Adjusted for FA.

[c] Adjusted for age.

Table S4. Correlations Between IQ and 6 Cognitive Domains.[1]

	Processing Speed	Attention	Spatial WM	Verbal Functioning	Visual Learning	Executive Functioning
IQ[2]	0.068	0.050	0.198*	0.318*	0.369*	0.244*

WM, working memory.
[1] Linear regressions; higher scores indicated better test performance across all domains.
[2] Wide Range Achievement Test 3.
* $p < 0.01$.

Supplemental References

1. Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K, *et al.* (2008): Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 40(2): 570-82.
2. Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, *et al.* (2006): An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31(3): 968-80.
3. Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, *et al.* (2008): Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. *Neuroimage* 39(1): 336-47.