Data supplement for Aggarwal et al., Sex-Specific Distributed White Matter Microarchitectural Alterations in Preadolescent Youths With Anxiety Disorders: A Mega-Analytic Study. Am J Psychiatry (doi: 10.1176/appi.ajp.20221048)

Supplemental Methods

Childhood Opportunity Index: The Childhood Opportunity Index (COI) is a census-derived composite metric of 29 indicators of neighborhood-level resources and conditions spanning three domains: Education, Health and Environment, and Social and Economic (<u>https://www.diversitydatakids.org/child-opportunity-index</u>). It captures facets of children's environment that are relevant to their future health and economic outcomes. COI data were generated by first aggregating home address information for our sample; valid information was available for 230 participants. Individual address information was then used to obtain a geographic identifier (i.e., GeoID) for each of these participants using the following website: https://geocoding.geo.census.gov/geocoder/geographies/addressbatch?form. Finally, GeoIDs were matched to the COI 2.0 Index Data sheet available here: https://data.diversitydatakids.org/dataset/coi20-child-opportunity-index-2-0-

database/resource/080cfe52-90aa-4925-beaa-90efb04ab7fb. This data sheet provides subscale and composite COI metric data for GeoIDs, or census tracts, across the country, including metro-, state-, and national-level z-scored. Because our data includes participants from two different states, we used the nationally z-scored composite COI score in our analyses. It is important to note the COI score is not an individual-difference measure; it is a census tract level measure.

DTI acquisition: Images were collected on a 3.0 Tesla GE MR750 scanner (GE Healthcare; Waukesha, WI). In sample 1, UW participants were scanned using an 8-channel head coil. NIH participants from sample 1, all of sample 2, and all of sample 3 were scanned using a 32-channel head coil. Diffusion-weighted MRI scans were obtained using a two-dimensional echo planar imaging diffusion-weighted spin-echo sequence (TR=6500ms, TE=59.6ms, flip angle=90 degrees, matrix=128x128 interpolated to 256x256, FOV=256mm,

2.9mm contiguous slices, echo-planar echo spacing=568µs, b-value of 1000s/mm², 48 optimal non-collinear directions and 8 non-diffusion-weighted images). Structural and functional MRI scans were collected during the same scan sessions but are not reported here. Before each scan, children completed mock MRI sessions, which have been shown to reduce movement in pediatric neuroimaging studies (1).

DTI processing, harmonization, and analysis: Methods were comparable to those previously described in Tromp et al., 2019 and Aggarwal et al., 2022 (2,3). Diffusion-weighted volumes from each individual were transformed into a 3-dimensional diffusion tensor for each voxel in the brain using the following procedures. FSL (4) tools for rigid registration were used to correct distortions resulting from head motion and eddy currents (5). The corresponding gradient direction matrix was corrected for the applied rotations after rigid registration. The brain was skull stripped using the FSL's brain extraction tool (4). Robust estimation of tensors by outlier rejection (RESTORE, as implemented in Camino software) (6) was used to minimize influence

of noise on tensor calculation, a step particularly important in image samples of young/clinical populations that are more sensitive to reduced image quality. RESTORE uses an average noise estimation to determine which diffusion measurements are outliers and excludes those from tensor computation; it has been shown to increase the reliability of tensor estimation in clinical populations (7). Resulting DTI scans contained 3 major vectors for each voxel in the brain that together model water diffusion as shaped by local tissue microstructure.

In order to compare diffusion measures across participants, scans were normalized across all participants to create a study-specific template that was then warped to MNI-152 standard space via rigid, affine, and diffeomorphic (i.e., nonlinear) registrations. Individual tensor maps were generated in MNI space. These steps were performed using a high-dimensional registration method that incorporates tensor orientation (DTI-TK) (8), a technique that outperforms intensity-based normalization of diffusion images and results in improved white matter shape and architecture representation (9,10). The population template was constructed via multiple registration iterations and then aligned to the 1mm isotropic MNI-152 template; this warp was then applied to all images. In MNI152 space, scalar maps for fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (XD) were calculated for each image. Finally, images were smoothed with a 4-mm full width at half maximum (FWHM) kernel. We note that field maps were not available for the full sample, so field map-based EPI distortion correction was not performed in our analyses. However, some studies have indicated that, in the absence of available field maps, non-linear registration of diffusion images to a structural image can be used as a substitute to help account for EPI-induced distortions (11), as detailed above as part of image normalization/registration process.

The population template in standard MNI space was used for deterministic tractography to delineate tracts of interest. Whole-brain fiber tracking was performed using Camino software, which implements a fourth-order Runge-Kutta method combined with a tensor deflection (TEND) algorithm for optimal estimation of the fiber tracking directions (12,13). Fiber tracking was terminated in voxels where FA was below 0.1 or where the angle between consecutive streamline steps was greater than 90 degrees. Seven fiber pathways were iteratively delineated in template space using anatomically defined waypoints (14–17) in TrackVis, a 3D tract visualization program (18). The 7 WM tracts of interest were selected based on substantial literature implicating alterations in these tracts in anxiety disorders and other internalizing disorders, in both adult and pediatric samples. In addition to the literature highlighted in relation to the UF, there is work suggesting other cortico-limbic association pathways may be affected in those with pathological anxiety and/or emotional dysregulation, including the cingulum bundle (CING) (19,20), the superior longitudinal fasciculus (SLF) (21,22), the fornix (FX) (23), and the inferior fronto-occipital fasciculus (IFO) (22,24). Additionally, several publications have reported alterations in the projection fibers of the internal capsule (IC) (22,25) and commissural fibers of the corpus callosum (CC) (19,26) in patients with anxious and internalizing pathology. In turn, these 7 tracts were included in our analysis.

In order to quantify the microstructure of entire white matter structures, weighted means were calculated per tract, per participant. The weighted mean of a tract was calculated by first creating a scalar image of the number of fibers in the tract passing through each voxel as a proportion of the total number of fibers in that tract. This weighting factor was then multiplied by the value of the diffusion measure in that voxel and averaged across the whole tract to produce the mean weighted scalar value for each tract (27). This approach enables differential weighting of voxels that have higher fiber counts, observed frequently in areas more central to the white matter tract of interest. Given no a priori hypotheses regarding laterality, right and left

hemisphere metrics were averaged to generate bilateral tract values. Importantly, tract-based analyses allow for detection of pervasive but subtle differences that are distributed across the length of a tract which may be missed using conventional voxel-based methods. In turn, this method is well-suited to identify tract-based associations in which alterations at any point in a tract might alter the efficiency of communication across a WM pathway.

To optimize the comparison of multi-site and multi-sample data and account for coil differences and disparate time intervals in data collection, we performed data harmonization on both the tract- and voxel-level data. The neuroCombat (28,29) and neuroHarmonize (30,31) programs were used to perform harmonization on the tract- based and voxel-based data, respectively. For both tract- and voxel-level harmonization, the dataset was separated in five data "batches" based on Site (UW vs. NIH), Sample (1 vs. 2. Vs. 3), and Coil (8- vs. 32- channel head coil). This resulted in five possible "batch" designations: Batch A (UW, Sample 1, 32-channel head coil); Batch B (NIH, Sample 1, 32-channel head coil); Batch C (UW, Sample 2, 32-channel head coil); Batch D (UW, Sample 3, 8-channel head coil); and Batch E (NIH, Sample 3, 32-channel head coil). For tract- level data harmonization, the neuroCombat algorithm was provided DTI metric data for each of the seven tracts of interest and the batch designation for each subject's data, as well as the model terms so as to allow the algorithm to preserve the variance of interest. Tract-level data harmonization was performed separately for FA, MD, RD, and XD. For voxel-level data harmonization, the neuroHarmonize algorithm was provided voxelwise diffusion parameter maps and the batch designation for each subject's data, in addition to the model predictors. Voxelwise data harmonization was also performed separately for FA, MD, RD, and XD. For both tract- and voxel-level data harmonization, batch information was provided, and the following analytic model was specified: DTI metric ~ Group*Sex + Group + Sex + Age. In all subsequent analyses at the tract- and voxel-level using the harmonized data, the above model was implemented, given that harmonization accounted for the effects of Site, Sample, and Coil.

Statistical analysis for voxelwise DTI analyses: Because FA changes in grey matter (GM) are difficult to interpret, voxelwise analyses were restricted to a liberal WM mask. The WM mask was generated by applying the FAST (FMRIB's Automated Segmentation Tool) algorithm, an MR image segmentation tool in FSL, to the MNI T1 template image to produce WM, GM, and cerebrospinal fluid (CSF) segmentations. The resulting WM segmentation was binarized and used as the WM mask for *randomise* analyses (see Figure S1).

Steroid hormone collection and analyses: Saliva samples were collected on the day of MRI scanning. Testosterone and estradiol levels were measured in separate enzyme immunoassays using kits purchased from Salimetrics (State College, PA). Prior to each assay, saliva was thawed and spun at 1,500 x g for 15 min at room temperature to remove particulate. The supernatant was assayed in duplicate following manufacturer's instructions. Samples that had assay results with CV% > 20 were repeated. The inter-assay CVs were determined using the high and low controls provided by the kits. For testosterone, the high control had a concentration of 186.9 ± 2.8 pg/ml and a CV of 4.2%, and the low control had a concentration of 28.8 ± 0.9 pg/ml and a CV of 8.5%. For estradiol, the high control had a concentration of 22.5 ± 0.4 pg/ml and a CV of 5.4%, and the low control had a concentration of 6.8 ± 0.1 pg/ml and a CV of 3.2%. For the subset of participants with usable sex hormone level data, testosterone and estradiol levels were first square-root transformed, and then linear regression models assessed three-way interactions between group (anxiety disorder vs. healthy volunteer), sex (male vs. female), and sex hormone (testosterone or estradiol) to investigate potential moderating effects of sex hormones on sex-specific anxiety-WM associations.

Supplemental Results

Voxelwise analyses of MD, RD, and XD: RD was increased in children with anxiety disorders relative to healthy volunteers, indicated by a main effect of group in clusters that overlapped with portions of the UF, EC, SS, IFOF, IFL, IC, STRIA, FX, CR, CBP, CP, CC, CST, CING, and SLF (TFCE P<0.05, FWE-corrected) (see Table S3 and Figure S3A). No significant group-by-sex interactions were found for RD. Separate RD analyses of the males and the females revealed no anxiety disorder-related effects in females, whereas males had significant RD reductions in regions consistent with those detected in the main effect of group, in addition to several other WM clusters throughout the brain (TFCE P<0.05, FWE-corrected) (see Table S3 and Figure S3C). Analyses of MD and XD did not reveal any significant effects of group or group-by-sex interactions.



FIGURE S1. Binary WM mask (in green) in MNI space used for voxelwise analyses of DTI metrics (FA, MD, RD, XD).



FIGURE S2. Group-by-sex interactions in relation to MD, RD, and XD in seven bilateral WM tracts. Panels A, B, and C represent the group-by-sex interaction in relation to MD, RD, and XD, respectively in the 7 WM tracts of interest. Red denotes children with anxiety disorders (n=163); blue denotes healthy volunteers (n=132). Plots connoted with a pound sign (#) indicate a group-by-sex interaction significant at the uncorrected threshold (p<0.05, uncorrected).

Voxelwise Analysis of RD



FIGURE S3. Voxelwise analysis of group differences and group-by-sex interactions across whole-brain WM RD. All analyses reflect harmonized data and include age as a covariate. All three panels show sagittal, coronal, and transverse views at MNI coordinates [92, 126, 74]. Results shown are using threshold-free cluster enhancement (TFCE) and corrected for multiple comparisons using the family-wise error rate (p<0.05, FWE-corrected). A) Voxels in which RD is significantly greater in children with anxiety disorders compared to healthy volunteers across the combined sample. B) Voxels in which there is a significant group-by-sex interaction in relation to RD. C) In the males alone, voxels in which RD is significantly greater in boys with anxiety disorders compared to healthy volunteer boys. In analyses of females alone, there were no significant differences in RD between girls with anxiety disorders and healthy volunteer girls.



FIGURE S4. Overlap of voxel maps depicting the main effects of group FA and RD in males alone (i.e., overlap of Figure 2C and Figure S3C). Results shown are TFCE P<0.05; FWE-corrected. Blue voxels indicate regions in which FA is significantly decreased in boys with anxiety disorders relative to healthy volunteer boys, while red voxels indicate regions in which RD is significantly increased in boys with anxiety disorders relative to healthy volunteer boys. Note the prominent overlap in the pattern of reduced FA and greater RD in boys with anxiety disorders.

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IC 2.031 225 0.044 2.036 224 0.043 0.249 224 0.803 IFO 2.400 225 0.017 2.371 224 0.019 -0.423 224 0.673 SLF 0.906 225 0.366 0.925 224 0.356 0.445 224 0.677 STRIA/FX 1.839 225 0.067 1.881 224 0.023 -0.877 224 0.387 UF 2.344 225 0.020 2.96 24 0.023 -0.877 224 0.382 FA - Analyses Controlling for Ace*Sex. Ace*Taures Cont. for CDI Cont. for CPRS Bilateral WM Tract t df p-value t df p-value CC 2.669 265 0.008 2.875 187 0.005 2.619 2.76 0.009 CING 1.318 265 0.189 1.946 187 0.053 1.875 276 0.062 IFO 2.479 265 0.046 1.268 187	CING	1.7	16	225	5		0.088		224	0.091	-0.241	+1 224		0.810		
IFO 2.400 225 0.017 2.371 224 0.019 -0.423 224 0.673 SLF 0.906 225 0.366 0.925 224 0.356 0.445 224 0.657 STRIA/FX 1.839 225 0.067 1.881 224 0.021 0.890 224 0.374 UF 2.344 225 0.020 2.296 224 0.023 -0.877 224 0.382 FA - Analyses Control of Colspan="4">Cont. for CDI Cont. for CPRS Cont. for Age*Sex + Age*Tarner Cont. for CDI Cont. for CPRS Cont. for CDI Cont. for CPRS Bilateral WM Tract t df p-value t df p-value CC 2.669 265 0.008 2.875 187 0.005 2.619 276 0.009 CING 1.318 265 0.189 1.946 187 0.003 1.875 276 0.005 SLF 2.272 265 0.024 2.102 187 0.003 1.922 </td <td>IC</td> <td>2.03</td> <td>31</td> <td>225</td> <td colspan="2">225</td> <td colspan="2">0.044</td> <td>224</td> <td>0.043</td> <td>0.249</td> <td>) 2</td> <td>24</td> <td>0.803</td>	IC	2.03	31	225	225		0.044		224	0.043	0.249) 2	24	0.803		
SLF 0.906 225 0.366 0.925 224 0.356 0.445 224 0.657 STRIA/FX 1.839 225 0.067 1.881 224 0.061 0.890 224 0.374 UF 2.344 225 0.020 2.296 224 0.023 -0.877 224 0.382 FA – Analyses Controling for Aqe*Sex. Aqe*Tanner Cont. for CDI Cont. for CPRS Bilateral WM Tract t df p-value CC 2.669 265 0.008 2.875 187 0.005 2.619 276 0.009 CING 1.318 265 0.146 1.268 187 0.207 2.367 276 0.005 SLF 2.272	IFO	2.40	00	225	5	0.017		2.371	224	0.019	-0.423	3 2	24	0.673		
STRIA/FX 1.839 225 0.067 1.881 224 0.081 0.890 224 0.374 UF 2.344 225 0.020 2.296 224 0.023 -0.877 224 0.382 FA - Analyses Controling for Age*Sex. Age*Tamer. CDI. and CPRS Cont. for Age*Sex + Age*Tamer Cont. for CD Cont. for CPRS Bilateral WM Tract t df p-value t df p-value CC 2.669 265 0.008 2.875 187 0.053 1.875 276 0.009 CING 1.318 265 0.189 1.946 187 0.053 1.875 276 0.062 IC 2.006 265 0.046 1.268 187 0.207 2.367 276 0.005 IFO 2.479 265 0.014 2.893 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.024 2.102 187 0.003	SLF	0.90	06	225	5		0.366	0.925	224	0.356	0.445	<u> 2</u>	24	0.657		
UF 2.344 225 0.020 2.96 224 0.023 -0.877 224 0.382 FA – Analvses Contruiting for Age*Sex. Age*Tanner Cont. for CDI Cont. for CDI Cont. for Age*Sex + Age*Tanner Cont. for CDI Cont. for CDRS Bilateral WM Tract t df p-value t df p-value t df p-value CC 2.669 265 0.008 2.875 187 0.053 1.875 276 0.009 CING 1.318 265 0.189 1.946 187 0.027 2.367 276 0.005 IC 2.006 265 0.046 1.268 187 0.037 2.656 276 0.005 IFO 2.479 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.024 2.102 187 0.037 2.856 2.060 0.056 <tr< td=""><td>STRIA/FX</td><td>1.8</td><td>39</td><td>225</td><td>5</td><td></td><td>0.067</td><td>1.881</td><td>224</td><td>0.061</td><td>0.890</td><td>) 2</td><td>24</td><td>0.374</td></tr<>	STRIA/FX	1.8	39	225	5		0.067	1.881	224	0.061	0.890) 2	24	0.374		
FA – Analyses Controlling for Ace*Sex. Ace*Tanner. CDI. and CPRS Cont. for Aqe*Sex + Aqe*Tanner Cont. for CDI Cont. for CPRS Bilateral WM Tract t df p-value CC 2.669 265 0.008 2.875 187 0.005 2.619 276 0.062 IC 2.006 265 0.046 1.268 187 0.207 2.367 276 0.005 IFO 2.479 265 0.024 2.102 187 0.003 1.922 276 0.056 UF 3.553	UF	2.34	14	225	5		0.020	2.296	224	0.023	-0.877	7 2	24	0.382		
Cont. for Age*Sex + Age*Tanner Cont. for CDI Cont. for CPRS Group*Sex Group*Sex Group*Sex Group*Sex Group*Sex Bilateral WM Tract t df p-value t 0.005 L365 0.005 L365 0.005 L365 L365 L365 L365 L365 L365 L365 L365 <td></td> <td></td> <td></td> <td colspan="8">FA – Analyses Controlling for Age*Sex, Age*Tanner, CDI, and CPRS</td> <td></td>				FA – Analyses Controlling for Age*Sex, Age*Tanner, CDI, and CPRS												
Group*Sex Group*Gained and and and and and and and and and an		Cont	t. for	Age*Sex	+ Age*	Age*Tanner 0			CDI		Cor	nt. for	CP	RS		
Bilateral WM Tract t df p-value t df p-value t df p-value CC 2.669 265 0.008 2.875 187 0.005 2.619 276 0.009 CING 1.318 265 0.189 1.946 187 0.053 1.875 276 0.062 IC 2.006 265 0.046 1.268 187 0.207 2.367 276 0.019 IFO 2.479 265 0.014 2.893 187 0.004 2.844 276 0.005 SLF 2.272 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.084 3.051 187 0.003 1.922 276 0.003 UF 3.553 265 <0.001 3.953 187 <0.001 2.982 276 0.003 CC 0.455 281 o.650 <		<u> </u>		Group*S	Sex			Group*8	Sex	_	G	roup	*Se>	(
CC 2.669 265 0.008 2.875 187 0.005 2.619 276 0.009 CING 1.318 265 0.189 1.946 187 0.053 1.875 276 0.062 IC 2.006 265 0.046 1.268 187 0.207 2.367 276 0.019 IFO 2.479 265 0.014 2.893 187 0.004 2.844 276 0.005 SLF 2.272 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.084 3.051 187 0.037 2.856 2.76 0.008 UF 3.553 265 <0.001	Bilateral WM Tract	t		df		-value	t	df	df p-valu		t	df		p-value		
CING 1.318 265 0.189 1.946 187 0.053 1.875 276 0.062 IC 2.006 265 0.046 1.268 187 0.207 2.367 276 0.019 IFO 2.479 265 0.014 2.893 187 0.004 2.844 276 0.005 SLF 2.272 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.084 3.051 187 0.003 1.922 276 0.056 UF 3.553 265 <0.001	CC	2.6	69	265		0.008	2.875	187	0.0	005 2	2.619	276		0.009		
IC 2.006 265 0.046 1.268 187 0.207 2.367 276 0.019 IFO 2.479 265 0.014 2.893 187 0.004 2.844 276 0.005 SLF 2.272 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.084 3.051 187 0.003 1.922 276 0.056 UF 3.553 265 <0.001	CING	1.3	18	265	265		1.946	187	0.0	053 1	.875	276		0.062		
IFO 2.479 265 0.014 2.893 187 0.004 2.844 276 0.005 SLF 2.272 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.084 3.051 187 0.003 1.922 276 0.056 UF 3.553 265 <0.001		2.0	06	265	265		1.268	187	0.2	207 2	2.367	276		0.019		
SLF 2.272 265 0.024 2.102 187 0.037 2.656 276 0.008 STRIA/FX 1.735 265 0.084 3.051 187 0.003 1.922 276 0.056 UF 3.553 265 <0.001	IFO		.79	265		0.014	2.893	187	0.0	004 2	2.844	2/6		0.005		
STRIA/FX 1.735 265 0.084 3.051 187 0.003 1.922 276 0.056 UF 3.553 265 <0.001	SLF	SLF 2.272		265		0.024	2.102	187	0.0	037 2	2.656	276		0.008		
OF 3.553 265 <0.001 3.953 187 <0.001 2.982 276 0.003 FA – Interactions Between SCARED Measures and Sex Child-SCARED*Sex Parent-SCARED*Sex Bilateral WM Tract t df p-value t df p-value CC 0.455 281 0.650 1.542 281 0.1242 CING 1.798 281 0.073 0.753 281 0.452 IC 1.017 281 0.310 1.426 281 0.155	STRIA/FX	1.7	35	265		0.084	3.051	187	0.0	03 1	.922	276		0.056		
FA – Interactions Between SCARED Measures and Sex Child-SCARED*Sex Parent-SCARED*Sex Bilateral WM Tract t df p-value t df p-value CC 0.455 281 0.650 1.542 281 0.1242 CING 1.798 281 0.073 0.753 281 0.452 IC 1.017 281 0.310 1.426 281 0.155	UF	3.553 265		5 < < 0.001		3.953	187	<0.	001 2	.982	276		0.003			
Bilateral WM Tract t df p-value t df p-value CC 0.455 281 0.650 1.542 281 0.1242 CING 1.798 281 0.073 0.753 281 0.452 IC 1.017 281 0.310 1.426 281 0.155						Interac	tions Betwe	en SCAR	ED Mea	Sures and						
Bilateral WW fract t or p-value t or p-value CC 0.455 281 0.650 1.542 281 0.1242 CING 1.798 281 0.073 0.753 281 0.452 IC 1.017 281 0.310 1.426 281 0.155			4			J	*Sex			Parent-5	arent-SCARED*Sex					
CC 0.455 281 0.650 1.542 281 0.1242 CING 1.798 281 0.073 0.753 281 0.452 IC 1.017 281 0.310 1.426 281 0.155		t 0.455			dt		p-value		t		0T		p-value			
IC 1.017 281 0.310 1.426 281 0.452		0.455		281		0.650	1.542		20	31	1 0.		1242			
		1./	98	2	281		0.073	0.753		20			0.	J.452		
		1.0	.70		201		0.510	1.	420	20	01	0.155		150		
IFO 0.070 201 0.004 1.442 261 0.151 SLE 0.047 204 0.200 4.200 204 0.400		0.5	10		201	0.564		1.442			201		0.131			
SLF U.917 ZOI U.300 1.398 Z81 0.163 STERATEX 0.000 294 0.029 4.204 294 0.404		0.9	217		201	+	0.300	1.	1.398		281		0.103			
LIF 0.296 281 0.767 1.428 281 0.154		0.0	296		281		0.928		1.301		201		0.194			

TABLE S1. Main effects of age and sex; three-way interactions between developmental covariates and the Group-by-Sex term; COI covariate analyses; Age*Sex, Age*Tanner, CDI, and CPRS covariate analyses; and SCARED-by-Sex effects in relation to FA in the 7 WM tracts analyzed via tractography. Tanner stages were log- transformed; testosterone, square-root transformed; estradiol, square-root transformed. All analyses controlled for age.

	MD													
		Combine	ed Sampl	e	E	Boys	Girls							
	G	roup	Group	o-by-Sex	G	roup	Group							
Bilateral WM Tract	t	p-value	t	p-value	t	p-value	t	p-value						
CC	1.470	0.143	-0.416	0.678	1.195	0.235	0.917	0.361						
CING	0.164	0.870	-0.767	0.444	0.557	0.579	-0.506	0.613						
IC	1.868	0.063	-1.640	0.102	2.041	0.044	0.206	0.837						
IFO	1.281	0.201	-1.155	0.249	1.445	0.152	0.122	0.903						
SLF	1.246	0.214	-1.172	0.242	1.405	0.163	0.083	0.934						
STRIA/FX	0.812	0.417	1.935	0.054	-0.736	0.464	2.343	0.020						
UF	1.389	0.166	-1.082	0.280	1.417	0.160	0.279	0.780						
				R	D									
		Combine	ed Sampl	е	E	Boys	Girls							
	G	roup	Group	-by-Sex	G	roup	Gr	oup						
Bilateral WM Tract	t	p-value	t	p-value	t	p-value	t	p-value						
CC	1.636	0.103	-1.051	0.294	1.688	0.095	0.517	0.606						
CING	0.570	0.569	-1.171	0.243	1.110	0.270	-0.500	0.618						
IC	1.964	0.050	-2.263	0.024	2.518	0.014	-0.258	0.797						
IFO	1.473	0.142	-1.960	0.051	2.089	0.039	-0.408	0.683						
SLF	1.220	0.224	-1.885	0.060	1.865	0.065	-0.570	0.57						
STRIA/FX	1.016	0.310	1.555	0.121	-0.363	0.718	2.173	0.031						
UF	2.067	0.040	-1.850	0.065	2.242	0.027	0.197	0.844						
				Х	D									
		Combine	ed Sampl	e	E	Girls								
	G	roup	Group	-by-Sex	G	roup	Gr	oup						
Bilateral WM Tract	t	p-value	t	p-value	t	p-value	t	p-value						
CC	0.820	0.413	0.933	0.352	-0.096	0.924	1.485	0.139						
CING	CING -0.708		0.124	0.902	-0.536	0.594	-0.498	0.619						
IC	1.393	0.165	-0.521	0.603	1.105	0.272	0.784	0.434						
IFO	0.572	0.568	0.564	0.573	0.017	0.987	1.004	0.316						
SLF	0.885	0.377	0.645	0.519	0.129	0.898	1.342	0.181						
STRIA/FX	0.379	0.705	2.448	0.015	-1.300	0.197	2.449	0.015						
UF	-0.164	0.870	0.477	0.634	-0.384	0.702	0.286	0.775						

TABLE S2. Tract-level analysis of group differences and group-by-sex interactions in the MD, RD, and XD of seven bilateral WM tracts. All analyses reflect harmonized data and include age as a covariate.

FA - Group						FA – Group-by-Sex							FA – Group - MALES							
				Peak MNI							Peak MNI							Peak MNI		
-			Coordinates		es					Coordinates						Co	ordinat	es		
Clust #	Vol. (mm ³)	Location	Hemi	x	Y	z	Clust #	Vol. (mm ³)	Location	Hemi	x	Y	z	Clust #	Vol. (mm ³)	Location	Hemi	x	Y	z
1	9193	CC; CR; EC; UF	R/L	105	161	71			EC; CR; IC: SFOF:							ILF; SLF; MLF:				
2	3560	IC; CR; FC	R/I	110	122	73	1	9225	CC; CING;	R/I	121	156	62			IFOF; UF;				
3	1250	IC: CR	L	74	122	74	· · ·	0220	AC' ATR'							CING: CR:				
4	1056	CC: CR	L	72	156	71			EC: IC:							IC; EC;				
		SS; ILF;					2	4418	CR; CP	R	121	130	71			SFOF;				
5	126	IFOF	R	143	97	61	3	2016	CP; IC	L	78	105	60			CC; CP;				
6	85	EC	R	125	137	66			CP; CST;					1	46967	FX	R/L	133	120	40
7	80	CP	R	79	106	59	4	1482	CBP; ML	R/L	95	97	47	2	1326	SLF; CST	L	80	106	133
		SS; ILF;	-				-	4070	IC; CR;		<u></u>	404	0.4	3	498		ĸ	102	98	138
8	/1	IFOF	R	133	115	60	5	1273	EC OD: FO:	L	69	134	84	1	335	AF; SLF;	R	133	80	90
9	29		L	82	104	73	6	793	UR; EU;	R	117	118	86	-	555		IX.	155	00	30
		KD - G	roup	F	eak MN	11	7	639	CR	R	111	98	114	5	301	CR	L	74	124	106
				Co	pordinat	es	8	499	CBP	R	113	87	31			UF; FX;				
Clust	Vol.					_	9	450	CST	R	100	94	136	6	221	ILF; IFOF;		50	114	51
#	(mm ³)	Location	Hemi	Х	Y	Z	10	411	CST	L	81	107	131	0	231	CBP	R	107	65	40
		EC; IC;					11	408	CR; EC	L	66	155	/1	8	209	CBP	R	95	70	40
1	4550		D	100	122	72	12	407		ĸ	107	107	102	9	130	CC	L	82	122	99
2	4330		R/I	109	162	67	13	205			67	1/12	103	10	120	CING: FX	L	64	119	41
	1216		R	104	156	61	14	253	CBP		71	85	31	11	89	CST; SLF	L	71	88	127
	1210	SS: ILF:		121	100	01	16	216	SLF	R	140	129	83	12	89	IFOF; UF	R	113	172	61
4	305	IFOF: IC	R	129	105	60	17	191	SLF	L	86	96	122	13	82	CST	L	84	83	143
5	137	CP; CST	R/L	95	101	48	18	181	CC; CR	L	74	122	107	14	65	AC	L	78	126	60
6	75	ATR	R	146	106	74	19	180	CST	L	83	96	141	15	57	ILF	R	138	65	60
7	59	CP	R	107	107	61	20	162	SLF	R	133	80	91	16	34	CC	R	94	115	95
8	21	ILF; IFOF	R	143	97	61	21	91	CST	L	68	103	127	17	31	IFOF	L	50	100	59
9	15	CP	R	99	114	58	22	70	CST	L	57	107	128	18	16		L	43	93	60
10	7	ILF/IFOF	R	141	102	57			SS; ILF;					19	11	SLF	L	47	117	90
11	4	IC	L	87	129	68	23	56	IFOF; UF	L	49	110	55	20	4			49	93	62
			24 49 SLF R 119 93			123		Peak N												
							25	30	SLF CST	R	74 100 132							ordinat	es	
							20	20		R	133 119 43		Clust	Vol.				orainat		
							28	18	CST	L	78	86	136	#	(mm ³)	Location	Hemi	Х	Y	Z
							29	5	CP	R	96	119	59			IFOF;				
																CBP				
																CST: UF:				
																AC; CING;				
																CC; CR;				
														1		CP; SS;				
														4	21042	ILF; IC;	D/I	109	150	60
														2	1758			106	118	90
														2	17.50			40	110	90
														3	1281	IFOF; SS	L	44	92	58
														4	110	SLF		54	101	107
														с I	44	JLF, AF	L	59	133	31

TABLE S3. Main effect of group in the full sample on FA, RD, and MD (yellow headings); group-by-sex interactions in relation to FA and RD (green headings); and main effect of group in the males alone on FA and RD (blue headings) in voxelwise analyses (TFCE P<0.05, FWE-corrected). Description of clusters in which FA, RD, or MD is significantly reduced (FA) or increased (MD, RD) in children with anxiety disorders compared to healthy volunteers (in the full sample and in males alone), as well group-by-sex interactions in relation to FA and RD. Tract abbreviations: AF=arcuate fasciculus; AC=anterior commissure; ATR=anterior thalamic radiation; CBP=cerebellar peduncle; CP=cerebral peduncle; CING=cingulum; CR=corona radiata; CC=corpus callosum; CST=corticospinal tract; EC=external capsule; FX=fornix; IFOF=inferior fronto-occipital fasciculus; PTR=posterior thalamic radiation; SS=sagittal striatum; STRIA=stria terminalis; SFOF=superior fronto-occipital fasciculus; SLF=superior longitudinal fasciculus; STR=superior thalamic radiation; UF=uncinate fasciculus; STR=superior thalamic radiation; UF=uncinate fasciculus; STR=superior thalamic radiation; UF=uncinate fasciculus.

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