Supplement 1

Outlier Determination

Within each volume, voxels were marked as outliers if the voxel value exceeded gnorminv(0.001/31) * sqrt(pi/2) * MAD (where gnorminv= inverse of the reversed Gaussian cumulative distribution function and MAD=median absolute deviation). In this instance the MAD is calculated across all voxels within the brain in the entire 4D volume of a subject. Due to the disbursement of the directions in the diffusion tensor magnetic resonance imaging (DTI) scan, the trend across all volumes was not removed prior to calculation of the MAD. This calculation yielded the number of outlier voxels within an individual volume. Thereafter, volumes were excluded from further analysis if the number of outlier voxels within the volume exceeded 2 standard deviations from the mean number of outliers across all volumes for a given subject.

Signal-to-Noise Calculation

Since larger *b* values tend to reduce the signal-to-noise ratio (SNR) of DTI scans (Jones et al., 2013), we calculated the SNR for each volume in the field-map--corrected images. For the background, we considered a 5×5×5 voxel region in the corner of each diffusion-weighted volume. We calculated the signal in each of the left and right uncinate fasculi and the left and right cingulum masks. The masks were the result of back-warping the standard space masks used for probabilistic tractography in DTI space using the methods detailed in the main manuscript. The SNR was then calculated as 0.655 * mean(signal) / sd(noise). The 0.655 scaling factor compensates for the noise rectification issue, wherein the standard deviation of the signal in the background region is smaller than it is in the signal region (see http://www2.fmrib.ox.ac.uk/education/graduate-training-course/programme/mri-physics/physics-practicals/signalsnr_2011-2.pdf). The average SNR across all subjects and diffusion directions was 12.22 for our sample, which should be more than adequate for accurate tensor estimation.[1]

Movement Analysis

To determine whether group differences in the amount of motion were present in our sample, we calculated the average amount of motion in each of 3 translational and 3 rotational planes for each participant. These were then subjected to linear mixed effects analysis implemented in R where participant was treated as a random effect. No between-group differences in the average amount of motion were observed: $F_{(1, 92)}=0.52$, $p=0.48$.

Furthermore, we repeated the linear mixed effects (LMEs) examining the presence of between-group effects in fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) in each of our 4 tracts of interest by adding average amount of motion per subject as an additional explanatory variable. The additional motion covariate had no effect on the results reported in the main manuscript.

References

1. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*. 2013;73:239–254.

Table S1. Sensitivity Analyses Excluding Outliers

FA ONLY	L UF [a]	R UF [a]	L Cingulum [a]	R Cingulum [a]
All MDD participants	$F_{(1, 88)}$=13.86, p<0.001 (MDD: 0.33, NCL: 0.34)	$F_{(1,88)}$=7.52, p=0.007 (MDD: 0.34, NCL: 0.35)	$F_{(1, 88)}$=3.64, p=0.057 (MDD: 0.35, NCL: 0.37)	$F_{(1, 88)}$=3.34, p=0.07 (MDD: 0.33, NCL: 0.34)
Without Outliers	$F_{(1, 85)}$ = 14.95, p=0.002 (MDD: 0.33, NCL: 0.34)	$F_{(1, 85)}$=12.13, p=0.0008 (MDD: 0.34, NCL: 0.35)	$F_{(1, 85)}$ = 2.075, p=0.15 (MDD: 0.36, NCL: 0.37)	$F_{(1, 85)}$ = 1.747, p=0.19 (MDD: 0.33, NCL: 0.34)
RD ONLY				
All MDD participants	$F_{(1,88)}$=6.59, p=0.012 (MDD: 0.0006, NCL: 0.0006)	$F_{(1, 88)}$=3.93, p=0.05 (MDD: 0.0006, NCL: 0.0005)	$F_{(1, 88)}$=3.48, p=0.06 MDD: 0.0005, NCL: 0.0005)	$F_{(1,88)}$=3.09, p=0.07 (MDD: 0.0005, NCL: 0.0005)
Without Outliers	F(1, 85) = 6.92, p=0.01 (MDD: 0.0006, NCL: 0.0006)	F(1, 85) = 7.47, p=0.008 (MDD: 0.0005, NCL: 0.0005)	F(1, 85) = 2.72, p=0.10 (MDD: 0.0005, NCL: 0.0005)	F(1, 85) = 2.29, p=0.13 (MDD: 0.005, NCL: 0.005)
AD ONLY				
All MDD participants	NS	NS	NS	NS
Without Outliers	NS	NS	NS	NS

Note: Outliers had fractional anisotropy (FA) values greater than two standard deviations from the mean. One control and three participants with major depressive disorder (MDD) were removed from the analysis excluding outliers based on these criteria. L = left; NCL = control; NS = not significant; R = right; UF = uncinate fasciculus.

[a] Models included group, Wechsler Abbreviated Scale of Intelligence (WASI) performance, and Tanner stage,

Table S2. Sensitivity Analysis Comparing Linear Mixed Effects (LME) Results From our Complete Sample and a Subsample

FA ONLY	L UF [a]	R UF [a]	L Cingulum a	R Cingulum [a]
All MDD participants (n=52) and controls (n=42)	$F_{(1,88)}$=13.86, p<0.001 (MDD: 0.33, NCL: 0.34)	$F_{(1,88)}$=7.52, p=0.007 (MDD: 0.34, NCL: 0.35)	$F_{(1,88)}$=3.64, p=0.057 (MDD: 0.35, NCL: 0.37)	$F_{(1,88)}$=3.34, p=0.07 (MDD: 0.33, NCL: 0.34)
MDD without comorbidity (n=33) and controls (n=42)	$F_{(1,70)}$=9.23, p=0.0033 (MDD: 0.33, NCL: 0.34)	$F_{(1,70)}$ = 4.947, p=0.0294 (MDD: 0.34, NCL: 0.35)	$F_{(1,70)}$ = 1.127, p=0.2920 (MDD: 0.35, NCL: 0.37)	$F_{(1,70)}$ = 0.797, p=0.2751 (MDD: 0.33, NCL: 0.34)
RD ONLY				
All MDD participants (n=52) and controls (n=42)	$F_{(1,88)}$=6.59, p=0.012 (MDD:0.0006, NCL: 0.0006)	$F_{(1,88)}$=3.93, p=0.05 (MDD: 0.0006, NCL: 0.0005)	$F_{(1,88)}$=3.48, p=0.06 (MDD: 0.0005, NCL: 0.0005)	$F_{(1,88)}$=3.09, p=0.07 (MDD: 0.0005, NCL: 0.0005)
MDD without comorbidity (n=33) and controls (n=42)	$F_{(1,70)}$ = 8.88, p=0.004 (MDD: 0.0006, NCL: 0.0005)	$F_{(1,70)}$ = 6.43, p=0.0135 (MDD: 0.0006, NCL: 0.0005)	$F_{(1,70)}$ = 3.47, p=0.0668 (MDD: 0.0005, NCL: 0.0005)	$F_{(1,70)}$=2.02, p=0.1599 (MDD: 0.0005, NCL: 0.0005)
AD ONLY				
All MDD participants (n=52) and controls (n=42)	NS	NS	NS	NS
MDD without comorbidity (n=33) and controls (n=42)	NS	NS	NS	NS

Note: analysis excludes those participants with major depressive disorder (MDD) and comorbid attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), enuresis, social phobia, oppositional defiant disorder (ODD), and conduct disorder (CD). AD = axial diffusivity; CTRL = control; FA = fractional anisotropy; L = left; NCL = control; R = right; RD = radial diffusivity; UF = uncinate fasciculus.

[a] Models included group, Wechsler Abbreviated Scale of Intelligence (WASI) performance, and Tanner stage,

Table S3. Sensitivity Analyses Including Average Motion Parameters in Our Adjusted Linear Mixed Effects (LME) Models Comparing All Participants With Major Depressive Disorder (MDD) to Controls (NCL)

FA ONLY	L UF [a]	R UF [a]	L Cingulum [a]	R Cingulum [a]
All MDD participants	$F_{(1, 88)}$=13.86, p<0.001 (MDD: 0.33, NCL: 0.34)	$F_{(1,88)}$=7.52, p=0.007 (MDD: 0.34, NCL: 0.35)	$F_{(1, 88)}$=3.64, p=0.057 (MDD: 0.35, NCL: 0.37)	$F_{(1, 88)}$=3.34, p=0.07 (MDD: 0.33, NCL: 0.34)
With motion adjustment	$F_{(1, 87)}$ = 13.88 ,p= 0.0003 (MDD=0.33, NCL=0.34)	F($_{1, 87)}$ = 7.46m p=0.007 (MDD: 0.33, NCL: 0.34)	$F_{(1, 87)}$ = 3.624, p=0.06 (MDD: 0.35, NCL: 0.36)	$F_{(1, 87)}$ = 3.308, p=0.07 (MDD: 0.33, NCL: 0.34)
RD ONLY				
All MDD participants	$F_{(1,88)}$=6.59, p=0.012 (MDD: 0.0006, NCL: 0.0006)	$F_{(1, 88)}$=3.93, p=0.05 (MDD: 0.0006, NCL: 0.0005)	$F_{(1, 88)}$=3.48, p=0.06 (MDD: 0.0005, NCL: 0.0005)	$F_{(1,88)}$=3.09, p=0.07 (MDD: 0.0005, NCL: 0.0005)
With motion adjustment	F($_{1, 88)}$= 6.54, p=0.0123 (MDD: 0.0006, NCL: 0006)	$F_{(1, 87)}$ = 3.95, p=0.05 (MDD: 0.0006, NCL: 0.0005)	$F_{(1, 87)}$ = 3.45, p=0.06 (MDD: 0.0005, NCL: 0.0005)	$F_{(1, 87)}$ = 3.08, p=0.08 (MDD: 0.0005, NCL: 0.0005)
AD ONLY				
All MDD participants	NS	NS	NS	NS
With motion	NS	NS	NS	NS

Note: AD = axial diffusivity; FA = fractional anisotropy; L = left; NS = not significant; R = right; RD = radial diffusivity; UF = uncinate fasciculus.

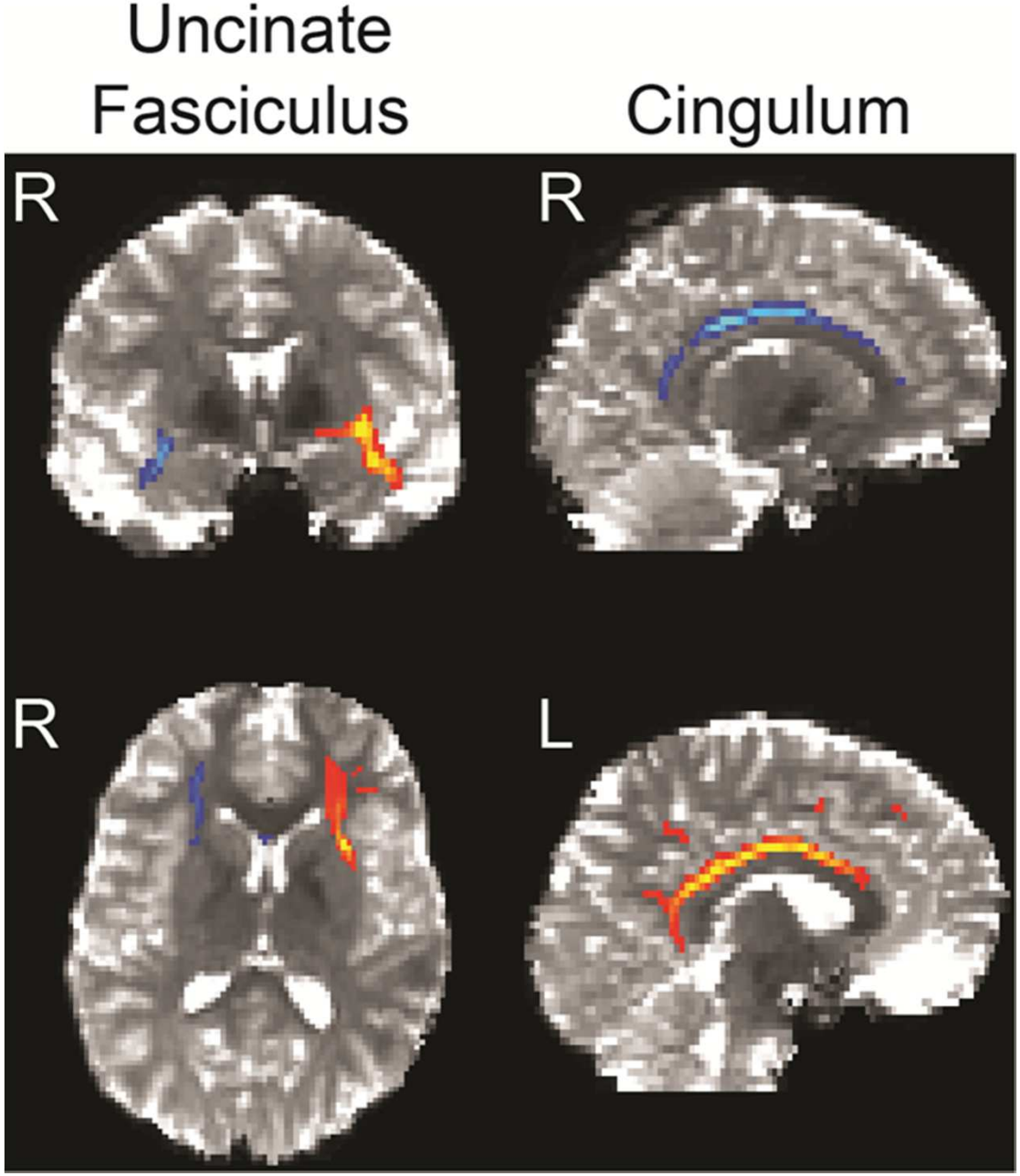
[a] Models included group, Wechsler Abbreviated Scale of Intelligence (WASI) performance, and Tanner stage,

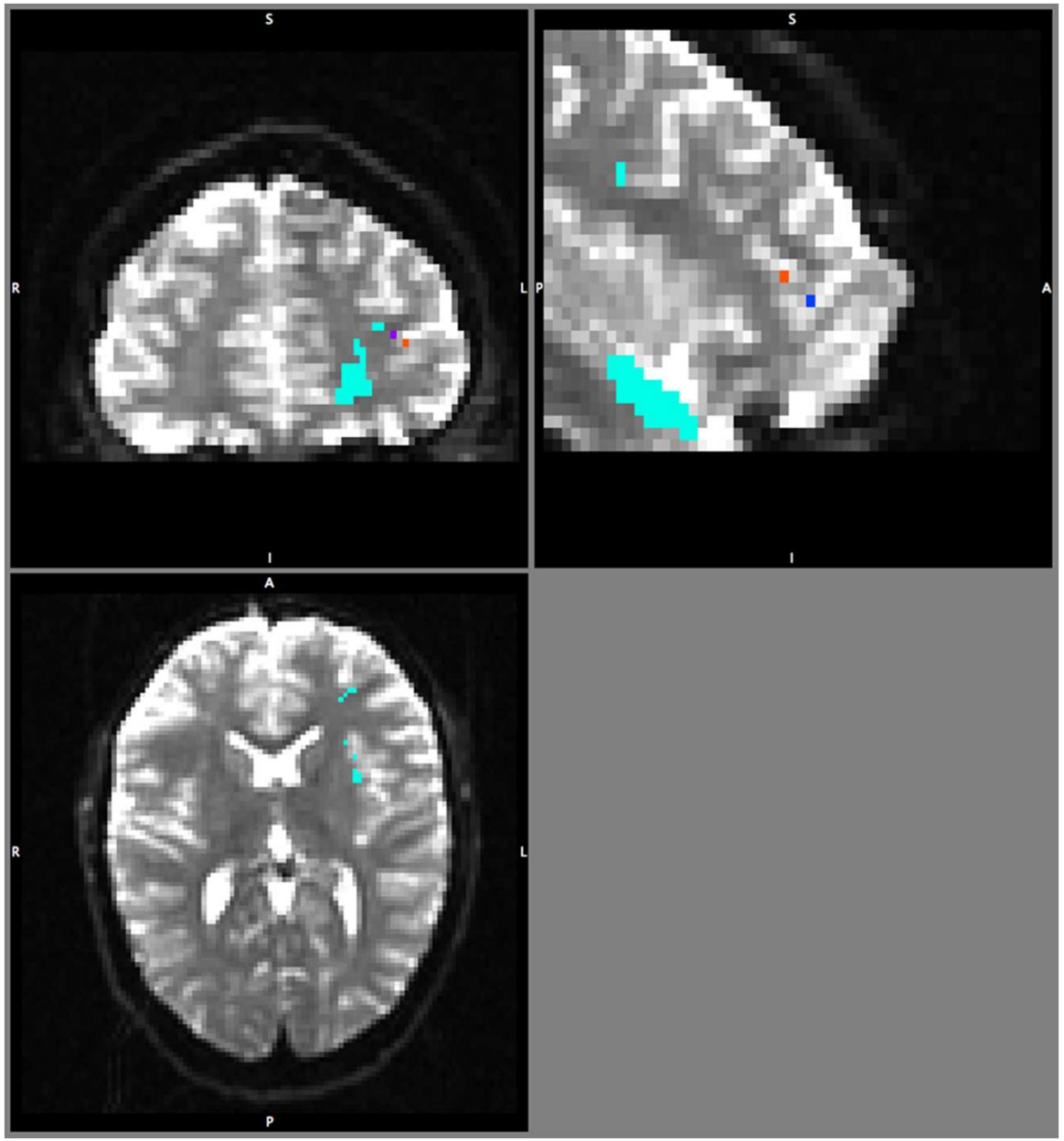
Supplemental Figure Captions

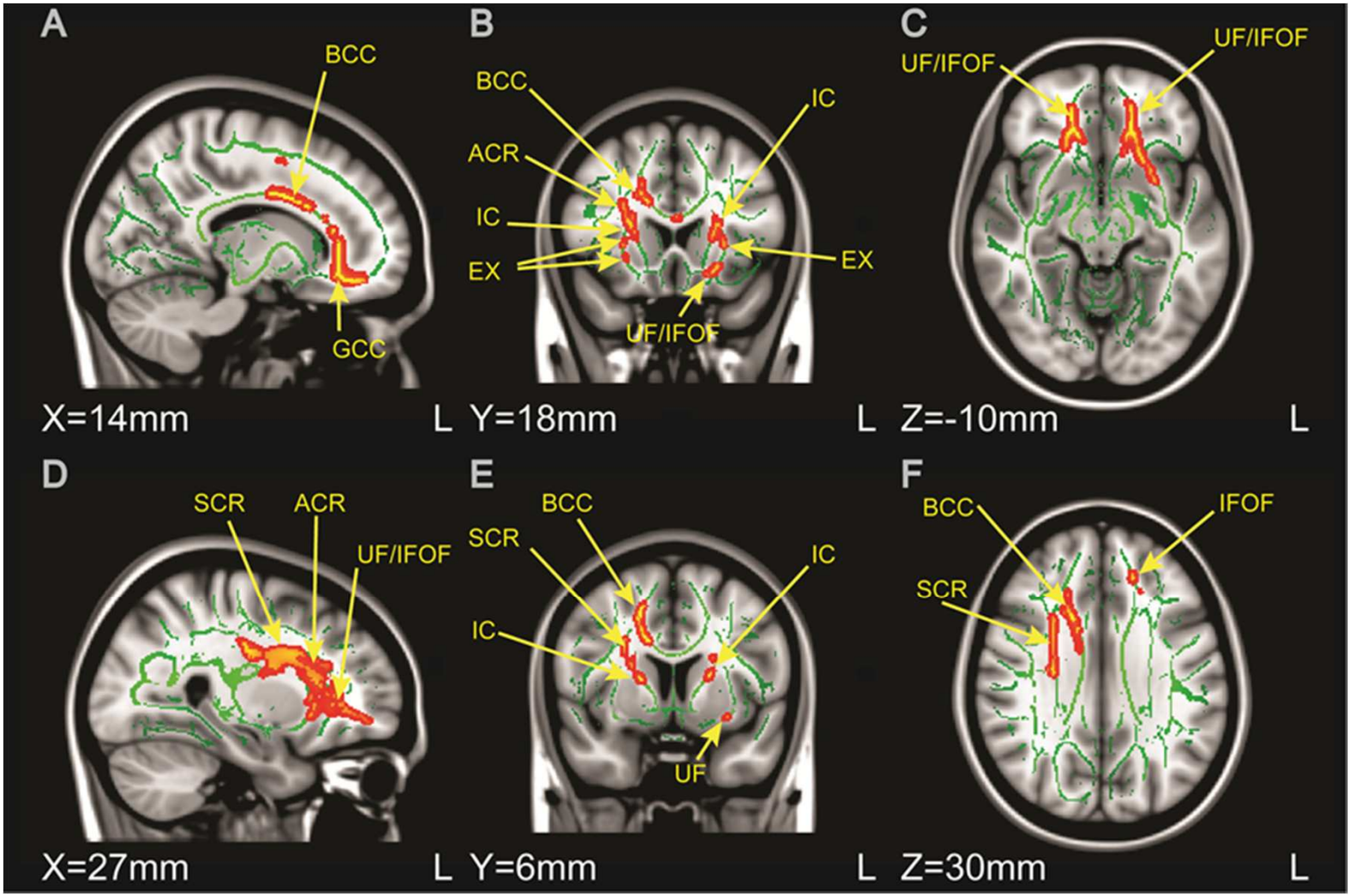
Figure S1: Standard masks from the ICBM-DTI-81 atlas in diffusion space for one example participant.

Figure S2: See below for a typical example of the probtrackx result for the uncinate fasciculus (UF) prior to the selection of the largest connected component. The largest connected and retained tract is in cyan, and the poorly connected tracts are in red and dark blue. Across all subjects, the largest disconnected component deleted was no more than 5 voxels.

Figure S3: Tract-based spatial statistics (TBSS) results comparing fractional anisotropy (FA) values in control adolescents and those with depression, excluding those participants with major depressive disorder (MDD) and comorbid attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder (PTSD), enuresis, social phobia, oppositional defiant disorder (ODD), and conduct disorder (CD) (MDD: n=32; control=42). FA maps show sagittal, coronal, and axial views (from left to right). Green voxels represent the mean white matter skeleton from the entire sample, and red-yellow voxels represent white matter regions with lower FA in participants with MDD compared with controls (p<.05, threshold-free cluster enhancement [TFCE]-corrected). In no regions were FA values significantly higher for participants with MDD. Note: ACR = anterior corona radiata; BCC = body of corpus callosum; EX -external capsule; GCC = genu of corpus callosum; IC = internal capsule; IFOF = inferior fronto-occipital fasciculus; SCR = superior corona radiate; UF = uncinate fasciculus.


Uncinate Fasciculus
Cingulum
R
R
R
L


S
R
L
I
S
P
A
I
A
R
L
P


A
BCC
GCC
X=14mm
L
B
BCC
ACR
IC
EX
IC
EX
UF/IFOF
Y=18mm
L
C
UF/IFOF
UF/IFOF
Z=-10mm
L
D
SCR
ACR
UF/IFOF
X=27mm
L
E
BCC
SCR
IC
IC
UF
Y=6mm
L
F
BCC
IFOF
SCR
Z=30mm
L