Appendix

Tract-based spatial statistics and a mean FA skeleton threshold of >0.25 were chosen to exclude voxels less likely to be part of fiber tracts common to the participants. Only voxels with FA <.25 in the mean skeleton were excluded (ie, all voxels with FA <.25 were not removed for all participants). It is still important to consider whether this threshold may impinge on the possibility of identifying areas of abnormally low FA in the present study. Any threshold conveys some risk in this regard, because some excluded voxels could represent WM areas with lower FA. However, it is essential to take into account both regional variability in fiber architecture (perhaps especially in children) and systematic anatomic variability across groups. In the present study, there were known anatomic group differences: The substance-exposed children had smaller intracranial and regional neuroanatomic volumes.[8] Hence, there was a possibility of overestimating effects because of anatomic misalignment. For instance, one could risk measuring FA in borderline gray matter in exposed children, while the comparison FA measurements in control children could be higher because these measurements would more often be correctly estimated in the bigger WM tracts in the control group. It has been found that thresholding the mean FA value between 0.2 and 0.3 successfully excludes voxels that are primarily gray matter or CSF in most subjects. This also ensures that the skeleton does not run up to the outermost cortical edges, where the tracts may be least well-aligned between subjects (for further details, see Smith et al[28]).

On-line Table 1: Description, size, and location of the clusters of significant group differences in FA[a]

Cluster	Voxels	X (max)	Y (max)	Z (max)	X (cog)	Y (cog)	Z (cog)
A) R occipital/lingual gyrus (ILF/Fmaj)	358	59	57	76	55.9	65	72.5
B) L deep temporal (ILF)	231	122	102	68	124	106	64.3
C) R deep temporal (ILF)	218	50	95	69	58.3	103	66.5
D) L lateral occipital/angular	150	121	66	102	123	66.8	102
E) L inferior temporal gyrus (SLF)	124	144	89	49	142	88	53.8
F) R occipital/fusiform temporal gyrus (ILF)	121	51	88	63	51.5	88	62.5
G) L middle temporal gyrus (ILF/UF)	111	135	117	49	130	122	46.2
H) R postcentral/supramarginal gyrus	109	59	97	108	60.4	95.5	109
I) L projection from splenium CC (Fmaj)	103	104	79	92	104	80.2	92.9
J) R frontal pole (Fmin)	100	71	180	89	72.5	178	91.1

[a] All clusters showed significantly lower FA ($P < .05$) in prenatally substance-exposed children. X, Y, and Z indicate the Montreal Neurological Institute coordinates. "max" signifies the coordinates of the voxel in each cluster showing the strongest effect, while "cog" signifies the coordinates of the center of gravity of each cluster.

On-line Table 2: Results for the split-half analysis[a]

Cluster	FA-A[b]		FA-B[c]	
	F	P Value	F	P Value
A) R occipital/lingual gyrus (ILF/Fmaj)	5.691	.038	6.704	.027
B) L deep temporal (ILF)	13.419	.004	9.308	.012
C) R deep temporal (ILF)	7.092	.024	8.264	.017
D) L lateral occipital/angular	18.840	.001	6.411	.030
E) L inferior temporal gyrus (SLF)	21.081	.001	3.262	.101
F) R occipital/fusiform temporal gyrus (ILF)	8.528	.015	6.126	.033
G) L middle temporal gyrus (ILF/UF)	24.931	.000	5.575	.040
H) R postcentral/supramarginal gyrus	12.226	.006	4.368	.063
I) L projection from splenium CC (Fmaj)	27.035	.000	3.697	.083
J) R frontal pole (Fmin)	10.371	.009	5.390	.043

[a] Results for group differences (Exposed vs Controls) in FA, DA, and from a GLM analysis, with age and gender entered as covariates.
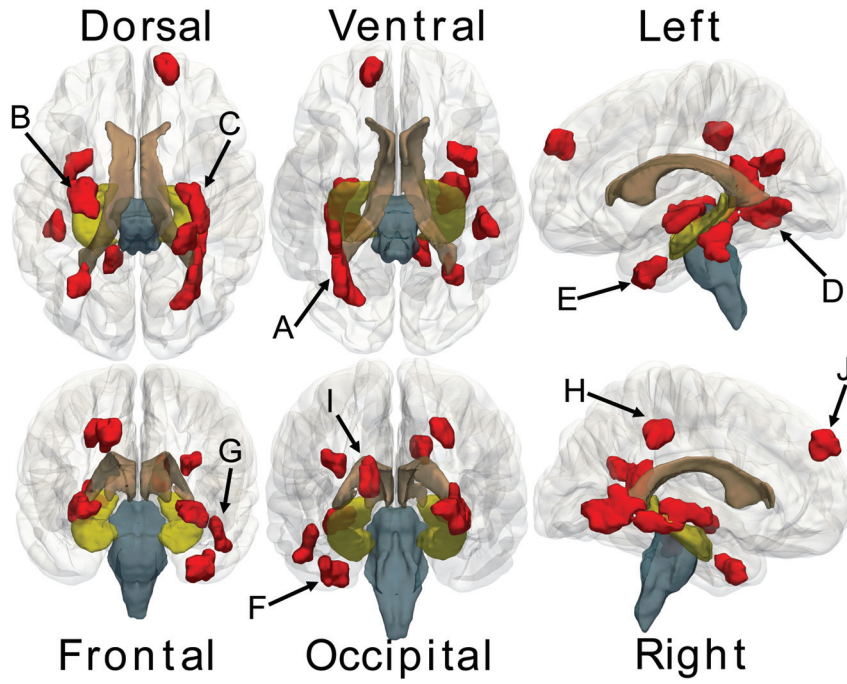[b] Exposed: mean age = 11.2 ± 1.8 years, 4 F/3 M; Controls: mean age = 9.8 ± 0.4 years, 3 F/4 M.
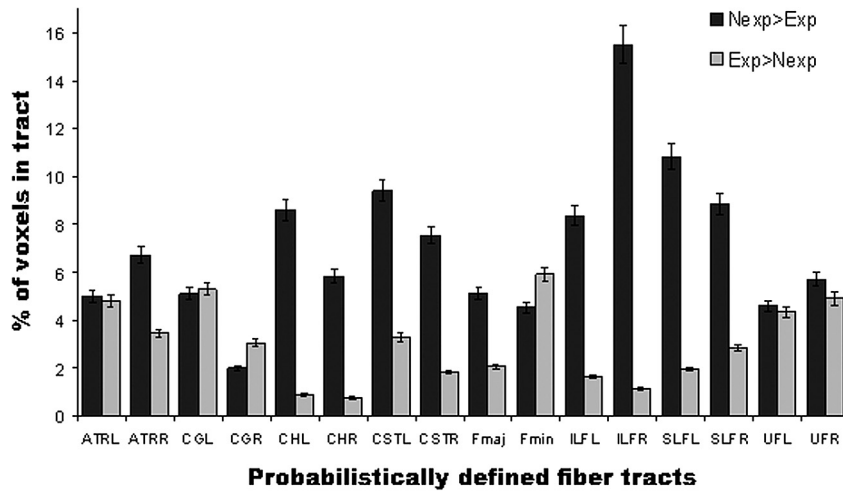[c] Exposed: mean age = 11.5 ± 1.8 years, 3 F/4 M; Controls: mean age = 9.8 ± 0.2 years, 2 F/5 M.

On-line Table 3: Group differences in FA, DR, and DA values within identified clusters subjected to reanalysis[a]

Cluster	Controls vs Term, Opiate Exposed ($n = 14 + 10$)						Controls vs Healthy, Opiate Exposed ($n = 14 + 6$)					
	FA		DR		DA		FA		DR		DA	
	F	P	F	P	F	P	F	P	F	P	F	P
A) R occipital/lingual gyrus (ILF/Fmaj)	8.376	.009	8.184	.010	4.933	.038	10.216	.006	9.160	.008	4.727	.045
B) L deep temporal (ILF)	10.630	.004	9.257	.006	2.825	.108	10.502	.005	7.453	.015	4.279	.055
C) R deep temporal (ILF)	8.300	.009	7.499	.013	1.728	.203	8.950	.009	7.051	.017	4.510	.050
D) L lateral occipital/angular	16.688	.001	11.168	.003	6.569	.019	15.735	.001	10.651	.005	4.389	.052
E) L inferior temporal gyrus (SLF)	10.713	.004	12.102	.002	1.630	.216	10.843	.005	11.215	.004	.884	.361
F) R occipital/fusiform temporal gyrus (ILF)	10.209	.005	4.537	.046	4.083	.057	10.199	.006	4.819	.043	3.342	.086
G) L middle temporal gyrus (ILF/UF)	11.160	.003	9.261	.006	.126	.726	12.462	.003	10.157	.006	.288	.599
H) R postcentral/supramarginal gyrus	16.029	.001	14.543	.001	3.550	.074	23.713	.000	15.483	.001	3.833	.068
I) L projection from splenium CC (Fmaj)	13.258	.002	8.572	.008	1.171	.292	15.752	.001	8.824	.009	1.150	.299
J) R frontal pole (Fmin)	12.269	.002	8.329	.009	.958	.339	10.485	.005	7.639	.014	.430	.521

[a] The exposed sample was limited to only children exposed to heroin and to only children exposed to heroin and born at term and not having a diagnosis of myelomeningocele or AS.

Dorsal   Ventral   Left

B   C

A

D

E

Frontal   Occipital   Right

G

H   J

I

F

On-line Fig 1.

On-line Fig 2.