Supplement for “Opposing Relationships of Childhood Threat and Deprivation with Stria Terminalis White Matter”

Short running title: Childhood Adversity and Visceral White Matter

Layla Banihashemi[1], Christine W. Peng[1], Timothy Verstynen[2], Meredith L. Wallace[1,3], Daniel N. Lamont[4], Hussain M. Alkhars[5], Fang-Cheng Yeh[6], Joseph E. Beeney[1], Howard J. Aizenstein[1], Anne Germain[1]

[1]Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA

[2]Department of Psychology, Carnegie Mellon University, Pittsburgh, Pennsylvania 15213, USA

[3]Department of Statistics, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA

[4]Petersen Institute of NanoScience and Engineering, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA

[5]Department of Neuroscience, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA

[6]Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA

Corresponding author:

Layla Banihashemi

3811 O’Hara St

Pittsburgh, PA 15213

Office phone: 412-383-2151

layla.banihashemi@pitt.edu

Methods and Materials

Study Protocol & Measures

HCP Image Acquisition and Reconstruction

HCP data was acquired on a Siemens Skyra 3T scanner with a customized SC72 gradient insert. Multi-shell diffusion MRI scans consisted of 3 shells of b=1000, 2000, and 3000 s/mm2 interspersed with an approximately equal number of acquisitions on each shell within each run using a spin-echo EPI sequence (TR = 5520 ms, TE = 89.5 ms, voxel size = 1.25 mm isotropic, FoV = 210 X 180, b-max = 3000 s/mm2). Diffusion MRI data were reconstructed using a Q-space diffeomorphic reconstruction (QSDR) (Yeh & Tseng, 2011) with a diffusion sampling length ratio of 1.25. The diffusion ODFs of all 488 subjects with diffusion MRI collected were averaged in MNI space to obtain a group atlas (Fig. S1). Analyses were performed on this atlas image.

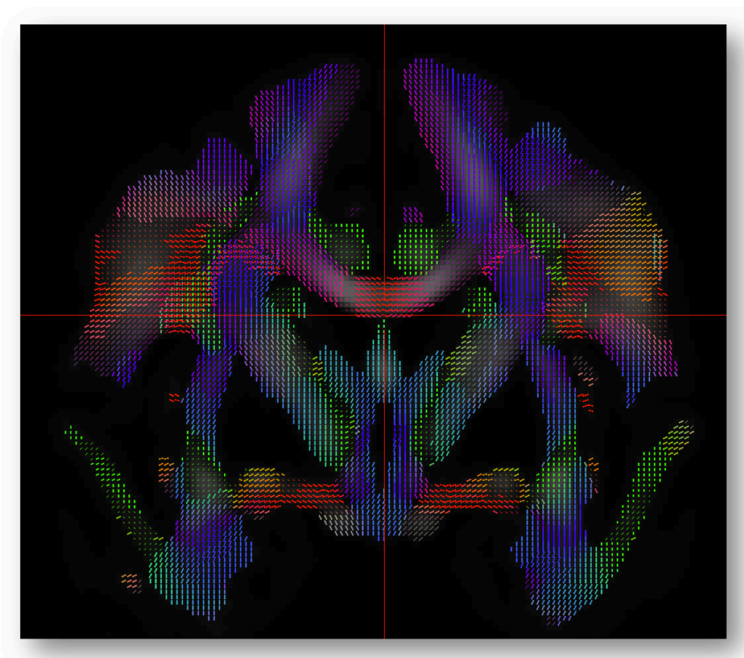

Fig. S1. Human Connectome Project Orientation Distribution Function Group Map.

HCP Tractography and Analysis

All tractography was performed using DSI Studio (http://dsi-studio.labsolver.org/). Fornix and stria terminalis tractography was performed using the ICBM152 template MPRAGE image. A section was located in which the lateral ventricles had broken through to merge with the third ventricle. A fornix (column and body) mask (Johns Hopkins University, JHU, White Matter Labels 1mm atlas) was dilated to the mid-point of the head of the caudate so as to encompass the ST and terminal vein and then was used as a ROI for tractography (Fig. S2 A). JHU masks for the anterior limb of the internal capsule (Fig. S2 B) and the corpus callosum (Fig. S2 B&C) were used as regions of avoidance (ROAs). Standard tracking parameters were used and tracking was set to terminate at 25,000 streamlines. Streamlines of the internal capsule, anterior commissure, and medial forebrain bundle were deleted. The left and right stria terminalis were separated from the fornix. MFB tractography was performed using a rectangular ROI covering the dorsal brainstem as a seed and fibers that coursed through the mid-brain tegmentum toward the BST and PVN were selected (Fig. 3 A & B in manuscript). Standard tracking parameters were used and tracking was set to terminate at 25,000 streamlines.

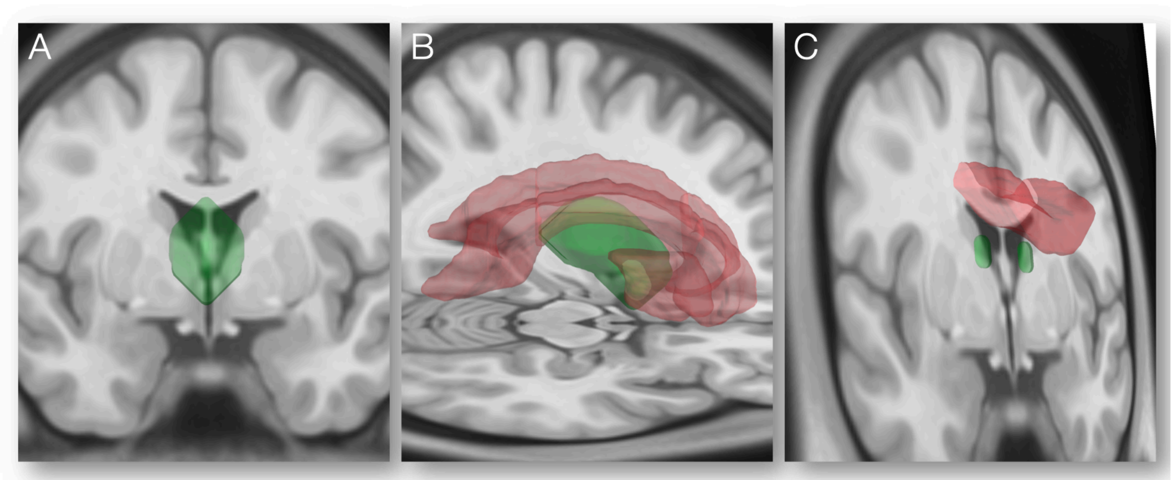

Fig. S2. Fornix and Stria Terminalis Tractography Approach.
Group: A fornix (column and body) mask (JHU White Matter Labels) was dilated to encompass the stria terminalis (ST) and used as a region of interest (ROI) (green, A). JHU masks for the corpus callosum (B & C) and anterior limb of the internal capsule (B) were used as regions of avoidance (ROA, red).

Human Connectome Project, Individual Tractography

We performed FX, ST and MFB tractography in 20 random individuals from the larger sample of 488 HCP participants and found that the individual FX, ST and MFB tractography was representative of the group analysis (See Figs. S3 & S4; See Table S1 for summary characterizations of the tractography).

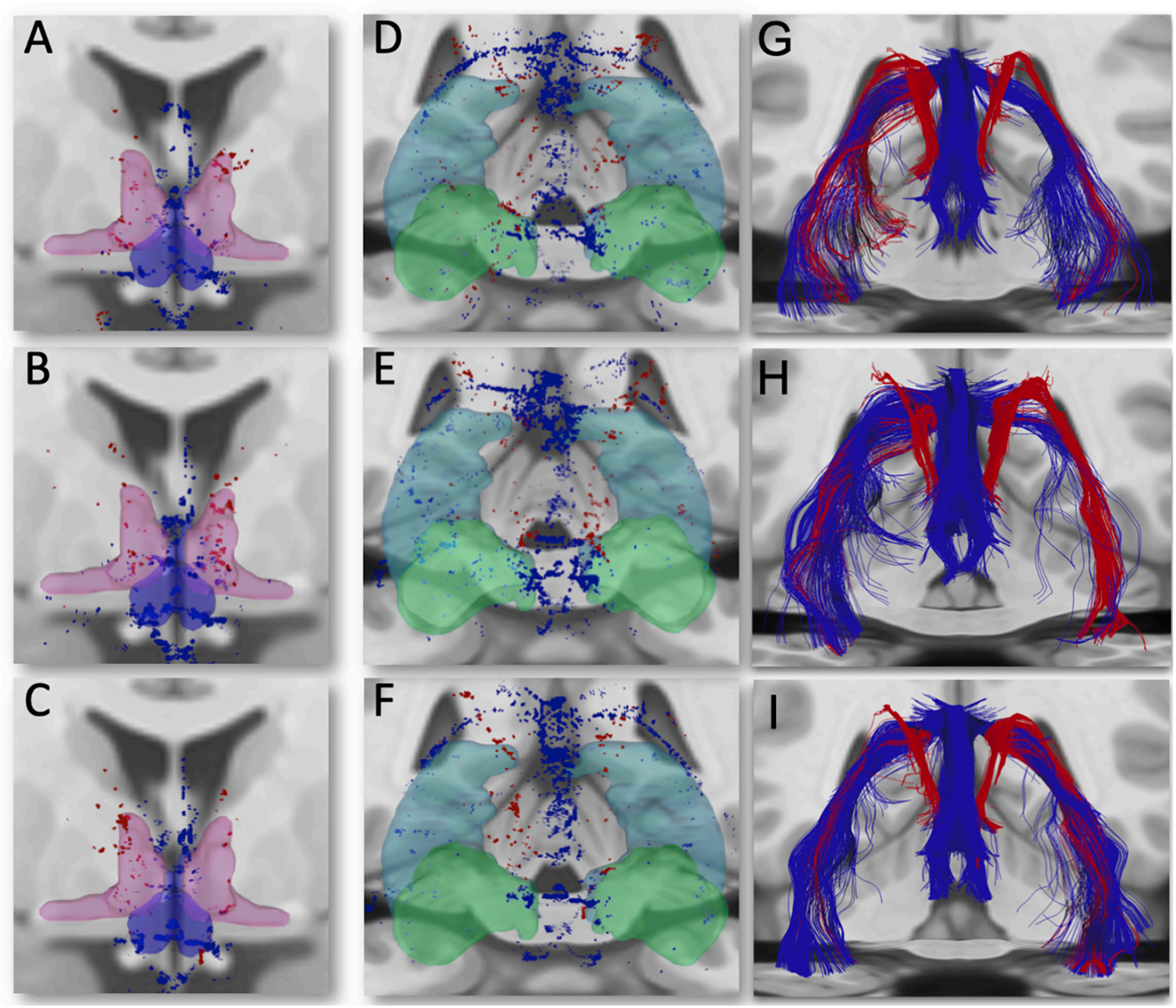

Fig. S3. Fornix and Stria Terminalis Tractography in Three Representative Individuals. Similar to the group analysis, fornix endpoints (blue) were located within the hippocampus (D-F) and within the medial preoptic nucleus and paraventricular hypothalamus (A-C). Stria terminalis endpoints (red) were localized primarily within the dorsal and ventral BST (A-C). Full tractography for fornix (blue) and stria terminalis (red) is shown alongside each individual's endpoint images (G-I). Dilated regions represent BST (magenta, A-C) and paraventricular/preautonomic hypothalamus (blue, A-C) ROIs used previously (Banihashemi et al., 2015) and hippocampus (light blue, D-F) and amygdala (aqua green, D-F) ROIs from the AAL atlas.

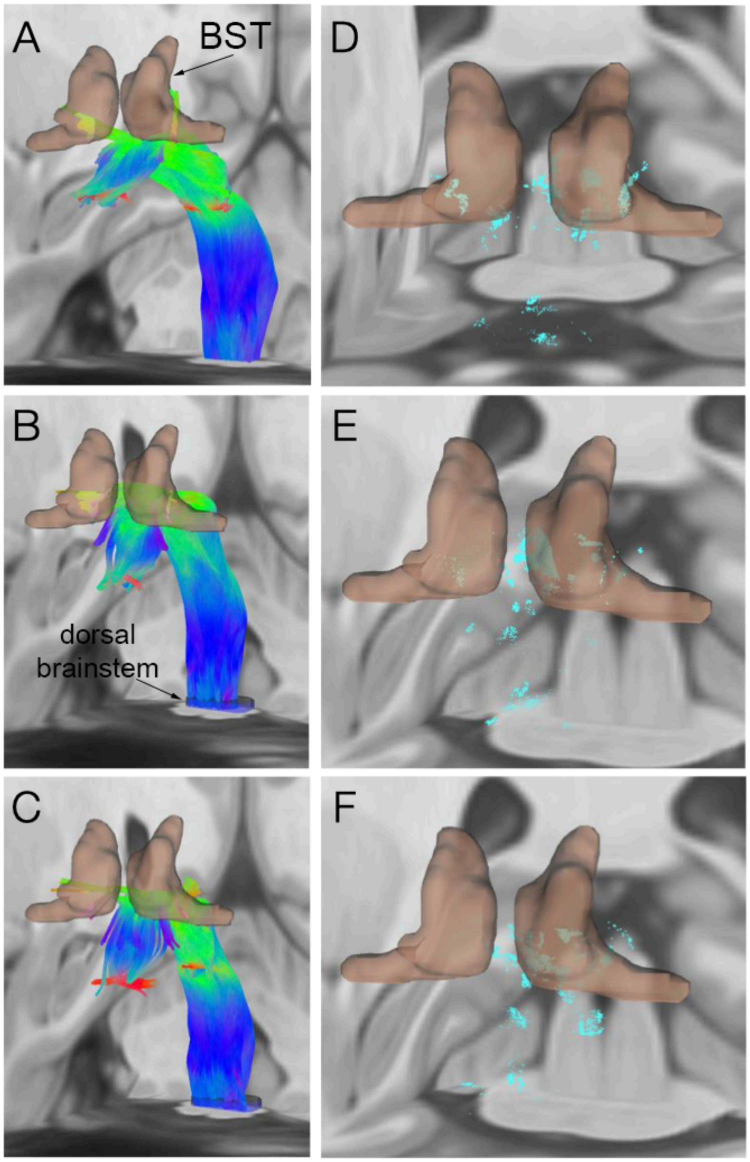

Fig. S4. Medial Forebrain Bundle Tractography in Three Representative Individuals. Tractography within three representative individuals (A-C) was similar to that of the group analysis; medial forebrain bundle endpoints (light blue) were located within the ventral BST (red, D-F). Dilated regions represent the BST (light red, A-F) ROI used previously (Banihashemi et al., 2015) and the dorsal brainstem seed (blue rectangular prism, B-C).

Table S1. Fornix, Stria Terminalis and Medial Forebrain Bundle Tractography Characterization (n=20).

	Fornix (mean)	**Fornix (S.D.)**	**ST (mean)**	**ST (S.D.)**	**MFB (mean)**	**MFB (S.D.)**
Tracts (number)	4097.50	1367.78	343.11	181.37	7367.15	1385.77
Tract Length (mean, mm)	78.82	13.58	68.87	23.41	63.18	3.31
Tract Volume (mm^3)	20302.95	4523.19	2650.43	1285.04	6488.20	538.11
QA (mean)	0.52	0.08	0.40	0.08	0.66	0.11

Results

CTQ Threat Subscale Post-hoc Analyses

Stria Terminalis

Table S2. Regression Results from CTQ Threat Subscale & Stria Terminalis Models.

		Stria Terminalis gFA		
Step	Variable	St. Beta	t	*p*
2	**Emotional Abuse**	-.249	-2.303	**.024***
	Socioeconomic Deprivation	.264	2.432	**.017***
3	**Emotional Abuse**	-.223	-2.024	**.046***
	Socioeconomic Deprivation	.228	1.926	.057
2	**Physical Abuse**	-.362	-3.222	**.002***
	Socioeconomic Deprivation	.340	3.059	**.003***
3	**Physical Abuse**	-.337	-2.805	**.006***
	Socioeconomic Deprivation	.299	2.458	**.016***
2	**Sexual Abuse**	-.215	-2.054	**.043***
	Socioeconomic Deprivation	.247	2.288	**.024***
3	**Sexual Abuse**	-.213	-2.032	**.045**
	Socioeconomic Deprivation	.226	1.912	.059

Step 2 includes age, sex and race, while Step 3 includes adulthood trauma, adulthood SES and negative life events. Bold values indicate significance at $p<0.05$; an asterisk indicates survival of FDR correction (0.05) for three tests.

Medial Forebrain Bundle

Table S3. Regression Results from CTQ Threat Subscale & Medial Forebrain Bundle Models.

		Medial Forebrain Bundle gFA		
Step	Variable	St. Beta	t	*p*
2	**Emotional Abuse**	-.200	-1.809	.074
	Socioeconomic Deprivation	.028	.252	.801
3	**Emotional Abuse**	-.192	-1.675	.097
	Socioeconomic Deprivation	.001	.011	.991
2	**Physical Abuse**	-.281	-2.408	**.018**
	Socioeconomic Deprivation	.085	.738	.462
3	**Physical Abuse**	-.277	-2.193	**.031**
	Socioeconomic Deprivation	.057	.448	.655
2	**Sexual Abuse**	-.175	-1.635	.106
	Socioeconomic Deprivation	.015	.134	.894
3	**Sexual Abuse**	-.167	-1.522	.132
	Socioeconomic Deprivation	-.005	-.038	.970

Step 2 includes age, sex and race, while Step 3 includes adulthood trauma, adulthood SES and negative life events. Bold values indicate significance at $p<0.05$; these did not survive multiple comparison correction (FDR <0.05).

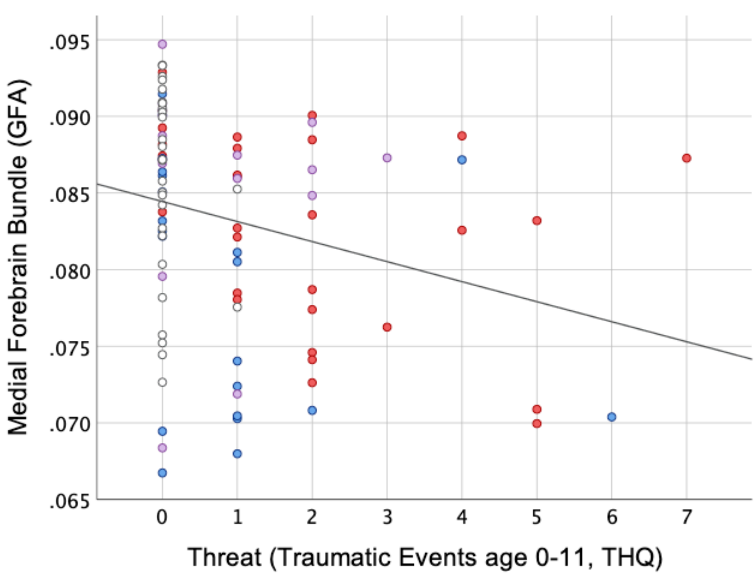

Fig. S5. Relationship between Early Repeated Traumatic Events and Medial Forebrain Bundle Structural Integrity. THQ 0-11 had a significant negative effect on MFB gFA (ß = -0.271; *p* = 0.011). [Removing one outlier (THQ 0-11 = 7) from this model makes the finding more robust (ß = -0.340; *p* = 0.001)]. Scatterplots indicate primary lifetime diagnosis from the SCID-IV (white – no history of affective diagnosis, red – post-traumatic stress disorder (PTSD), blue – depressive disorder, purple – anxiety disorder).

Later Childhood Threat (Repeated Traumatic Events, age 12-17), Deprivation and Visceral White Matter

Stria Terminalis

Both THQ 12-17 and socioeconomic deprivation (SED, maximum parental education level reverse coded) had significant effects on ST gFA; THQ 12-17 had a negative effect (ß = -0.331; p = 0.002), while SED had a positive effect (ß = 0.272; p = 0.010) on ST gFA. Both survived multiple comparison correction and remained significant with the additional adulthood covariates (Table S4, left).

Medial Forebrain Bundle

There were no significant effects of THQ 12-17 or SED on MFB gFA (Table S4, right).

Table S4. Regression Results: Childhood Threat (Repeated Traumatic Events, age 12-17), Socioeconomic Deprivation and Visceral White Matter Models.

		Stria Terminalis gFA			***Medial Forebrain Bundle gFA***		
Step	Variable	St. Beta	t	*p*	St. Beta	t	*p*
1	Age	.060	.571	.570	.087	.835	.406
	Sex	-.146	-1.411	.162	.062	.602	.548
	Race	-.062	-.597	.552	-.126	-1.211	.229
2	Age	.028	.278	.782	.105	.975	.332
	Sex	-.123	-1.255	.213	.057	.551	.583
	Race	.016	.162	.872	-.094	-.887	.377
	THQ 12-17	-.331	-3.268	**.002**	-.177	-1.651	.102
	Socioeconomic Deprivation	.272	2.617	**.010**	.013	.121	.904
3	Age	.010	.085	.932	.118	.951	.344
	Sex	-.137	-1.291	.200	.067	.592	.555
	Race	-.006	-.064	.949	-.105	-.977	.331
	THQ 12-17	-.338	-3.042	**.003**	-.187	-1.573	.119
	Socioeconomic Deprivation	.210	1.859	**.066**	-.026	-.212	.833
	THQ >18	.106	.878	.382	-.023	-.176	.861
	Adulthood SES	-.157	-1.502	.137	-.105	-.937	.351
	Negative Life Events	-.067	-.540	.590	.028	.208	.836

Threat, Deprivation (Neglect) and Stria Terminalis White Matter

To investigate whether opposing relationships of threat and socioeconomic deprivation (SED) on ST structural integrity are robust to other measures of deprivation, we examined the additive effects of threat (abuse or early, repeated traumatic events) and CTQ Deprivation (sum of the CTQ neglect subscales). Regression analyses revealed similar trends of opposing effects of CTQ Threat and CTQ Deprivation on ST structural integrity (gFA). In the CTQ Threat and CTQ Deprivation model, CTQ Threat had a negative effect (ß

= -.375; *p* = .018), while CTQ Deprivation had a positive, although non-significant, effect on ST gFA (ß = 0.213; *p* = 0.179, Table S5). Thus, CTQ Deprivation had a positive relationship with stria terminalis gFA with a small-to-moderate effect size, similar to the parental education level variable used to defined SED in the primary analyses. (VIF)

In the THQ 0-11 model and CTQ Deprivation model, THQ 0-11 had a significant, negative effect on ST gFA (ß = -0.304; *p* = 0.009), while CTQ Deprivation did not have a significant effect on ST gFA (Table S6).

Table S5. Regression Results: Childhood Threat (Abuse), Childhood Deprivation (Neglect) and Stria Terminalis Structural Integrity

		Stria Terminalis gFA				
Step	Variable	St. Beta	t	*p*	Tolerance	VIF
1	Age	.060	.571	.570	.967	1.035
	Sex	-.146	-1.411	.162	.985	1.015
	Race	-.062	-.597	.552	.978	1.022
2	Age	.087	.815	.417	.880	1.136
	Sex	-.177	-1.712	.090	.949	1.053
	Race	-.023	-.221	.826	.955	1.047
	CTQ Threat	-.375	-2.407	**.018**	.417	2.401
	CTQ Deprivation	.213	1.355	.179	.410	2.441
3	Age	.066	.557	.579	.697	1.436
	Sex	-.204	-1.879	.064	.838	1.193
	Race	-.044	-.432	.667	.944	1.059
	CTQ Threat	-.363	-2.324	**.022**	.405	2.469
	CTQ Deprivation	.187	1.182	.240	.393	2.542
	THQ >18	.124	.997	.321	.641	1.559
	Adulthood SES	-.189	-1.834	.070	.932	1.073
	Negative Life Events	-.131	-1.072	.287	.659	1.518

Bold values indicate significance at $p<0.05$

Table S6. Regression Results: Childhood Threat (Repeated Traumatic Events, age 0-11), Childhood Deprivation (Neglect) and Visceral White Matter Analyses

		Stria Terminalis gFA				
Step	Variable	St. Beta	t	*p*	Tolerance	VIF
1	Age	.060	.571	.570	.967	1.035
	Sex	-.146	-1.411	.162	.985	1.015
	Race	-.062	-.597	.552	.978	1.022
2	Age	.069	.647	.519	.880	1.136
	Sex	-.148	-1.443	.153	.954	1.048
	Race	-.019	-.185	.853	.955	1.047
	THQ 0-11	-.304	-2.678	**.009**	.773	1.293
	CTQ Deprivation	.077	.648	.519	.714	1.400
3	Age	.019	.161	.872	.671	1.490
	Sex	-.155	-1.426	.157	.826	1.210
	Race	-.040	-.389	.698	.942	1.062
	THQ 0-11	-.304	-2.499	**.014**	.661	1.514
	CTQ Deprivation	.040	.337	.737	.679	1.472
	THQ >18	.156	1.245	.217	.620	1.612
	Adulthood SES	-.164	-1.585	.117	.910	1.099
	Negative Life Events	-.070	-.560	.577	.622	1.607

Bold values indicate significance at p<0.05

Stria Terminalis Regression Results Stratified by Sex

To investigate whether opposing relationships of threat and socioeconomic deprivation on ST gFA is driven by a particular sex, we examined the same models within females and males separately (Tables S7-8). These analyses reveal similar trends within both males and females, with greater threat associated with less ST gFA and greater SED associated with greater ST gFA. While results are more robust in females, the female sample is better powered to detect these effects.

Table S7. Regression Results Stratified by Sex: Childhood Threat (Abuse), Socioeconomic Deprivation and Stria Terminalis Structural Integrity (gFA)

		Females (n=56)			***Males (n=40)***		
Step	Variable	St. Beta	t	*p*	St. Beta	t	*p*
1	Age	.050	.372	.711	.067	.411	.684
	Sex	-.224	-1.658	.103	.131	.800	.429
2	Age	.069	.466	.643	-.016	-.102	.919
	Sex	-.136	-.984	.330	.135	.889	.380
	CTQ Threat	-.255	-1.617	.112	-.423	-2.622	**.013**
	Socioeconomic Deprivation	.290	1.921	.060	.316	1.933	.061
3	Age	.050	.274	.785	-.063	-.382	.705
	Sex	-.172	-1.265	.212	.051	.304	.763
	CTQ Threat	-.193	-1.228	.225	-.438	-2.620	**.013**
	Socioeconomic Deprivation	.362	2.204	**.032**	.256	1.441	.159
	THQ >18	.187	.968	.338	.062	.373	.712
	Adulthood SES	-.024	-.165	.870	-.167	-.981	.334
	Negative Life Events	-.398	-2.435	.019	.115	.670	.508

Bold values indicate significance at p<0.05

Table S8. Regression Results Stratified by Sex: Childhood Threat (THQ), Socioeconomic Deprivation and Stria Terminalis Structural Integrity (gFA)

		Females (n=56)			***Males (n=40)***		
Step	Variable	St. Beta	t	*p*	St. Beta	t	*p*
1	Age	.050	.372	.711	.067	.411	.684
	Sex	-.224	-1.658	.103	.131	.800	.429
2	Age	.063	.486	.629	.011	.067	.947
	Sex	-.097	-.768	.446	.147	.892	.379
	THQ 0-11	-.451	-3.479	**.001**	-.177	-1.059	.297
	Socioeconomic Deprivation	.309	2.334	**.024**	.201	1.193	.241
3	Age	-.046	-.267	.790	-.029	-.163	.872
	Sex	-.114	-.888	.379	.076	.418	.679
	THQ 0-11	-.414	-2.748	**.008**	-.200	-1.135	.265
	Socioeconomic Deprivation	.378	2.512	**.015**	.128	.700	.489
	THQ >18	.261	1.412	.164	.062	.337	.738
	Adulthood SES	.068	.491	.626	-.207	-1.133	.265
	Negative Life Events	-.259	-1.571	.123	.057	.310	.759

Bold values indicate significance at $p<0.05$

Relationships between Childhood Adversity and Affective Symptoms

Our childhood adversity measures were significantly associated with depression and post-traumatic stress symptoms, and the number of lifetime mood and anxiety/trauma-related diagnoses ranging from small to large effect sizes (see Table 9).

Table S9. Relationships between Childhood Adversity and Affective Symptoms.

		CTQ Threat	THQ 0-11	THQ 12-17	CTQ Deprivation	chSES	BDI-II	PCL-C	Lifetime Diagnoses
CTQ Threat	r	--	.647**	.653**	.756**	.403**	.511**	.571**	.629**
	p	--	.000	.000	.000	.000	.000	.000	.000
THQ 0-11	r	.647**	--	.770**	.454**	.232*	.267**	.408**	.438**
	p	.000	--	.000	.000	.023	.009	.000	.000
THQ 12-17	r	.653**	.770**	--	.551**	.236*	.259*	.281**	.428**
	p	.000	.000	--	.000	.020	.011	.006	.000
CTQ Deprivation	r	.756**	.454**	.551**	--	.399**	.491**	.566**	.621**
	p	.000	.000	.000	--	.000	.000	.000	.000
Deprivation (chSES, reverse coded)	r	.403**	.232*	.236*	.399**	--	.334**	.294**	.371**
	p	.000	.023	.020	.000	--	.001	.004	.000
BDI-II	r	.511**	.267**	.259*	.491**	.334**	--	.852**	.672**
	p	.000	.009	.011	.000	.001	--	.000	.000
PCL-C	r	.571**	.408**	.281**	.566**	.294**	.852**	--	.695**
	p	.000	.000	.006	.000	.004	.000	--	.000
Lifetime diagnoses	r	.629**	.438**	.428**	.621**	.371**	.672**	.695**	--
	p	.000	.000	.000	.000	.000	.000	.000	--

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

References

Banihashemi, L., Sheu, L. K., Midei, A. J. & Gianaros, P. J. (2015). Childhood physical abuse predicts stressor-evoked activity within central visceral control regions. *Social cognitive and affective neuroscience 10*(4), 474-85.

Yeh, F.-C. & Tseng, W.-Y. I. (2011). NTU-90: A high angular resolution brain atlas constructed by q-space diffeomorphic reconstruction. *Neuroimage 58*(1), 91-9.