Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supporting Information

Results

Group Demographic Differences

Psychiatric comorbidity was significantly lower in healthy controls (n = 10, 10.2%) than substance dependent individuals (n = 25, 31.6%), $\chi^2 = 12.68$, $p < .001$. However, if one considers groups by the presence or absence of childhood maltreatment (see Table 1), healthy controls and substance dependent samples w/out CM are not statistically different (5.5% and 8.6% psych history), while healthy controls w/ CM have a significantly higher prevalence than both these groups (24.0%), in addition to a significantly lower prevalence than substance dependent individuals w/ CM (50%). Additionally, when looking at categorical associations, childhood abuse/neglect is more strongly related to psychiatric comorbidity (Cramer's V = .418, $p < .001$) than substance dependence (Cramer's V = .268, p < .001).

Psychiatric Comorbidity Contributions to CM-Related GMV

To assess the possibility that lifetime psychiatric history of major depression and anxiety disorders including lifetime PTSD may have had significant influences on GMV, we examined potential volume differences for the CM-identified ROI in those with versus without a lifetime psychiatric diagnosis for the above conditions. There was no difference in the standardized volumes of the ROI between those with a trauma history minus a psychiatric diagnosis ($n = 41$; $M = -0.34$, $SD = 0.89$) and those with a trauma history plus a psychiatric diagnosis ($n = 28$, $M = -0.45$, $SD = 0.97$), $t(67) = 0.51$, $p = .61$. Additionally, there was no difference in the standardized volumes of the ROI between those with a trauma history minus PTSD ($n = 53$; $M = -0.31$, $SD = 0.89$) and those with a trauma history plus PTSD ($n = 16$; $M = -0.64$, $SD = 1.00$), $t(67) = 1.26$, $p = .21$.

Effect of Group Differences in Education Level on CM- and SD-Related GMV

To assess whether educational differences by group contributed to CM-related GMV differences, we examined analyses both with and without education as a covariate in the model. As is evident in **eFigure 2A**, essentially the same cluster was identified by CM regardless of whether education was included in the model. Cluster size was actually slightly larger (k = 1,137 voxels) when education was included vs. than when it was not (k = 1,087 voxels). The overlap was 1,043 voxels (96.0% overlap with original model; 91.7% overlap with education covariate model).

A similar approach was taken to examine the impact of educational differences on SD-related GMV differences. When education is included as a covariate, only the cluster originating in the mid-cingulate cortex remains, though there is some new activity identified for that cluster (see **eFigure 2B**).

Childhood Trauma Questionnaire as Continuous Regressor

As CTQ cut-off threshold scores can create categorical boundaries that are not always consistent with clinical presentation, it is important to consider continuous scores as well. Categorical classification does have its value though[1]; in the present case, our focus was on moderate – severe CM in order to minimize the rate of false positives. Furthermore, we also sought to validate the CTQ clinical cut-off thresholds in SD samples to establish the utility the CTQ clinical cut-off scores. Nonetheless, we conducted a regression analysis using continuous Childhood Trauma Questionnaire (CTQ) scores (with age, gender, and TICV as covariates). As can be seen in **eFigure 3** and **eTable 3**, CTQ was related to decreased GMV bilaterally in the medial temporal lobe. The left-sided cluster was largely comparable to that observed in the larger model (including substance dependence, psychiatric comorbidity, and age x group as

coavariates; see **eTable 2**), but a right-sided medial temporal lobe cluster also emerged as significant after FDR correction in the continuous CTQ model.

Additional Survival Curve Analyses for Relapse

The Mantel-Cox (or log-rank) chi-square was also computed, in addition to the Generalized Wilcoxon chi-square (of the Kaplan-Meier estimator function). While both tests are considered valid means of examining survival differences, they measure slightly different aspects of the survival curve. The Mantel-Cox test places greater emphasis on later (in time) survival differences. To examine whether there were later survival differences, this test was also computed. Those in the trauma group exhibited a trend to significantly shorter time to relapse (M = 27.6 ± 5.07 days) than those in the no trauma group (M = 42.03 ± 6.08 days), Mantel-Cox χ^2 = 2.85, p = .09.

Discussion

Ways of Measuring Childhood Adversity

Childhood adversity can be assessed in a variety of ways. The National Child Traumatic Stress Network (http://www.nctsn.org/) provides 12 broad categories of childhood traumatic stress: community and school violence, complex trauma, domestic violence, early childhood trauma, medical trauma, natural disasters, neglect, physical abuse, refugee and war zone trauma, sexual abuse, terrorism, and traumatic grief. Notably, the CTQ [2] only assesses a few (emotional abuse and neglect, physical neglect, physical abuse, and sexual abuse) of these 12 categories. Thus, the use of other measures (see e.g., [3]) could provide a more comprehensive assessment of these adverse experiences.

Group Demographic Differences

Apparent group differences are a complex methodological issue for research into childhood adversity. As the Adverse Childhood Experiences study has shown, increasing adverse childhood environments contribute to increased rates of a number of negative health outcomes (both physical and mental; see e.g., [4]). Thus, recruiting adults to study childhood adversity presents unique challenges. It would seem that one is unlikely to recruit an adult sample that experienced childhood abuse/neglect without also recruiting individuals with psychiatric and/or medical problems. The concomitant life circumstances that often accompany both the disorders and the environments that often place one at risk for childhood maltreatment (e.g., low family income, low family educational attainment, single-parent home) [5] present additional challenges. One might expect a complex sociobiological interplay at work that leads to individuals with certain predispositions in certain environments being more likely to use/abuse drugs and less likely to obtain higher education[6]; similar sociobiological factors are often at play in those who develop substance dependence[7].

In the present study, we were able to statistically control for all significant group differences and still show significant hippocampal complex differences related to CM (**eFigure 2A**). The same result was not true of substance dependence; when we included educational attainment as a covariate, many of the significant GMV differences were no longer significant (**eFigure 2B**). This finding is not entirely surprising given that those who developed substance dependence as a result of CM likely dealt with a confluence of adverse factors, some of which were likely not conducive to high educational attainment [7].

eReferences

1. Kraemer HC, Noda A, O'Hara R. Categorical versus dimensional approaches to diagnosis: methodological challenges. *Journal of Psychiatric Research.* 2004;38(1):17-25.
2. Bernstein D, Fink L. *Childhood Trauma Questionnaire: A retrospective self-report questionnaire and manual*. San Antonio, TX: Psychological Corp; 1998.
3. Strand VC, Sarmiento TL, Pasquale LE. Assessment and Screening Tools for Trauma in Children and Adolescents: A Review. *Trauma, Violence, & Abuse.* 2005;6(1):55-78.
4. Felitti VJ, Anda RF. The relationship of adverse childhood experiences to adult medical disease, psychiatric disorders and sexual behaviora: Implications for healthcare. In: Lanius RA, Vermetten E, Pain C, eds. *The impact of early life trauma on health and disease: The hidden epidemic*: Cambridge University Press; 2010:77-87.
5. Brown J, Cohen P, Johnson JG, Salzinger S. A longitudinal analysis of risk factors for child maltreatment: findings of a 17-year prospective study of officially recorded and self-reported child abuse and neglect. *Child Abuse & Neglect.* 1998;22(11):1065-1078.
6. Wickrama KA, Simons LG, Baltimore D. The influence of ethnicity and adverse life experiences during adolescence on young adult socioeconomic attainment: the moderating role of education. *J Youth Adolesc.* 2012;41(11):1472-1487.
7. Galea S, Nandi A, Vlahov D. The Social Epidemiology of Substance Use. *Epidemiologic Reviews.* 2004;26(1):36-52.

eTable 1. Cluster Details for Gray Matter Difference in Relation to Childhood Maltreatment

Region	L/R	BA	*MNI coordinates*			*Z*	*p*	k
			x	*y*	*z*			
Parahippocampal Gyrus	L	28	-20	-16	-26	3.94	<.001	1087
Fusiform Gyrus	L	36	-27	-30	-20	3.89	<.001	
Fusiform Gyrus	L	37	-36	-37	-18	3.33	.001	
Parahippocampal Gyrus	L	28	-24	-10	-29	3.31	.001	
Cerebellum 4/5	L	-	-32	-31	-30	3.18	.001	

eTable 2. Cluster Details for Group Volumetric Difference in Relation to Substance Dependence Diagnosis

Region	L/R	BA	*MNI coordinates*			*Z*	*p*	k
			x	*y*	*z*			
Thalamus	R	-	6	-4	10	5.80	<.001	1337
Mid Cingulate Gyrus	L	31	-6	-31	48	4.56	<.001	3899
Paracenttral Lobule	L	4	-6	-37	69	4.39	<.001	
Mid Cingulate Gyrus	L	31	-5	-21	46	4.04	<.001	
Paracentral Lobule	L	4	-14	-28	69	3.78	<.001	
Paracentral Lobule	-	6	0	-24	60	3.77	<.001	
Supplemental Motor Area	R	6	3	-10	60	3.72	<.001	
Mid Cingulate Gyrus	L	24	-2	-4	46	3.67	<.001	
Supplemental Motor Area	L	6	-12	-10	72	3.61	<.001	
Supplemental Motor Area	R	6	9	-1	60	3.59	<.001	
Supplemental Motor Area	R	6	5	-7	63	3.55	<.001	
Supplemental Motor Area	R	6	12	-6	69	3.59	<.001	
Supplemental Motor Area	L	6	-6	2	63	3.48	<.001	
Supplemental Motor Area	R	24	5	-1	49	3.46	<.001	
Supplemental Motor Area	L	6	-5	6	63	3.44	<.001	
Supplemental Motor Area	L	6	-2	11	52	3.36	<.001	
Middle Frontal Gyrus	L	6	-29	-6	58	3.35	<.001	
Posterior Cingulate Gyrus	L	30	-5	-61	7	4.44	<.001	2166
Cuneus	R	19	14	-91	30	4.20	<.001	
Posterior Cingulate Gyrus	R	30	2	-63	10	3.92	<.001	
Precuneus	R	31	9	-61	25	3.67	<.001	
Posterior Cingulate Gyrus	R	23	6	-57	15	3.37	<.001	
Precuneus	R	7	9	-73	34	3.33	<.001	
Middle Occipital Gyrus	R	18	21	-97	15	3.29	<.001	
Lingual Gyrus	L	19	-17	-54	-2	3.23	.001	
Cuneus	R	19	11	-82	36	2.92	.002	
Vermis 6	R	-	3	-61	-18	2.86	.002	
Lingual Gyrus	L	19	-20	-60	1	2.71	.003	
Fusiform Gyrus	R	19	35	-73	-15	3.65	<.001	1157
Fusiform Gyrus	R	19	26	-73	-17	3.41	<.001	
Fusiform Gyrus	R	37	21	-46	-15	3.34	<.001	
Fusiform Gyrus	R	37	42	-57	-20	3.17	.001	
Cerebellum 6	R	-	23	-60	-15	3.13	.001	
Fusiform Gyrus	R	37	26	-54	-15	2.92	.002	

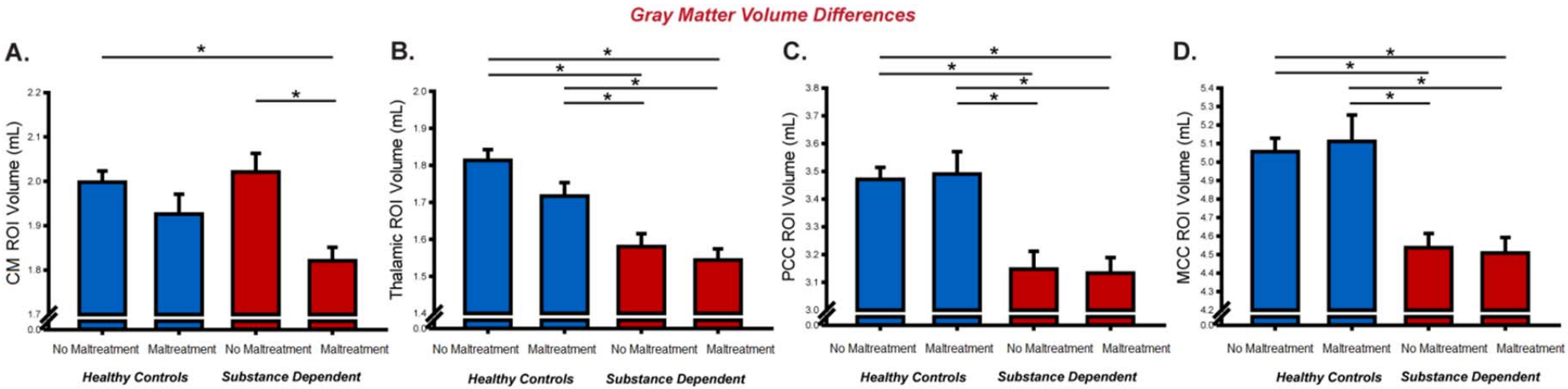
eTable 3. Cluster Details for Gray Matter Difference in Relation to Continuous Childhood Trauma Questionnaire Scores

Region	L/R	BA	*MNI coordinates*			*Z*	*p*	k
			x	*y*	*z*			
Parahippocampal Gyrus	L	28	-21	-18	-24	4.69	<.001	1036
Fusiform Gyrus	L	36	-33	-18	-24	3.73	<.001	
Parahippocampal Gyrus	L	34	-20	5	-26	3.34	<.001	
Fusiform Gyrus	L	20	-35	-10	-29	2.96	.002	
Parahippocampal Gyrus	R	28	23	-18	-24	3.88	<.001	1641
Fusiform Gyrus	R	38	26	12	-45	3.71	<.001	
Parahippocampal Gyrus	R	36	33	-21	-20	3.63	<.001	
Superior Temporal Gyrus	R	38	29	11	-50	3.57	<.001	
Inferior Frontal Gyrus	R	47	26	24	-27	3.48	<.001	
Superior Temporal Gyrus	R	38	29	21	-29	3.38	<.001	
Parahippocampal Gyrus	R	38	30	3	-35	3.02	.001	
Parahippocampal Gyrus	R	36	23	-6	-35	2.98	.001	
Fusiform Gyrus	R	20	21	3	-48	2.98	.001	
Fusiform Gyrus	R	20	30	-3	-42	2.96	.002	
Amygdala	R	-	29	5	-29	2.95	.002	
Inferior Temporal Gyrus	R	38	32	3	-39	2.94	.002	
Fusiform Gyrus	R	35	30	-27	-29	2.92	.002	

Note: Model only contained age, gender, total intracranial volume, and (continuous) Childhood Trauma Questionnaire scores.

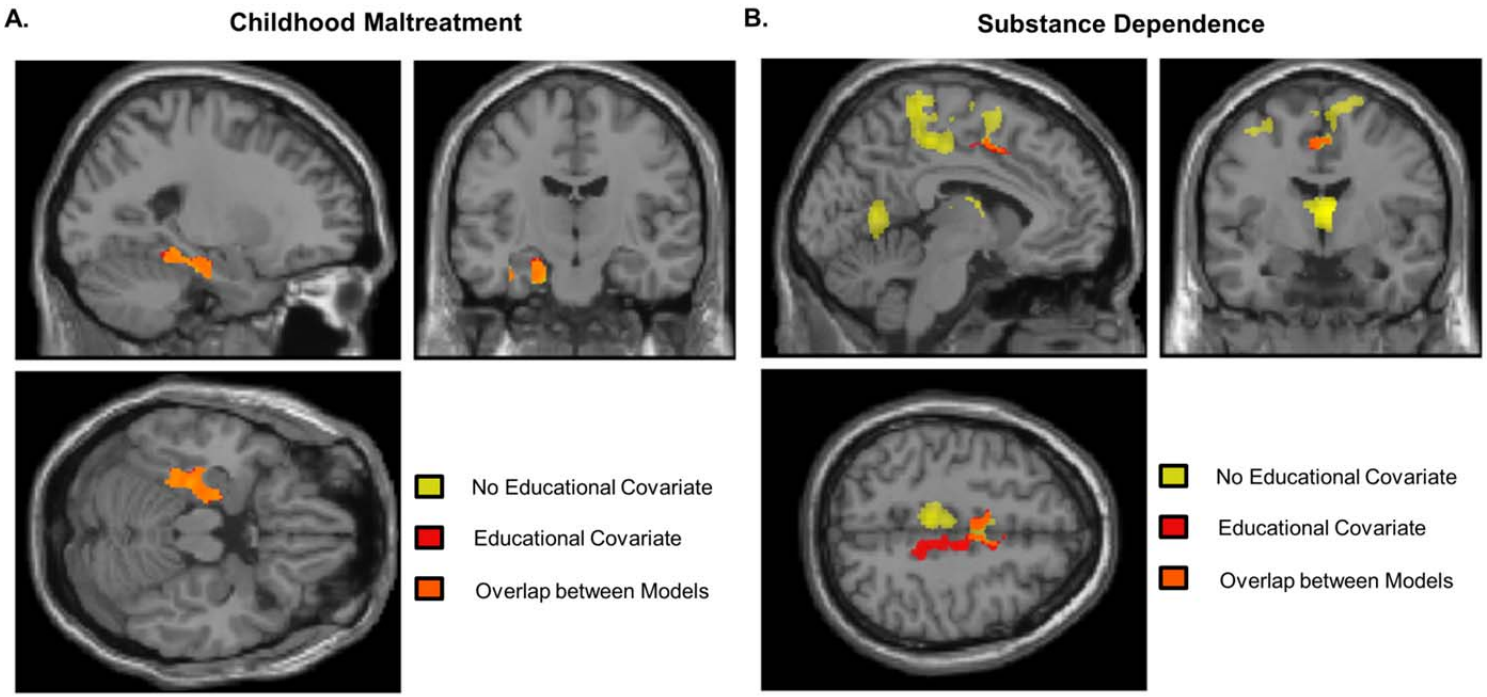
eFigure 1. Main Effects of Childhood Maltreatment and Substance Dependence on Regions of Interest

Volume estimates for the trauma derived (**Panel A**) and substance-dependence derived (**Panels B, C, D**) regions of interest (ROI) are depicted as bar graphs by group (Healthy controls without maltreatment, Healthy controls with maltreatment, Substance dependent subjects without maltreatment, Substance dependent subjects with maltreatment). * Represents significance at $p < .05$ after corrections for multiple comparisons. **Panel A** shows main effect of maltreatment only in an ROI that includes the left hippocampus, parahippocampus, and anterior fusiform gyrus. **Panel B** shows a main effect of substance dependence only in an ROI that includes the thalamus. **Panel C** shows a main effect of substance dependence only in an ROI that is centered on the Posterior Cingulate Cortex (PCC), Cuneus, and Precuneus. **Panel D** shows a main effect of substance dependence only in an ROI that includes the Mid-Cingulate Cortex (MCC) and Supplemental Motor Area (SMA). Note: Right Fusiform cluster related to substance dependence is not shown, but main effects for substance dependence are comparable (to **Panels B, C, D**) for this region.



eFigure 2. Effects of Educational Attainment on Childhood Maltreatment and Substance Dependence Predictions of Gray Matter Volume

Panel A shows childhood maltreatment predicted decreases in gray matter volume (GMV) for a model *not* including educational attainment as a covariate (yellow), one including educational attainment as a covariate (red), and the overlap between the two models (orange). The regions in common between the two models show 96.0% overlap with original model (no educational covariate) and 91.7% overlap with the new model (educational covariate). **Panel B** shows substance dependence predicted decreases in GMV for models *without* (yellow) and *with* (red) educational attainment as a covariate. Overlap is shown in orange.



eFigure 3. Gray Matter Volume Differences Related to Continuous Childhood Trauma Questionnaire Scores

Using whole-brain voxel-based morphometery, childhood maltreatment was associated with lower mean GMV in the left (1036 voxels, maximum: $x = -21$, $y = -18$, $z = -24$) and right (1641 voxels, maximum: $x = 23$, $y = -18$, $z = -24$) medial temporal lobes, after controlling for age, sex, and total intracranial volume. The statistical maps have been heighted thresholded at $p < .005$ ($T \geq 2.61$) and cluster thresholded using topological False Discovery Rate to set the overall error rate to $p < .05$. The regions of lower mean GMV bilaterally are similar to those in the more complex childhood maltreatment model in the main text shown in Figure 1, and with greater breadth. This preliminary model does not statistically control for psychiatric comorbidity with increasing CTQ scores as does the final model presented in the main paper and shown in Figure 1.