Child Abuse, Neural Structure, and Adolescent Psychopathology: A Longitudinal Study

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Objective: Child abuse exerts a deleterious impact on a broad array of mental health outcomes. However, the neurobiological mechanisms that mediate this association remain poorly characterized. Here, we use a longitudinal design to prospectively identify neural mediators of the association between child abuse and psychiatric disorders in a community sample of adolescents.

Method: Structural magnetic resonance imaging (MRI) data and assessments of mental health were acquired for 51 adolescents (aged 13-20; M=16.96; SD=1.51), 19 of whom were exposed to physical or sexual abuse. Participants were assessed for abuse exposure (time 1), participated in MRI scanning and a diagnostic structured interview (time 2), and 2 years later were followed-up to assess psychopathology (time 3). We examined associations between child abuse and neural structure, and identified whether abuse-related differences in neural structure prospectively predicted psychiatric symptoms.

Results: Abuse was associated with reduced cortical thickness in medial and lateral prefrontal and temporal lobe regions. Thickness of the left and right parahippocampal gyrus predicted antisocial behavior symptoms, and thickness of the middle temporal gyrus predicted symptoms of generalized anxiety disorder. Thickness of the left parahippocampal gyrus mediated the longitudinal association of abuse with antisocial behavior.

Conclusion: Child abuse is associated with widespread disruptions in cortical structure, and these disruptions are selectively associated with increased vulnerability to internalizing and externalizing psychopathology. Identifying predictive biomarkers of vulnerability following childhood maltreatment may uncover neurodevelopmental mechanisms linking environmental experience with the onset of psychopathology.

Key words: child abuse, trauma, psychopathology, neural structure, parahippocampal gyrus

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Childhood maltreatment, including physical and sexual abuse, poses a persistent and intractable public health problem that affects upward of 6 million children in the United States each year.[1] Exposure to maltreatment is a robust predictor for the development of chronic psychiatric problems in adolescence and adulthood, including depression, anxiety, and antisocial behavior.[2] Epidemiologic studies indicate that childhood adversity, including maltreatment, is associated with nearly 45% of childhood-onset mental disorders and up to 32% of adult-onset mental disorders.[3] Recent efforts have attempted to identify the neurobiological sequelae of childhood maltreatment, highlighting one important mechanism through which these experiences become developmentally embedded.[4]

The widespread associations of childhood maltreatment with neural structure are now well established.[4] Early neuroimaging studies documented reduced overall brain volume, reduced total gray matter, and specific reductions in the volume of prefrontal cortex in maltreated relative to nonmaltreated children.[5,6] More recent studies have focused on a cortico-limbic network that includes the medial prefrontal cortex (mPFC) and medial temporal lobe.[7-9] The mPFC and medial temporal lobe operate synergistically to initiate and to regulate physiological and behavioral responses to environmental threats.[10]

The medial temporal lobe includes the amygdala, hippocampus, and parahippocampal cortex. The amygdala is involved in perception and associative learning of threat-related stimuli.[11] Although stress-related perturbations in amygdala structure are well-documented in rodents,[10] findings in children and adults exposed to maltreatment are mixed (e.g. [6,7,12,13]). In contrast, functional imaging studies of maltreated children consistently document elevated amygdala response to negative emotional cues, including to facial displays of anger and negative emotional stimuli.[8,14] Reduction in hippocampal volume following stress exposure is well documented in rodents[10] and in both children and adults with childhood maltreatment exposure.[7,9,15,16] Finally, reductions in the volume of the parahippocampal gyrus and other regions of the medial temporal lobe have been consistently observed in previous studies of children and adults with histories of childhood maltreatment.[12,17-19]

Childhood maltreatment also appears to influence the development of brain regions that modulate limbic response to threatening or emotionally evocative stimuli. For example, activity in subdivisions of the mPFC, including orbitofrontal (OFC) and ventromedial (vmPFC) regions, is

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associated with reduced amygdala activity during both automatic (e.g., fear extinction) and effortful (e.g., cognitive reappraisal) forms of emotion regulation.[20] OFC and vmPFC volume and thickness are reduced in children and adults with exposure to physical and sexual abuse.[12,17,21-23] The vmPFC is centrally involved in the inhibition of conditioned fear, and may therefore play an important role in the pathophysiology of fear-related psychopathology, including anxiety disorders.[24] Similarly, the OFC is implicated in both emotion regulation and emotion-based decision making, as evidenced by neuroimaging and lesion studies.[25,26]

In sum, existing work indicates that childhood maltreatment is associated with widespread structural brain changes, specifically in the mPFC and medial temporal lobe. However, we know comparatively little about the implications of these differences for the onset of psychopathology. A crucial goal for translational research is to identify predictive markers of vulnerability that can be used to identify subgroups of maltreated individuals most at risk for future psychopathology.[27] However, extant research is predominantly cross-sectional, and so it is unclear whether structural brain differences identified in previous samples of maltreated children represent predictors or consequences of psychopathology.

To date, only three studies of maltreatment have examined prospective associations between regional gray matter and psychopathology,[15,18,28] and none have focused on neural development during early to middle adolescence. This window of time is associated with a precipitous increase in the incidence of multiple forms of psychopathology, and also with structural brain changes, particularly in the prefrontal cortex.[29] Thus, it is of considerable interest to explore how experiences of maltreatment interact with normative risk processes to create vulnerability to psychopathology during this time.

The aim of the present study was to examine whether alterations in neural structure mediate the prospective association of childhood maltreatment with psychopathology during adolescence. We specifically focus on maltreatment experiences that involve environment threat (physical and sexual abuse), as they most closely meet criteria for trauma as an experience involving threats to one's physical integrity or the physical integrity of others, or sexual violation.[30] Child abuse, neural structure, and psychopathology were measured separately at three distinct time points, allowing us to identify latent markers of vulnerability to psychopathology. To our knowledge, no prior study of mid-adolescence has explored prospective associations among abuse, cortical development, and psychopathology using a three–time-point longitudinal design. We assessed the impact of child abuse on cortical thickness and subcortical volume, and then tested whether these differences mediated the association between abuse exposure and psychiatric symptoms across adolescence.

METHOD

Participants

Participants were initially recruited for a larger study on child maltreatment.[31] At time 1, a total of 169 adolescents (aged 13–17 years; mean = 15.14; standard deviation [SD] = 1.46) provided detailed assessments of family history and maltreatment. Initial recruitment efforts focused on local schools, after-school programs, and medical clinics in neighborhoods in Boston and Cambridge, MA, that were known to have high rates of community violence and poverty. At time 2 (mean time to follow-up = 14.5 months; SD = 9.9 months), a subsample of 59 adolescents was selected to complete a neuroimaging session that included a structural scan, as well as a diagnostic clinical interview. All females were postmenarchal at time of scan. Exclusion criteria included use of psychiatric medication (with the exception of medication for attention-deficit/hyperactivity disorder [ADHD], which was discontinued 24 hours before scanning), use of metal orthodontics or other metal contraindications for magnetic resonance imaging (MRI), claustrophobia, presence of an active substance use disorder or pervasive developmental disorder, and inability to speak English. Nine participants were recruited only for the neuroimaging portion at time 2 (time 1 abuse data were reported at time 2 for these participants).

Finally, at time 3 (mean time to follow-up = 23.1 months; SD = 3.24 months), 51 participants completed additional assessments of mental health (retention rate of 86%). The eight participants lost to follow-up between times 2 and 3 did not differ by abuse status, age, gender, or internalizing psychopathology (all $p > .25$), but had greater symptoms of externalizing psychopathology ($p = .04$). Parents provided informed consent, and adolescents provided assent (or informed consent for those ≥18 years of age). Experimental procedures were approved by the Institutional Review Boards of Boston Children's Hospital and Harvard University.

The analytic sample for the current study includes the 51 adolescents who were assessed at time 2 (time 2; aged 13–20 years; mean = 16.96 years; SD = 1.51 years) and time 3 (aged 15–22 years; mean = 18.92; SD = 1.50 years), 18 with exposure to serious physical or sexual abuse. Sample demographics, by abuse status, are presented in Table 1. Abused adolescents and controls were matched on age, gender, race, IQ, handedness, and socioeconomic status. IQ was assessed at time of scan (time 2) using the matrix reasoning scale of the Wechsler Abbreviated Scale of Intelligence (WASI).

Measures

Child Abuse. Child abuse was assessed using the Childhood Trauma Questionnaire, a 28-item self-report measure (CTQ[32]), and the Childhood Experiences of Care and Abuse (CECA[33]), an interviewer-led measure administered by trained research assistants. The CTQ assesses frequency of emotional, sexual, and physical abuse and has excellent psychometric properties, including test–retest reliability and convergent validity with a structured trauma interview.[32] The CECA assesses numerous aspects of caregiving experiences, including abuse, and has high interrater reliability and agreement between reporters.[34,35] Our primary measure of abuse was a dichotomous variable indicating the presence or absence of exposure. Participants were classified as abused if they reported physical or sexual abuse on the CECA, or scored above a validated threshold on the physical and sexual abuse subscales of the CTQ.[36] Follow-up analyses also assessed abuse severity, calculated as the sum of CTQ physical and sexual abuse subscale items.

Psychopathology. Psychopathology was measured using the Diagnostic Interview Schedule for Children–Version IV (DISC-IV[37]) to assess past-year internalizing (major depressive disorder [MDD], generalized anxiety disorder [GAD], posttraumatic stress disorder [PTSD]) and externalizing (conduct disorder [CD], oppositional defiant disorder [ODD]) symptoms and diagnoses at times 2 and 3. The DISC-IV is a highly structured interview that assesses

TABLE 1 Distribution of Key Study Variables, by Exposure to Childhood Abuse (N = 51)

	Abused (n = 18)		Controls (n = 33)			
	%	n	%	n	χ^2	*p* Value
Female	61.11	11	60.61	20	0.00	.97
Race/Ethnicity					9.56	.09
White	11.11	2	36.36	12		
African American	38.89	7	21.21	7		
Hispanic/Latino	11.11	2	12.12	4		
Asian	0.00	0	12.12	4		
Middle Eastern	0.00	0	3.03	1		
Other/biracial	38.89	7	15.15	5		
Parent Education					2.79	.43
High school or less	22.22	4	15.15	5		
Some college	22.22	4	18.18	6		
College degree	22.22	4	45.45	15		
Graduate school	33.33	6	21.21	7		
Time 2 Diagnosis						
GAD	11.11	2	3.03	1	1.37	.24
MDD	5.56	1	3.03	1	0.19	.66
PTSD	5.56	1	0.00	0	1.87	.17
ODD	5.56	1	3.03	1	0.19	.66
CD	5.56	1	0.00	0	1.87	.17
Time 3 Diagnosis						
GAD	11.11	2	0.00	0	3.82	.05
MDD	16.67	3	3.03	1	3.26	.07
PTSD	5.56	1	0.00	0	1.87	.17
ODD	0.00	0	3.03	1	0.55	.46
CD	0.00	0	0.00	0	0.00	.99
	Mean	**SD**	**Mean**	**SD**	***t* Value**	***p* Value**
Age at Time 3 (y)	18.63	1.62	19.08	1.43	1.02	.31
CTQ Abuse Subscales[a]						
Physical abuse	10.11	4.35	5.13	0.34	6.39	<.01
Sexual abuse	9.00	5.36	5.09	0.53	4.12	<.01
IQ (WASI total score)	100.11	16.89	99.36	13.88	0.17	.87
Time 2 Disorder Symptoms						
GAD	5.11	2.91	3.12	2.32	2.68	.01
MDD	9.50	4.62	6.33	4.56	2.36	.02
PTSD	3.33	4.41	0.61	1.43	3.27	<.01
ODD	5.61	2.83	3.55	2.53	2.67	.01
CD	1.39	1.38	0.85	0.97	1.63	.11
Time 3 Disorder Symptoms						
GAD	4.66	2.00	3.58	2.73	1.49	.14
MDD	8.61	4.02	6.03	4.53	2.02	.05
PTSD	3.44	3.91	0.64	1.82	3.50	<.01
ODD	5.44	2.04	3.36	2.55	2.98	<.01
CD	1.64	1.61	0.83	0.78	2.42	.02

Note: All p values refer to two-sided tests; diagnoses of mental disorders refer to past-year diagnoses. CD = conduct disorder; CTQ = Childhood Trauma Questionnaire; GAD = generalized anxiety disorder; MDD = major depressive disorder; ODD = oppositional defiant disorder; PTSD = posttraumatic stress disorder; WASI = Wechsler Abbreviated Scale of Intelligence.

[a]CTQ measured at time 1 for all but nine participants, who were measured at time 2.

numerous psychiatric disorders, and was conducted by trained research assistants. For participants over the age of 18 years, we administered the young adult version of the DISC, which is appropriate for those up to 24 years. Symptoms of ODD and CD were combined to form an antisocial behavior (ASB) composite by dividing symptoms of each disorder by the number of total possible symptoms, and then summing them. PTSD symptoms were square root transformed before analysis to improve normality. Information on changes in symptoms of psychopathology between times 2 and 3 is presented in Table S1, available online.

Magnetic Resonance Imaging Acquisition

Structural magnetic resonance imaging (MRI) was performed at time 2 using a 3T Siemens Trio scanner located at the Harvard Center for Brain Science. Participants were positioned in a 32-channel head coil, and T1-weighted volumes were acquired using a multi-echo magnetization-prepared rapid acquisition with gradient echo sequence (TR = 2530 milliseconds, TE = 1640−7040 milliseconds, flip angle = 7 degrees, field of view = 220 mm^2, 176 slices, voxel size = 1 mm^3). To reduce motion-related artifacts, a navigator echo was used before scan acquisition, which compared slices to this echo online and permitted up to 20% of slices to be reacquired.

Image Processing

T1-weighted scans were processed using the Freesurfer analysis pipeline (http://surfer.nmr.mgh.harvard.edu), which performs automated cortical reconstruction and volumetric segmentation of the human brain.[38-40] Gray/white and gray/cerebrospinal fluid (CSF) boundaries were constructed using spatial intensity gradients across tissue classes. Segmentation of tissue types was visually inspected for each participant, and manual edits were made as necessary to improve the placing of gray/white and gray/CSF borders. After tissue reconstruction, the cortex was parcellated based on the structure of gyri and sulci.[41] Freesurfer morphometric procedures have been validated against manual measurement[42] and histological analysis,[43] have demonstrated good test−retest reliability across scanner manufacturers and field strengths,[44] and have been widely used in prior samples of adolescents.[45,46]

Neural Regions of Interest

For our cortical thickness analyses, we selected 13 regions of interest (ROIs) based on a careful review of the relevant literature on maltreatment exposure and neural structure; baseline associations between childhood abuse and neural structure in the full sample are reported elsewhere.[47] Prior structural MRI studies have found associations with maltreatment exposure in the vmPFC,[12,17,22,23,48,49] lateral OFC,[17,19] anterior and posterior cingulate cortices,[17,23,49] ventrolateral PFC (including inferior frontal gyrus [IFG]),[19] dorsolateral PFC (including middle and superior frontal gyri),[17,22,23,49] insular cortex,[19,23] parahippocampal gyrus,[19] temporal pole,[17,22] and lateral temporal cortex (spanning inferior, middle, and superior temporal gyri).[12,17,19,22,23,48] Based on these prior pediatric morphometry findings and the volumetric maltreatment meta-analysis by Lim *et al.*,[19] we selected ROIs in these prefrontal and temporal cortical regions.

These ROI labels were derived from the Desikan−Killiany atlas in Freesurfer,[41] and defined according to the automated parcellation labels as follows: vmPFC (average of left and right orbitofrontal regions); left and right lateral OFC (average of lateral OFC, frontal pole and pars orbitalis for each hemisphere separately); left and right inferior frontal gyrus (average of pars opercularis and pars triangularis for each hemisphere separately); anterior cingulate cortex (average of left and right rostral and caudal anterior cingulate); posterior cingulate cortex (average of left and right posterior cingulate and isthmus cingulate); left and right middle frontal gyrus (average of rostral middle frontal and caudal middle frontal for each hemisphere separately); medial superior frontal gyrus (average of left and right superior frontal); left and right insula cortex; left and right temporal pole; left and right parahippocampal gyrus; and left and right inferior, middle, and superior temporal gyri.

For our subcortical gray matter volume (GMV) analyses, prior studies found maltreatment to be associated with the hippocampus[7,9,50] and amygdala.[7,9,19,22] Consequently, based on our review of the literature, we selected ROIs derived from the FreeSurfer automated segmentation procedures that corresponded to these regions.

Statistical Analyses

Mediation analyses were performed using standard procedures based on ordinary least squares regression.[51] First, we examined the total effect of child abuse on psychiatric symptoms and diagnoses (*c* path). Next, we examined associations between child abuse and neural structure across 24 ROIs (*a* path). False discovery rate (FDR) correction was applied to reduce type 1 error ($p < .05$). Next, we examined associations between cortical thickness and psychopathology at time 3 (*b* path). For this stage, we focused only on ROIs that were significantly associated with abuse (significant *a* path), and corrected for multiple comparisons. Next, if *a, b,* and *c* paths were significant, we tested the indirect effects of abuse on psychopathology through neural structure using the *sgmediation* program in Stata 13.0 (StataCorp, College Station, TX). Using the *sgmediation* program, boot-strapped, bias-corrected CIs were estimated (5000 resamples) for the indirect effect, which are appropriate for small samples and non-normality in the standard errors of indirect effects.[52] A 95% CI that excludes zero indicates a significantly mediated effect. Finally, we conducted analyses to test whether neural structure mediated the association between abuse and change in psychopathology between times 2 and 3. Time 2 psychopathology was entered as a covariate in all prior mediation analyses with a significant indirect effect. All analyses controlled for age and gender, and those predicting cortical thickness additionally controlled for parent education, given its known associations with neural structure.[53]

RESULTS

Child Abuse and Psychopathology

Abused adolescents reported significantly greater symptoms of ASB ($\beta = 0.19$, $p = .01$), MDD ($\beta = 2.71$, $p = .04$), and PTSD ($\beta = 1.09$, $p < .001$) at time 3, adjusting for age and gender. No association was observed between abuse and GAD ($\beta = 1.06$, $p = .16$). At follow-up, abused adolescents were marginally more likely to have a diagnosis of GAD ($\chi^2 = 3.82$, $p = .05$) and MDD ($\chi^2 = 3.26$, $p = .07$). However, no differences in diagnoses were found for ODD, CD, or PTSD. This lack of differences was likely due to overall low rates of diagnoses in our sample (Table 1), and thus subsequent analyses focused on symptoms of psychiatric disorders reported in the diagnostic structured interview.

Child Abuse and Neural Structure

We examined group differences in brain structure among adolescents exposed to child abuse, compared to controls. Regression coefficients, standard errors, and significance values for all cortical and subcortical regions are presented in Table 2. After FDR correction, reduced cortical thickness was observed for abused adolescents in vmPFC, right inferior frontal gyrus, left and right parahippocampal gyri, right inferior temporal gyrus, and right middle temporal gyrus. For all significant regions, severity of abuse across the whole sample was linearly related to the degree of cortical thinning (all $p < .05$). No association was found between abuse and volume of the amygdala and hippocampus.

TABLE 2 Coefficients, Standard Errors, and Significance Values for Associations Between Child Abuse and Neural Structure

	Abuse Exposure		
Characteristic	**β**	**SE**	***p* Value**
Cortical Thickness (mm)			
Ventromedial PFC	−0.12	0.03	**.001**
Left lateral OFC	−0.05	0.05	.040
Right lateral OFC	−0.10	0.05	.068
Left inferior frontal gyrus	−0.06	0.04	.083
Right inferior frontal gyrus	−0.12	0.04	**.002**
Anterior cingulate cortex	−0.02	0.05	.712
Posterior cingulate cortex	−0.01	0.04	.822
Left middle frontal gyrus	−0.05	0.03	.161
Right middle frontal gyrus	−0.05	0.03	.165
Medial superior frontal gyrus	−0.08	0.04	.039
Left insular cortex	−0.04	0.05	.412
Right insular cortex	0.03	0.04	.475
Left temporal pole	−0.20	0.08	.020
Right temporal pole	0.00	0.11	.951
Left parahippocampal gyrus	−0.24	0.08	**.005**
Right parahippocampal gyrus	−0.24	0.07	**.001**
Left inferior temporal gyrus	−0.09	0.04	.019
Right inferior temporal gyrus	−0.09	0.03	**.004**
Left middle temporal gyrus	−0.02	0.04	.682
Right middle temporal gyrus	−0.11	0.04	**.008**
Left superior temporal gyrus	−0.05	0.04	.263
Right superior temporal gyrus	−0.08	0.04	.069
Subcortical Volume (mm^3)			
Amygdala	−25.58	55.44	.647
Hippocampus	−125.29	45.31	.374

Note: β Values are unstandardized. Boldface data are significant after false discovery rate correction. SE = standard error.

Cortical Thickness and Psychopathology

Next, we examined associations between thickness of neural structures associated with abuse and psychopathology (Table 3; in Table S2 [available online], we present associations between neural structure and psychopathology for all ROIs). In addition to the covariates described above, analyses controlled for time in months between scanning and follow-up, and significance values were FDR corrected. Thickness of the left and right parahippocampal gyrus predicted ASB symptoms, and thickness of the middle temporal gyrus predicted GAD symptoms.

Mediation Analyses

Finally, for associations with significant *a*, *b*, and *c* paths, we tested indirect effects of abuse on psychopathology through neural structure. Thickness of the left parahippocampal gyrus significantly mediated the association of abuse and ASB symptoms (CI: 0.01, 0.18) (34% of the total effect was mediated). In contrast, no mediation of the right parahippocampal gyrus and ASB was observed (CI: −0.02, 0.15).

The above mediation analyses were performed without controls in place for time 2 symptoms of psychopathology. Thus, these mediations may simply reflect existing associations between cortical thickness measured at time 2 and symptoms of psychopathology at time 2. To address this possibility, we assessed whether cortical thickness mediated the association between child abuse and change in psychopathology across adolescence by including a control for symptoms of psychopathology at time 2. After including this control in every path, the indirect effect of child abuse on ASB through left parahippocampal gyrus thickness remained significant (CI: 0.00, 0.16) (Figure 1).

DISCUSSION

Childhood maltreatment is strongly associated with risk for psychopathology,[2] and prior cross-sectional research has been limited by an inability to disentangle the associations of maltreatment and psychopathology on neural structure. Here, we provide evidence for a potential neural pathway linking exposure to child abuse with psychopathology. Specifically, we find that child abuse is associated with reduced cortical thickness in numerous regions of lateral and medial PFC and temporal cortex. Reduced thickness of the parahippocampal gyrus is prospectively associated with increased vulnerability to antisocial behavior 2 years later.

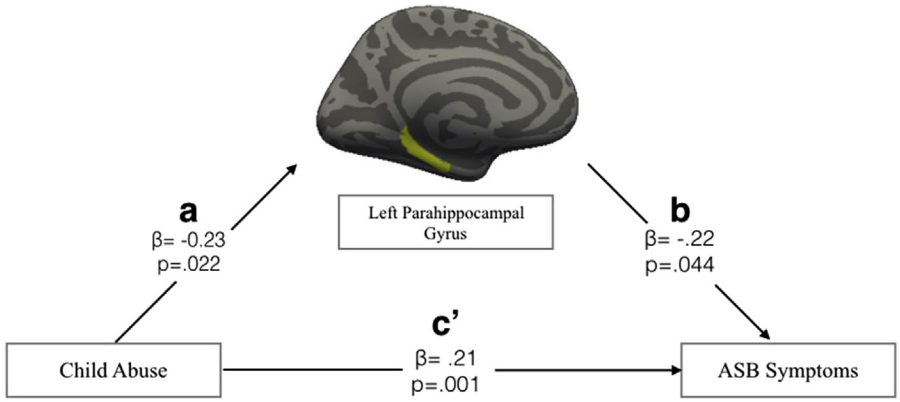
Abuse-related abnormalities in the vmPFC observed here are consistent with prior studies of maltreated children and adolescents.[9,12,17,22,23] The vmPFC is engaged during fear

TABLE 3 Associations Among Thickness of Regions of Interest Sensitive to Abuse, and Symptoms of Psychopathology at Time 3

	GAD			MDD			PTSD			Antisocial Behavior		
	β	**SE**	***p* Value**	**β**	**SE**	***p* Value**	**β**	**SE**	***p* Value**	**β**	**SE**	***p* Value**
VmPFC	5.83	2.84	.046	1.99	5.13	.700	−1.59	1.22	.199	−0.29	0.27	.298
Right IFG	3.89	2.82	.174	4.22	2.94	.397	−1.74	1.17	.145	0.10	0.26	.703
Right ITG	4.67	3.15	.145	3.71	5.55	.507	−1.16	1.34	.390	0.13	0.30	.662
Right MTG	7.79	2.49	**.003**	8.57	4.58	.068	−0.46	1.15	.692	0.29	0.25	.252
Left PHG	−0.60	1.26	.636	−4.87	2.07	.023	−1.13	0.50	.029	−0.35	0.10	**.001**
Right PHG	1.62	1.51	.289	−3.63	2.59	.168	−1.02	0.62	.108	−0.33	0.12	**.016**

Note: Boldface data are significant after false discovery rate correction within each psychopathology scale. GAD = generalized anxiety disorder; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; MDD = major depressive disorder; MTG = middle temporal gyrus; PHG = parahippocampal gyrus; PTSD = posttraumatic stress disorder; SE = standard error; vmPFC = ventromedial prefrontal cortex.

FIGURE 1 Variations in left parahippocampal gyrus thickness mediate the association between child abuse and antisocial behavior (ASB) at time 3. Note: The significance of the indirect effect was tested using a bootstrapping approach and was controlled for age at scan, gender, parent education, time 2 ASB symptoms, and time between scan and follow-up. c′ = direct effect of abuse on ASB.



extinction and the suppression of negative emotion,[20] and is thought to modulate and inhibit the amygdala during these processes.[20,24] Prior studies have linked vmPFC structure to GAD in both healthy adolescents[54] and clinical samples.[55] It is possible that this reflects a lag in typical age-related synaptic pruning, and that maltreated adolescents may be less able to recruit the vmPFC in the service of emotional control, resulting in greater anxiety symptoms. Further research is needed to examine the role of the vmPFC as a neurobiological mediator linking childhood maltreatment with psychopathology.

In addition, child abuse was associated with reduced cortical thickness in the temporal lobe, specifically the middle temporal gyrus and parahippocampal gyrus. Notably, our analyses revealed that thickness of the left parahippocampal gyrus mediated the association of child abuse and ASB symptoms, with and without controlling for baseline symptoms. The parahippocampal gyrus has extensive neuroanatomical connections to regions involved in memory and emotion processing and regulation, including the hippocampus, amygdala, and OFC.[56,57] Furthermore, it has been implicated in the emotional enhancement of memory representations.[58,59] A recent meta-analysis of whole-brain, voxel-based morphometry studies identified maltreatment-related reductions in parahippocampal gyrus volume across multiple studies,[19] a finding corroborated by subsequent research.[18] Moreover, changes in the structure of the medial temporal lobe, including the parahippocampal gyrus, have been observed in both cross-sectional and prospective studies of early adversity.[7,60] In sum, our findings reflect the impact of abuse on cortico-limbic areas implicated previously in behavioral and emotional control functions. The medial temporal lobe and interconnected limbic structures are involved in the pathophysiology of both internalizing and externalizing psychopathology, including ODD/CD,[61] ASB,[62] and depression,[63] potentially because they reflect underlying deficits in emotion processing or regulation that are relevant to these disorders.

Notably, we found no associations between child abuse and volume of the amygdala and hippocampus. Altered hippocampal volume has been observed in prior samples of maltreated children and adolescents,[7,15,22] although others have found no association.[12,13] Maltreatment-related differences in amygdala structure remain decidedly mixed,[4] despite wide support in the rodent literature.[10] These divergent findings may be accounted for by differences in developmental timing of maltreatment, co-occurrence of psychopathology, age at scan or MRI analysis type (whole-brain versus region-based approach), explored in prior studies. For example, a recent study found peak sensitivity of exposure to maltreatment on amygdala volume in pre-adolescent children aged 10 to 11 years.[64]

This study had notable strengths, including its longitudinal design, the use of a structured clinical interview to assess symptoms and diagnoses of psychiatric disorders, and the use of cortical thickness to index neural structure, complementing and extending previous volumetric approaches. Nevertheless, several limitations should be noted. First, our sample size was small, which is important when considering the null findings in regions that have been previously identified as sensitive to abuse. Second, rates of psychiatric diagnosis in our sample were quite low, restricting our analyses to focus on symptoms of psychopathology instead of rates of diagnosis. It may be that our use of community recruitment techniques resulted in us identifying a particularly resilient sample. It is also possible that the exclusion of adolescents taking psychiatric medication might remove those with more severe psychopathology, although this would likely lead to conservative estimates of the effects of abuse. Third, future research will be needed to assess whether structural markers can predict the onset of a psychiatric diagnosis. Fourth, our use of a multiple ROI approach required stringent multiple comparison correction, and therefore only the most robust associations may have emerged in our analysis. Fifth, our assessments of abuse relied on retrospective reporting,

which may be prone to recall bias. Sixth, our control group had a higher proportion of adolescents of white ethnicity than our abused group, which should be addressed in future studies. Finally, future research should focus more specifically on emotional abuse and neglect, other forms of childhood maltreatment that are significantly associated with risk for psychopathology and neural structure.[65-67] Examining the differential impact of multiple forms of childhood maltreatment, as well as variations in timing, chronicity, and severity of exposure, represent important goals for future research. This work should also examine the impact of these maltreatment variables across males and females, highlighting potential sex differences in neural structure and psychopathology.

Adolescence is a uniquely vulnerable window for the onset of internalizing and externalizing psychopathology,[29] and child abuse is a known risk factor for myriad psychiatric disorders across the lifespan.[2] Our findings suggest that structural changes within the medial temporal lobe may be one pathway underlying this association. Recent theoretical approaches have highlighted the need to identify intermediate neural phenotypes that predict risk for later psychopathology, raising the possibility of targeted intervention approaches for those most at risk.[27] The present study contributes to this objective by suggesting that this latent vulnerability in adolescence may be indexed by measures of neural structure. &

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TABLE S1 Change in Symptoms of Psychopathology Between Time 2 and Time 3

	GAD		MDD		PTSD		Antisocial Behavior	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Abused (n = 18)	−0.44	2.64	−0.89	4.50	0.21	1.39	−0.00	0.34
Controls (n = 33)	0.45	2.58	−0.30	3.39	−0.05	1.08	−0.02	0.22
Total sample (n = 51)	0.14	2.61	−0.51	3.78	0.04	1.19	−0.01	0.27

Note: Change scores are calculated by subtracting time 2 symptoms from time 3 symptoms. Thus, positive values for the mean indicate increased psychopathology over time; negative values indicate decreased psychopathology over time. GAD = generalized anxiety disorder; MDD = major depressive disorder; PTSD = posttraumatic stress disorder.

TABLE S2 Associations Among All Regions of Interest and Symptoms of Psychopathology at Time 3

	GAD			MDD			PTSD			Antisocial Behavior		
	β	SE	*p* Value	β	SE	*p* Value	β	SE	*p* Value	β	SE	*p* Value
VmPFC	5.830	2.840	.046	1.990	5.130	.700	−1.590	1.220	.199	−0.290	0.270	.298
L Lateral OFC	3.110	2.190	.160	1.350	3.866	.729	−1.537	0.908	.097	−0.193	0.205	.350
R Lateral OFC	4.069	1.935	.041	3.337	3.472	.341	−1.625	0.813	.052	−0.128	0.186	.494
Left IFG	7.979	2.783	**.006**	7.496	5.112	.149	−0.876	1.258	.490	0.018	0.279	.948
Right IFG	3.890	2.820	.174	4.220	2.940	.397	−1.740	1.170	.145	0.100	0.260	.703
Anterior cingulate	5.908	2.065	**.006**	7.970	3.697	.036	0.758	0.931	.420	0.579	0.189	**.004**
Posterior cingulate	6.016	2.721	.032	13.755	4.520	.004	0.576	1.195	.632	0.397	0.258	.130
L MFG	5.373	3.434	.125	2.708	6.088	.659	−1.513	1.458	.305	−0.095	0.325	.771
R MFG	6.939	3.169	.034	7.696	5.652	.180	−1.739	1.370	.211	0.029	0.307	.926
Medial SFG	5.703	2.669	.038	5.909	4.765	.221	−1.631	1.146	.161	0.096	0.258	.711
L insular cortex	1.909	2.478	.445	5.264	4.246	.221	−0.076	1.043	.942	0.035	0.230	.878
R insular cortex	8.239	2.671	**.003**	11.623	4.782	.019	0.592	1.225	.631	0.115	0.270	.673
L temporal pole	0.830	1.325	.534	1.060	2.299	.647	−0.692	0.548	.213	−0.063	−0.063	.611
R temporal pole	−0.042	0.974	.966	1.307	1.674	.439	−0.009	0.407	.983	0.104	0.089	.246
L PHG	−0.600	1.260	.636	−4.870	2.070	.023	−1.130	0.500	.029	−0.350	0.100	**.001**
R PHG	1.620	1.510	.289	−3.630	2.590	.168	−1.020	0.620	.108	−0.330	0.120	.016
L ITG	5.670	2.819	.050	7.069	4.982	.163	−0.743	1.226	.547	0.205	0.270	.451
R ITG	4.670	3.150	.145	3.710	5.550	.507	−1.160	1.340	.390	0.130	0.300	.662
L MTG	7.566	2.336	**.002**	6.968	4.361	.117	0.354	0.330	.745	0.424	0.231	.073
R MTG	7.790	2.490	**.003**	8.570	4.580	.068	−0.460	1.150	.692	0.290	0.250	.252
L STG	2.616	2.621	.323	1.663	4.578	.718	−0.474	1.106	.670	0.160	0.243	.515
R STG	5.315	2.455	.036	6.726	4.349	.129	−0.345	1.077	.750	0.113	0.237	.635
Amygdala	−0.001	0.002	.692	−0.002	0.004	.656	−0.001	0.001	.453	0.000	0.000	.349
Hippocampus	0.001	0.001	.227	−0.001	0.001	.587	−0.001	0.000	.099	0.000	0.000	.021

Note: Boldface data are significant after false discovery rate correction within each psychopathology scale. GAD = generalized anxiety disorder; IFG = inferior frontal gyrus; ITG = inferior temporal gyrus; MDD = major depressive disorder; MFG = middle frontal gyrus; MTG = middle temporal gyrus; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus; PTSD = posttraumatic stress disorder; STG = superior temporal gyrus.