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Amygdala, Hippocampus, and Ventral Medial Prefrontal Cortex Volumes Differ in Maltreated Youth with and without Chronic Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is considered a disorder of recovery where individuals fail to learn and retain extinction of the traumatic fear response. In maltreated youth, PTSD is common, chronic, and associated with comorbidity. Studies of extinction-related structural volumes (amygdala, hippocampus, anterior cingulate cortex (ACC), and ventral medial prefrontal cortex (vmPFC)) and this stress diathesis, in maltreated youth were not previously investigated. In this cross-sectional study, neuroanatomical volumes associated with extinction in maltreated youth with PTSD ($N = 31$), without PTSD ($N = 32$), and in non-maltreated healthy volunteers ($n = 57$) were examined using magnetic resonance imaging. Groups were sociodemographically similar. Participants underwent extensive assessments for strict inclusion/exclusion criteria and DSM-IV disorders. Maltreated youth with PTSD demonstrated decreased right vmPFC volumes compared with both maltreated youth without PTSD and non-maltreated controls. Maltreated youth without PTSD demonstrated larger left amygdala and right hippocampal volumes compared with maltreated youth with PTSD and non-maltreated control youth. PTSD symptoms inversely correlated with right and left hippocampal and left amygdala volumes. Confirmatory masked voxel base morphometry analyses demonstrated greater medial orbitofrontal cortex gray matter intensity in controls than maltreated youth with PTSD. Volumetric results were not influenced by psychopathology or maltreatment variables. We identified volumetric differences in extinction-related structures between maltreated youth with PTSD from those without PTSD. Alterations of the vmPFC may be one mechanism that mediates the pathway from PTSD to comorbidity. Further longitudinal work is needed to determine neurobiological factors related to chronic and persistent PTSD, and to PTSD resilience despite maltreatment.

INTRODUCTION

Child maltreatment is a serious public health problem that leads to psychopathology (De Bellis and Zisk, 2014). Abuse and neglect are developmental traumas that are interpersonal, enduring, co-occurring, and associated with high rates of pediatric and adult posttraumatic stress disorder (PTSD). Although many cases of youth with maltreatment-related PTSD recover with time, the limited published longitudinal data suggest that chronic PTSD is seen in 20–30% of maltreated youth identified by Child Protective Services (CPS) (Famularo et al, 1993, 1996; McLeer et al, 1998; McLeer and Ruggiero, 1999).

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Children who suffer from PTSD generalize fear to traumatic stimuli, experience difficulty extinguishing fear associations, and exhibit anxiety-related behaviors based on traumatic reminders (De Bellis and Zisk, 2014). The influence of early life trauma on the brain structures implicated in extinction learning (the ability to inhibit the fear response in relationship to traumatic reminders) and extinction recall (the ability to maintain this new learning after a time period) in maltreated youth who suffer from PTSD, compared with those without PTSD, may elucidate neuro-mechanisms of the stress diathesis that leads to chronic PTSD vs those without PTSD.

In adults, PTSD is considered a disorder of recovery, where individuals who suffer from trauma fail to learn extinction and extinction recall of the fear response elicited by traumatic reminders, an active process of acquiring and maintaining new learning (Yehuda and LeDoux, 2007; Milad and Quirk, 2012; Pitman et al, 2012). The key brain structures involved in these processes are the amygdala, hippocampus, anterior cingulate cortex (ACC), and ventral medial prefrontal cortex (vmPFC). These brain regions are rich in glucocorticoid

receptors, are stress-sensitive (Lupien et al, 2009), and the connections between these cortical and limbic regions are tightly regulated in humans and primates (Beckmann et al, 2009). Effective regulation of the amygdala leads to successful extinction learning and extinction recall in the context of trauma stimuli (Milad and Quirk, 2012); and may be markers of resilience to PTSD following maltreatment.

Although neuroanatomical studies of maltreatment are limited, adults with PTSD secondary to maltreatment have smaller hippocampal (Thomaes et al, 2010), ACC (Kitayama et al, 2006; Thomaes et al, 2010), and vmPFC volumes (Thomaes et al, 2010) compared with adults without maltreatment. Healthy adults with maltreatment histories also demonstrated smaller hippocampal (Dannlowski et al, 2012; Teicher et al, 2012), ACC (Cohen et al, 2006; Dannlowski et al, 2012; van Harmelen et al, 2010), and vmPFC volumes (Dannlowski et al, 2012). The inverted U-shaped model predicts that, although acute stress might be adaptive through acute adrenergic and cortisol effects that promote increased dendritic and apical spines along with vigilance and learning, chronic stress leads to neural damage and smaller brain structures (Lupien et al, 2009). The adult data support structural abnormalities in some extinction-related structures of adults with PTSD and those resilient to adult PTSD from maltreatment. Thus, investigations of structural brain differences in maltreated youth may elucidate these developmental mechanisms.

Unlike findings in adult PTSD, maltreated youth with PTSD show no anatomical differences in stress-sensitive hippocampal or amygdala structures, either cross-sectionally (Carrion et al, 2001; De Bellis et al, 2002) or longitudinally (De Bellis et al, 2001). However, the majority of studies show higher basal cortisol levels in maltreated youth compared with non-maltreated youth (De Bellis and Zisk, 2014), which may lead to damage in these structures in some individuals later in life. Smaller prefrontal cortex (PFC) volumes were not seen in maltreated children with PTSD, after controlling for smaller cerebral volumes (De Bellis et al, 1999, 2002), but attenuation of frontal lobe asymmetry (Carrion et al, 2001), larger (Richert et al, 2006; Carrion et al, 2009) and smaller gray matter volumes in ventral PFC were reported in youth with PTSD (Keding and Herringa, 2014) and maltreatment (Hanson et al, 2010) compared with non-maltreated controls. In these studies, it was not known whether brain differences were due to PTSD or maltreatment. Additionally, peer-reared juvenile monkeys showed larger dorsomedial prefrontal and dorsal ACC and no differences in CSF cortisol levels or hippocampal volumes compared with mother-reared monkeys, indicating that stress-sensitive brain structures can increase during atypical primate development (Spinelli et al, 2009). Nevertheless, it is not known whether these differences in brain structures are compensatory adaptive responses or markers of increased risk.

Therefore, this study examined the brain structures associated with extinction in maltreated youth with and without PTSD, noting that these structures are also involved in other functions (emotional regulation, decision-making, and reward processes) that are impaired in PTSD (Schoenbaum and Shaham, 2008; Pitman et al, 2012). Identifying the neuro-mechanisms that lead to PTSD resilience despite the severe allostatic load from childhood maltreatment may lead to previously unidentified targets for

intervention designed to diminish the enduring effects of maltreatment. We examined key brain structural volumes involved in extinction (amygdala, hippocampus, ACC, and vmPFC) in three groups of medically healthy youth: maltreated youth with PTSD, maltreated youth without PTSD, and healthy non-maltreated volunteers. We hypothesized that maltreated youth with PTSD would show smaller vmPFC and ACC volumes compared with healthy volunteers and maltreated youth without PTSD; while maltreated youth without PTSD youth would show larger amygdala, hippocampus, ACC, and vmPFC compared with both healthy volunteers and PTSD youth. Planned comparisons were undertaken to determine the relationship between these brain structures, PTSD variables, and trauma load.

MATERIALS AND METHODS

Subjects

Originally, the sample consisted of maltreated youth with chronic PTSD ($N = 38$), without PTSD ($N = 35$), and non-maltreated participants ($n = 59$), who underwent studies of cerebral and cerebeller volumes, and diffusion tensor imaging measures of the corpus callosum using semi-automatic and hand-tracing approaches (De Bellis et al, 2015). Of these subjects, 120 had image quality data that were suitable for analyses with FreeSurfer to obtain data on these specific regions of interest (ROIs). Subjects consisted of 57 non-maltreated healthy youth and 63 maltreated youth assessed with DSM-IV-TR and DSM-5, resulting in a maltreated without PTSD ($n = 32$) and a PTSD group ($n = 31$). The maltreated groups were defined by a positive forensic investigation conducted by CPS that indicated physical and sexual abuse and/or neglect. Maltreated participants were recruited through statewide advertisements targeted at CPS agencies. To reduce bias, participants who lived more than 75 miles from the research program were given overnight accommodations. Non-maltreated healthy volunteers, with no history of DSM Axis I disorders or Type A traumas, recruited from schools and community settings, had a negative maltreatment screen on initial telephone interview. Comprehensive research interviews that indicated any positive history of participant or participant sibling maltreatment, or positive review of pediatric and birth medical records that met or would have met state CPS maltreatment criteria, excluded a potential healthy volunteer. Healthy volunteers were recruited to be of similar age, gender, handedness, race, and socio-economic status (SES), and their IQ for inclusion was limited to within 1 standard error of measure (~3 IQ points) (Wechsler, 1991) of the lowest and highest scores of the maltreated youth. Because lower IQ (Perez and Widom, 1994; De Bellis et al, 2009; De Bellis et al, 2013) is an inherent confound in maltreatment studies, this procedure was used as an attempt to control for this confound. After complete description of the study was given to the legal guardians and participants, written informed consent/assent were obtained to undertake this IRB-approved study.

Exclusion criteria were: IQ < 70; chronic medical illness; daily prescription medication; head injury with loss of consciousness; traumatic brain injury; neurological disorder; schizophrenia; anorexia nervosa; pervasive developmental disorder; obsessive compulsive disorder; bipolar I disorder or

Table 1 Demographic and Clinical Characteristics of the Study Participants

Variable	Healthy controls (Group 1) N = 57		Maltreated (Group 2) N = 32		Maltreated with PTSD (Group 3) N = 31		Statistic	p	Pairwise group difference
	Mean	SD	Mean	SD	Mean	SD			
Age (years) (age range)	10.82 (6.4–16.1)	2.5	10.0 (6.3–16.2)	2.7	9.9 (6.2–15.7)	2.5	$F_{(1,119)} = 1.79$	0.17	
Female/Male	32/25		17/15		16/15		$X^2 = 0.18$	0.91	
Right/Left Handed	51/6		30/2		28/3		$X^2 = 0.50$	0.78	
Race (Caus/AA/other)	23/26/8		13/14/5		14/15/2		$X^2 = 1.63$	0.80	
SES (SES range)	41.9 (14–65)	12.9	38.5 (14–61)	15.8	37.5 (14–60.4)	13.8	$F_{(1,119)} = 1.2$	0.30	
FSIQ (FSIQ range)	102.2 (74–118)	11.6	93.0 (71–115)	12.6	92.6 (71–115)	12.1	$F_{(1,119)} = 9.27$	0.0002	Groups: 1 > 2,3[a]
CBCL Total Score (CBCL range)	40.39 (24–58)	8.83	57.16 (40–83)	11.68	64.55 (43–78)	9.73	$F_{(1,119)} = 68.2$	< 0.0001	Groups: 1 < 2 < 3[a]
CGAS (CGAS range)	89.2 (70–98)	5.8	67.8 (50–90)	9.1	55.0 (40–70)	7.4	$F_{(1,119)} = 242.4$	< 0.0001	Groups: 1 > 2 > 3[a]

Abbreviations: AA, African American; Caus, Caucasian; CBCL, Child Behavior Checklist total score; CGAS, Children's Global Assessment Scale score; FSIQ, Full Scale IQ estimated from 2-factors; Other, Multi-racial; SES, socio-economic status measured by the Hollingshead Four factor index.
[a]Comparisons tests for all pairs using Tukey-Kramer honestly significant difference (HSD) $q = 2.37$, $p < 0.05$.

mania; birth weight under 5 lbs.; or severe prenatal (eg, fetal alcohol and/or drug exposure) or perinatal complications (eg, NICU stay); current or lifetime nicotine dependence/alcohol/substance use disorder; contraindications for safe MRI scan; and Axis I disorder or report of maltreatment that warranted CPS investigation in non-maltreated controls. Recruitment was challenging given that prenatal substance exposure, low SES, alcohol and substance dependence, use of psychotropic medications, and medical illnesses are over-represented in maltreated youth (Smith et al, 2007) and can independently negatively influence brain maturation. Initial recruitment and scanning begin in 2003 and ended in 2011.

Measures

To examine psychiatric diagnoses and maltreatment characteristics, the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (KSADS-PL) (Kaufman et al, 1997) was administered to all caregivers and youth. Because multiple sources of information are needed to gather accurate maltreatment history and related symptoms, we requested and reviewed archival records (eg, pediatric records, school attendance records, birth records, forensics records) as sources of mental health, birth history, trauma history, and pediatric health data (Kaufman et al, 1994). If information from these data sources produced evidence meeting exclusionary criteria, the participant was excluded. KSADS-PL interviewer training and modifications were previously described (De Bellis et al, 2009). Child maltreatment was defined as witnessing domestic violence, experiencing physical, sexual, or emotional abuse, and/or neglect that resulted in eight maltreatment categories (failure to supervise, failure to provide, physical abuse, witnessing intimate partner violence, emotional abuse, sexual abuse, witnessing or victim of other interpersonal violence, and corporal punishment).

The Child Behavior Checklist (CBCL) measured total behavior problems reported by the child's caregiver. Children Global Assessment Scale score (Shaffer et al, 1983) was scored by the interviewer after assessment of all clinical data to provide a continuous measure of child function. Participants

were administered the 2-subtest short-form (Vocabulary and Block Design) of the Wechsler Intelligence Scale for Children-III to obtain an IQ score (Wechsler, 1991).

Demographic and Behavioral Characteristics of the Groups

Demographic, clinical, and maltreatment information are reported by group in Tables 1 and 2. The groups were similar in age, gender, race, handedness, and SES. Post hoc pairwise group differences revealed that IQ scores were similar in both maltreated groups and significantly lower than controls. The relationship between IQ and PTSD symptoms ($p = 0.67$), and IQ scores and trauma load ($p = 0.18$) were not significant. The PTSD group showed the most emotional and behavioral symptoms and lowest levels of global function than the maltreated youth without PTSD, whose symptoms were also significantly different from the non-maltreated group.

Maltreated youth with PTSD were more likely to experience sexual and emotional abuse, greater trauma load, and have more total Axis I disorders than the maltreated youth without PTSD. Their PTSD was both chronic and persistent with a mean duration of 2.89 years. However, both groups of maltreated youth experienced multiple types of severe and continuing maltreatments. Although the maltreated youth without PTSD group did not have PTSD, they had lesser degrees of clinical impairment including adjustment disorders with anxiety. Only five participants in maltreated youth without PTSD youth had no current Axis I diagnosis, while only two subjects in the PTSD group had chronic PTSD as the sole diagnosis. Four of the maltreated youth without PTSD had met DSM-IV criteria for PTSD in the past, but were in complete remission for 12 months prior to this study.

Magnetic Resonance Imaging and Structural Image Analysis

All anatomical images were acquired using the same Siemens Trio 3.0 Tesla MRI system (Trio, Siemens Medical Systems) scanner (3D, GRE (MPRAGE), axial, TR = 1750 ms,

Table 2 Maltreatment, PTSD Symptoms, and Diagnostic Clinical Characteristics of Maltreated Youth and Maltreated Youth with PTSD

History of maltreatment types	Maltreated $N=32$		Maltreated with PTSD $N=31$		Statistic	p
	Mean	SD	Mean	SD		
Witnessing Intimate partner violence (Yes/No)	26/6		26/5		FET	1.0
Physical abuse (Yes/No)	20/12		26/5		FET	0.09
Sexual abuse (Yes/No)	6/26		14/17		FET	0.03
Neglect-failure to supervise (Yes/No)	30/2		28/3		FET	0.67
Neglect-failure to provide (Yes/No)	15/17		17/14		FET	0.62
Emotional abuse (Yes/No)	13/19		23/8		FET	0.01
Witnessing or victim of other personal violence (violent crime) (Yes/No)	18/14		16/15		FET	0.80
Corporal punishment (Yes/No)	30/2		30/1		FET	1.0
Mean Number of maltreatment types (8 total) Mean ± SD (range)	5.22 (2–8)	1.34	6.19 (3–8)	1.40	$F_{(1,62)}=7.98$	0.006
DSM-IV TR Diagnoses						
PTSD chronic	—	—	31			
Age of onset PTSD years (Mean ± SD) (range)	—	—	6.88 (3.0–12.5)	2.26		
Duration of PTSD years (Mean ± SD) (range)	—	—	2.89 (0.25–8.33)	2.31		
Total # of PTSD symptoms (Mean ± SD) (range)	3.57 (0–8)	2.5 (7–15)	11.51	2.3	$F_{(1,62)}=162.1$	<0.0001
Mean number of Internalizing disorders	0.22	0.42	2.1	0.94	$F_{(1,62)}=105.3$	<0.0001
Major depression (Yes/No)	3/29		15/16		FET	0.0008
Dysthymia (Yes/No)	0/32		6/25		FET	0.01
Major depressive disorder NOS (Yes/No)	1/31		0/31		FET	1.0
Generalized anxiety disorder (Yes/No)	4/28		8/23		FET	0.21
Separation anxiety disorder (Yes/No)	0/32		5/26		FET	0.02
Mean number of disruptive disorders	0.78	0.83	1.48	1.03	$F_{(1,62)}=8.91$	0.004
ADHD (any) (Yes/No)	17/15		23/8		FET	0.12
ADHD-combined type (Yes/No)	6/26		15/16		FET	<0.02
ADHD-inattentive type (Yes/No)	8/24		4/27		FET	0.34
ADHD-hyperactive type (Yes/No)	1/31		1/30		FET	1.0
ADHD NOS (Yes/No)	2/30		3/28		FET	0.67
Oppositional defiant disorder (Yes/No)	5/27		15/16		FET	0.007
Conduct disorder (Yes/No)	1/31		6/25		FET	0.05
Disruptive behavioral disorder NOS (Yes/No)	2/30		2/29		FET	1.0
Mean number of above Axis I disorders	1.00	0.98	3.58	1.61	$F_{(1,62)}=59.5$	<0.0001
Adjustment disorder with depressed mood (Yes/No)	1/31		0/31		FET	1.0
Adjustment disorder with mixed anxiety and depressed mood (Yes/No)	4/28		0/31		FET	0.11
Adjustment disorder with anxiety (Yes/No)	7/25		0/31		FET	0.01
Mean total number of Adjustment Disorders	0.38	0.49	0	0	$F_{(1,62)}=18.0$	<0.0001

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; FET, Fisher's Exact Test; NOS, not otherwise specified.

T1 = 1100 ms, 25.6 cm FOV, 1.0 mm slice thickness, flip = 20°, Bandwidth: (220 Hz/pixel), 256 (phase) × 256 (frequency), number of excitations = 1). All T1 images were visually inspected to assure appropriate quality. Automated segmentation and labeling of the amygdala, hippocampus, ACC, and vmPFC, and estimation of total intracranial volume from participants' T1 images were performed using the FreeSurfer image analysis suite (version 5.1.0; http://surfer.nmr.mgh.harvard.edu/) and its library tool *recon-all*. Details of these FreeSurfer parcellations were previously described (Fischl et al, 2004; Desikan et al, 2006; Destrieux et al, 2010). The use of FreeSurfer segmentation has been validated in youth as young as age 3, with results published in high-quality journals (Østby et al, 2009; Fjell et al, 2012). Automated segmentation of the amygdala and hippocampus compared with manual tracing with FreeSurfer was previously validated (Morey et al, 2009). Spatial normalization by affine registration to Talairach space and skull stripping were performed on the T1 images. FreeSurfer registration, segmentation, and labeling of structures were previously described (Morey et al, 2012). Registration and segmentation of the ROI were overlaid on original T1 images and visually inspected (CCH, RAM) slice-by-slice for correct location and shape. All scans were reviewed by a neuroradiologist who
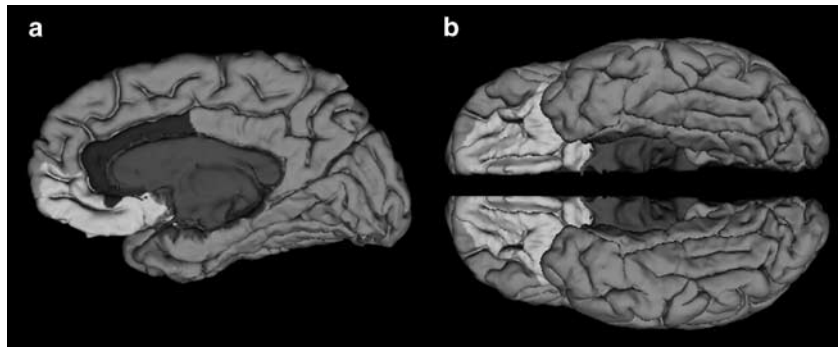
Figure 1 (a) Ventromedial prefrontal cortex (vmPFC) and anterior cingulate cortex (ACC) regions-of-interest as defined by FreeSurfer on a medial view of the right hemisphere (vmPFC in green and ACC in fuchsia). (b) This image of the vmPFC is from the ventral view in both hemispheres. The vmPFC, defined by FreeSurfer, is the sum of the right and left medial orbitofrontal and lateral orbitofrontal cortexes.

ruled out clinically significant abnormalities. Total vmPFC was composed of two regions defined by FreeSurfer terminology, the sum of the right and left medial orbitofrontal and lateral orbitofrontal cortexes (Desikan *et al*, 2006). This includes the ventral sector of the medial PFC, the orbitofrontal cortex medial to the straight gyrus, and the orbital sulcus laterally, and is consistent with other approaches (Boes *et al*, 2009). Total ACC volumes were summed from the following FreeSurfer parcellations: rostral and caudal ACC divisions; ACC sulcus and gyri; and subcallosal gyrus (Desikan *et al*, 2006; Destrieux *et al*, 2010) (Figure 1).

To confirm any of the main results from the present ROI approach study, we performed an optimized masked (ie, orbitofrontal cortex, amygdala, hippocampus, and the ACC) voxel-based morphometry (VBM) protocol using FSL-VBM tools (Smith *et al*, 2004; Douaud *et al*, 2009) www.fmrib.ox.ac.uk/fsl; Version 1.1) to assess significant differences between groups. For these between-group comparisons, a left-right symmetric study-specific gray matter template was built using the scans from the group with fewer subjects and an equal number of subjects from the larger group; 31 maltreated youth with PTSD and 31 randomly selected maltreated youth without PTSD contributed to gray matter-segmented native images. Equal numbers of images were selected from each of the groups to minimize the chance of a particular group introducing a bias into the template. These 62 gray matter images underwent non-linear registration with FNIRT to the ICBM-152 gray matter template (http://www.fmrib.ox.ac.uk/fsl/fnirt) and then flipped along the x-axis and averaged to create a contrast-specific template for comparing the maltreated group with the PTSD group. Subsequently, the complete set of 63 gray matter images were non-linearly registered to this contrast-specific template. Likewise, the comparison of the maltreated group with the control group and the comparison of the PTSD group with the control group followed the same approach for creating contrast-specific templates. The optimized protocol introduces a compensation (modulation) for the non-linear contraction/enlargement component of the transformation. For the modulation, each voxel of each registered gray matter image was divided by the Jacobian of the warp field. Finally, all 120 modulated registered gray matter volume images were smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (~7-mm FWHM). To achieve accurate inference between-group comparisons, we used permutation-based

nonparametric inference within the framework of the general linear model based on a study sample-specific distribution obtained from 5000 permutations of group assignment (Nichols and Holmes, 2002). Our statistical design involved the following contrasts: control > maltreated, maltreated > control, control > PTSD, PTSD > control, maltreated > PTSD, and PTSD > maltreated. The masked images were analyzed with nonparametric permutation-based inferential statistics that included voxelwise regressors for age and sex as adjustment for ICV and are part of the VBM analyses. Results in gray matter were calculated for significant voxels at $p < 0.05$ (corrected) based on the threshold-free cluster enhancement method (Smith and Nichols, 2009).

Statistical Analysis

Outcome measures were the *a priori* four extinction structures segmented by FreeSurfer. We used general linear modeling to examine group effects on amygdala, hippocampus, ACC, and vmPFC volumes. The general linear modeling included the following covariates that are known to be associated with brain structural volumes in this age range: intracranial volume (Carrion *et al*, 2001; De Bellis *et al*, 1999, 2002; De Bellis and Kuchibhatla, 2006; Giedd and Rapoport, 2010; Satterthwaite *et al*, 2014); age (Giedd and Rapoport, 2010); gender (Giedd and Rapoport, 2010; Satterthwaite *et al*, 2014); SES (De Bellis *et al*, 1999); IQ (Andreasen *et al*, 1993; Reiss *et al*, 1996; Lange *et al*, 2010); and their interactions with group. If covariates demonstrated $p \geqslant 0.2$, they were dropped from the model. We examined the relationship between ROIs and PTSD symptoms, trauma load (defined as the number of maltreatment types experienced), and comorbidity (defined as the current number of Axis I disorders) on ROI. Because clinical data were not normally distributed, we used Spearman's rho correlations. Alpha was 0.05 (two-tailed) given our *a priori* hypotheses of volume differences in these ROI. Analyses were undertaken using JMP Pro 11 software (SAS).

RESULTS

Volumetry Results

Group means, standard deviations, and the general linear modeling results are summarized in Table 3. Pairwise

Table 3 Brain Volumes in Healthy Non-Maltreated Youth, Maltreated Youth, and Maltreated Youth with PTSD

Structure mm³ (mean ± SD adjusted for ICV)	Healthy controls (Group 1) N = 57		Maltreated (Group 2) N = 32		Maltreated with PTSD (Group 3) N = 31		Statistic	p	Pairwise group difference
	Mean	SD	Mean	SD	Mean	SD			
Amygdala									
Total	3055.66	286.08	3182.13	328.05	3017.43	365.91	$F_{(2,109)} = 4.30$	<0.02	2>3[a]
Left	1490.69	156.51	1569.85	193.55	1438.46	208.78	$F_{(2,109)} = 7.39$	0.001	2>1,3[a]
Right	1564.96	163.62	1612.28	160.63	1578.97	184.48	$F_{(2,111)} = 0.81$	0.45	
Hippocampus									
Total	7758.10	672.51	7916.36	673.25	7504.48	801.39	$F_{(2,105)} = 4.16$	<0.02	2>3[a]
Left	3823.55	367.61	3881.97	361.17	3698.24	410.13	$F_{(2,105)} = 3.28$	0.04	2>3[a]
Right	3934.55	337.14	4034.39	345.40	3806.24	428.40	$F_{(2,102)} = 4.43$	<0.02	2>1,3[a]
Anterior cingulate cortex									
Total	22853.4	2458.57	22847.0	2343.4	22395.4	2075.75	$F_{(2,115)} = 0.84$	0.43	
Left	11851.5	1441.97	11901.8	1479.06	11616.0	1158.51	$F_{(2,115)} = 0.66$	0.52	
Right	11743.5	1290.59	11744.1	1162.74	11579.8	1100.01	$F_{(2,115)} = 0.46$	0.63	
vmPFC									
Total	28367.8	2149.24	28584.2	2304.44	27504.3	2530.00	$F_{(2,115)} = 2.86$	0.06	
Left	14212.7	1055.76	14224.0	1255.41	13867.9	1614.37	$F_{(2,115)} = 1.41$	0.25	
Right	14155.1	1270.88	14360.2	1357.75	13636.3	1071.40	$F_{(2,115)} = 3.62$	<0.03	1,2>3[a]

Abbreviations: ICV, intracranial volume; vmPFC, ventral medial prefrontal cortex.
[a]Least Means Differences Dunnett Test, Q = 2.24, p ⩽ 0.05.

planned comparisons between groups revealed that the PTSD group had smaller right vmPFC volumes than the maltreated youth without PTSD and non-maltreated control group. There was a trend for smaller total vmPFC volumes in the PTSD group. Right vmPFC volumes remained smaller when controlling for trauma load ($p = 0.02$) and comorbidity ($p < 0.005$). We saw no differences between groups in the ACC or the subregions that made up the ROI. *Post hoc* pairwise group differences revealed that the maltreated youth without PTSD had greater left amygdala and right hippocampal volumes than non-maltreated control and PTSD groups. *Post hoc* pairwise group differences revealed that maltreated youth without PTSD showed greater total amygdala and hippocampal volumes compared with PTSD youth and a trend for larger volumes than controls in the amygdala ($p < 0.08$) and hippocampus ($p < 0.09$). Greater left amygdala and right hippocampal volumes remained significant when controlling for trauma load ($p = 0.02$; $p < 0.03$) and comorbidity ($p = 0.01$; $p < 0.05$), respectively.

In maltreated youth, PTSD symptoms significantly and negatively correlated with right (Spearman's rho = −0.37, $p < 0.008$), left (Spearman's rho = −0.32, $p < 0.03$), total hippocampal (Spearman's rho = −0.36, $p < 0.02$), and left amygdala volumes (Spearman's rho = −0.32, $p < 0.03$). No other significant relationships were seen between PTSD variables, internalizing or externalizing symptoms, and

trauma load, and ROIs. Please see Supplementary Tables 1 and 2 for Spearman's rho correlations of variables for the non-maltreated and maltreated groups, respectively. Intracranial volume was significantly correlated with all ROIs (all p-values < 0.01) in the non-maltreated and maltreated groups, respectively. Controls showed significantly greater correlations than maltreated youth between ICV and (i) total and left amygdala volumes; (ii) age; (iii) gender; and (iv) SES. Controls showed significantly greater correlations than maltreated youth between SES and (i) left ACC; and (ii) total, left, and right vmPFC. See Supplementary Table 3.

Confirmatory Analyses with VBM

The masked VBM analysis only showed greater gray matter intensity in controls than PTSD ($p < 0.05$; corrected) in the left medial orbitofrontal cortex (x = − 10, y = 52, z = − 26; t = 4.33; 114 voxels) (Figure 2). We also performed a correlation between mean gray matter intensity of the orbitofrontal cluster obtained from the VBM and the number of PTSD symptoms and maltreatment types. The correlations were non-significant. We performed an additional exploratory whole-brain VBM analyses to examine whether there were any other brain regions which significantly differed between groups. This analysis showed no significant group differences at the corrected threshold.
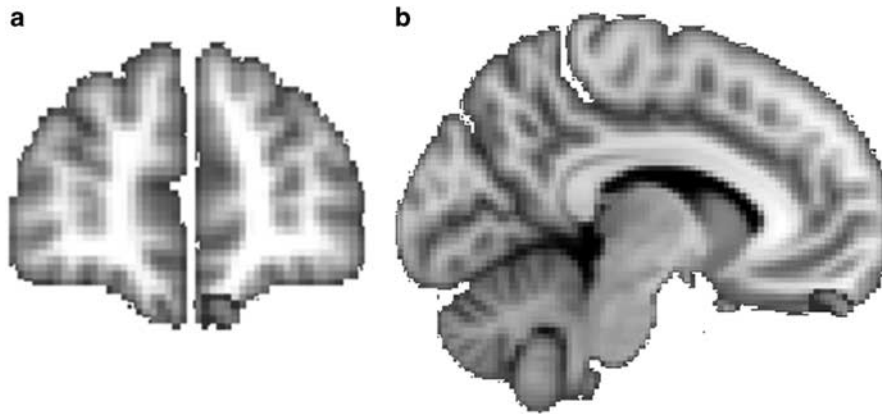
Figure 2 (a and b) The confirmatory masked VBM analysis showing greater gray matter intensity in controls than maltreated youth with PTSD ($p < 0.05$; corrected) in the left medial orbitofrontal cortex (MNI: $x = -10$, $y = 52$, $z = -26$; $t = 4.33$; 114 voxels). The mask, obtained from the FreeSurfer, included voxels within the orbitofrontal cortex, amygdala, hippocampus, and the anterior cingulate cortex. The masked images were analyzed with nonparametric permutation-based inferential statistics that included voxelwise regressors for age and sex.

DISCUSSION

To the best of our knowledge, this is the first study to examine brain differences in extinction-related structures in maltreated youth with and without chronic PTSD. Maltreated youth with PTSD were neurobiologically different from maltreated youth without PTSD and non-maltreated controls by demonstrating smaller right vmPFC volumes, a complex brain structure with many functions including emotional regulation, decision-making, assignment of value to context, and the mediation of extinction learning and retention (Schoenbaum and Shaham, 2008). VBM analyses also confirmed less gray matter in the left orbital frontal cortex in the PTSD group compared with controls. This finding extends and agrees with a study of adults who have child maltreatment-related PTSD (Thomaes et al, 2010) and a youth study of PTSD that was secondary to heterogeneous trauma types compared with healthy youth (Keding and Herringa, 2014) both of which also demonstrated smaller vmPFC volumes. Trauma studies in adults showed smaller ACC (Cohen et al, 2006; Kitayama et al, 2006; Thomaes et al, 2010) and hippocampal (Dannlowski et al, 2012; Teicher et al, 2012) volumes, and no differences (Woon and Hedges, 2009), smaller (Morey et al, 2012) and larger amygdala volumes (Kuo et al, 2012). By contrast, maltreated youth without PTSD demonstrated larger left amygdala and right hippocampal volumes compared with maltreated youth with PTSD and non-maltreated controls. PTSD symptoms inversely correlated with hippocampal and left amygdala volumes. As in our study, one of the adult cross-sectional studies also found significant correlational interactions between smaller amygdala volumes and trauma before age 13, and higher degree of combat exposure (Kuo et al, 2012). The results of this study also agreed with an investigation finding larger amygdala volumes in adults without PTSD who experienced adversity at ages 10–11 years (Pechtel et al, 2014). Taken together, the results from our cross-sectional study suggest dynamic changes in the amygdala associated with sensitive developmental periods, higher degrees of trauma, and PTSD symptoms that need to be confirmed in longitudinal investigations. No differences were seen in ACC volumes between maltreated youth and controls. Although

maltreated youth with PTSD had greater numbers of Axis I disorders and trauma load, both maltreatment groups suffered from significant traumas. The group differences remained significant when controlling for trauma load and comorbidity.

Individuals who suffer from PTSD exhibit anxiety-related behaviors (ie, conditioned responses) to traumatic reminders based on previous trauma. The vmPFC tracks predictions of stimuli associated with safety and danger (Schiller et al, 2008). This tracking is adaptive to allow the individual to easily shift fear responses from one stimulus to another based on the environment. Thus, dysregulation of the vmPFC can lead to PTSD resulting from failing to learn extinction of traumatic reminders. In healthy adults, investigators found positive correlations between vmPFC cortical thickness and successful extinction retention (Hartley et al, 2011). Thus, the structural compromise in vmPFC in pediatric maltreatment-related PTSD may represent neurobiological factors that predate the trauma, or alternatively a PTSD-related process secondary to maltreatment exposure. Although our cross-sectional study cannot determine this, a twin study of combat-related PTSD suggests that the deficit of extinction recall is acquired as a result of trauma leading to PTSD, because extinction retention (assessed by skin conductance response) was greater in the twins with PTSD compared with their co-twins and non-PTSD combat veterans (Milad et al, 2008). Additionally, another investigation demonstrated that fear extinction is impaired in adult PTSD (Milad et al, 2009). It is possible that the effects of maltreatment and having PTSD on the vmPFC, a structure rich in glucocorticoid receptors (Lupien et al, 2009), leads to volume differences over time along with decreased ability to learn extinction of traumatic reminders, and inability to respond appropriately to the current environment.

The vmPFC is a complex structure with complex function. Deficits in this structure may be a developmentally shared mechanism that leads to disruptions in emotional regulation, decision-making, cognitive functions, fear learning, extinction retention, and fear generalization, and may contribute to the high prevalence of comorbid disorders common to youth PTSD. In our sample, the PTSD group suffered from numerous Axis I comorbidities, including depressive and

behavioral disorders that put the PTSD group at a higher risk for adolescent onset SUD than the maltreated youth without PTSD. Depression in adulthood, which has significant symptom overlap and comorbidity with PTSD throughout the lifespan, is associated with smaller vmPFC volumes (Wagner et al, 2008). SUD are neurobiological disorders of impulsiveness or failure to postpone short-term desires, with serious long-term costs. Although our subjects did not have a history of SUD, smaller right vmPFC volumes in youth are associated with impulsivity (Boes et al, 2009), a common symptom of PTSD and SUD. Adults with SUD have smaller vmPFC volumes (Tanabe et al, 2009). Hypoactivation of the vmPFC during response inhibition predicts early initiation of substance use (Cheetham et al, 2012). Thus, studies of childhood maltreatment should consider focusing on altered vmPFC structure and function as an early neurodevelopmental cortical pathway to PTSD that can lead to adolescent and young adult depression and SUD. The vmPFC is a relatively large and complex structure and one study showed a smaller vmPFC volume cluster in healthy adults with maltreatment histories (Dannlowski et al, 2012), suggesting that future studies of maltreatment-related PTSD and its resilience should focus on specific vmPFC subregion connectivity to limbic areas. In fact, a recent meta-analysis demonstrated that maltreated individuals with a variety of disorders and studied across the lifespan exhibited significantly smaller gray matter volumes in the right orbitofrontal/superior temporal gyrus extending to the amygdala, insula, and parahippocampal and middle temporal gyri, and in the left inferior frontal and postcentral gyri; which suggests deficits in structures that mediate emotional regulation, cognitive control, social cognition, and extinction processes (Lim et al, 2014). Our study did not find widespread voxel-based differences perhaps owing to the younger age of sample, as the later study (Lim et al, 2014) consisted mainly of adults with maltreatment histories.

Our data are consistent with previous studies showing no amygdala and hippocampus volume differences in maltreated youth with PTSD compared with non-maltreated controls (Carrion et al, 2001; De Bellis et al, 2002). Instead, we found that maltreated youth without PTSD demonstrated larger left amygdala and right hippocampal volumes compared with maltreated youth with PTSD and non-maltreated controls. In rodents, chronic stress leads to increased dendrites and apical spines in the basolateral nucleus of the amygdala, whose function is to activate the central nucleus of the amygdala, the subregion responsible for the fear response. This inverted U-shaped model predicts that exposure to stress might be adaptive through acute adrenergic and cortisol effects to promote vigilance and learning processes (Lupien et al, 2009). This modulation of noradrenergic function by cortisol may explain the enhanced memory for emotional events experienced under stress (Lupien et al, 2009; Roozendaal et al, 2009). Peer-reared juvenile monkeys showed larger dorsomedial prefrontal and dorsal ACC compared with mother-reared monkeys, indicating that stress-sensitive brain structures can increase during atypical primate development (Spinelli et al, 2009). Maltreatment stress might lead to increased hippocampal and amygdala volume until a critical threshold of exposure to maltreatment and/or persistent PTSD symptoms are reached,

which is subsequently followed by atrophy of the hippocampus and amygdala. Such an explanation would be consistent with our results of inverse PTSD symptom correlations with hippocampal and left amygdala volumes. A longitudinal study demonstrated that maltreated adolescents had larger left hippocampal volumes at baseline; but, if the youth had psychopathology, the hippocampus grew more slowly over an approximately 4-year follow-up period (Whittle et al, 2013). Another study suggested that hippocampal atrophy in youth with impairing PTSD symptoms may be a latent developmental effect (Carrion et al, 2007). The one study showing greater right hippocampal volume in youth with maltreatment-related PTSD compared with controls (Tupler and De Bellis, 2005) enrolled youth who were in active PTSD treatment, leading to speculation that neurobiological markers may show neuroplasticity that resembles the maltreated youth without PTSD group when patients are given treatment. It is possible that neurobiological markers change with maturation and treatment, prior to alleviation of the PTSD symptoms, and this begs the question of including such markers as outcomes in treatment studies of pediatric PTSD. Consequently, these markers may have clinical significance as the current evidence-based treatment, trauma focused cognitive behavioral therapy, shows small-to-medium effects sizes (MacMillan et al, 2009) indicating that this treatment is not successful for all youth with PTSD. However, future longitudinal studies must determine whether maltreatment stress might lead to increased hippocampal and amygdala volume until a critical threshold of exposure to maltreatment and/or persistent PTSD symptoms are reached, which is subsequently followed by atrophy of the hippocampus and amygdala.

There are a number of limitations of this study. The maltreated youth differed from the control group in IQ, which may contribute to results independently from maltreatment. However, the two maltreatment groups showed very similar means and distribution of IQ scores. This limitation is inherent in child maltreatment studies where both cross-sectional (De Bellis et al, 2013) and longitudinal studies demonstrate lower IQ in victims of maltreatment (Perez and Widom, 1994). Because higher IQ participants demonstrate a linear relationship with neural efficiency compared with lower IQ participants (Neubauer and Fink, 2009) and cortical thickness in this study's age range and IQ range (average to high average) show linear associations (Shaw et al, 2006), we believe IQ group differences were appropriately addressed using general linear modeling statistical methods; however, the lower IQ in the maltreated groups compared with the non-maltreated group remains a limitation when interpreting maltreatment imaging studies in youth. Additionally, although having a lower IQ is considered a risk factor for combat PTSD (Macklin et al, 1998; Gilbertson et al, 2006), lower IQ was not associated with PTSD in the maltreated youth studied here. We were not able to examine age of maltreatment onset or duration because maltreated youth had multiple episodes and types of maltreatment experiences. Thus, determining the age of maltreatment was not a simple construct and was not feasible in our study. We note that the masked VBM analyses only confirmed vmPFC differences between controls and maltreated youth with PTSD. Although we attempted to control for developmental effects by using

group-specific templates, it is possible these types of analyses are too conservative for pediatric studies where individuals show high variance in brain maturation measures (Ridgway et al, 2008). Further, this study used a cross-sectional design, which limits inferences about the causal relationships between maltreatment, PTSD status, and brain structures.

We studied the extremes of psychopathology (PTSD) and the volumes of brain structures associated with extinction in a group of youth with an extraordinary level of trauma exposure. Both maltreatment groups suffered a mean of at least four maltreatment types, putting both groups at extremely high risk for adolescent and adult psychopathology and health risk behaviors associated with the leading causes of death in adulthood (Felitti et al, 1998). We recruited a reasonably large sample of maltreated youth who were medically healthy and non-medicated. This was challenging given that prenatal substance exposure, low SES, alcohol and substance dependence, use of psychotropic medications, and medical illnesses are overrepresented in maltreated youth (Smith et al, 2007) and can cause study confounds by negatively influencing brain maturation. Within the constraints of our stringent inclusion/exclusion criteria, we enrolled a sufficient sample size for this MRI study to have confidence in our findings.

This study demonstrated volumetric differences in brain structures associated with extinction between maltreated youth with chronic and persistent PTSD and those without PTSD, using automated ROI methods. This advances the field by providing evidence that cortical differences are seen in childhood PTSD, early in the development of this illness. These brain structures are also associated with the successful attainment of age-appropriate emotional regulation and decision-making. Longitudinal research is needed to determine whether the neurobiology associated with PTSD is a shared mechanism for disorders that reflect impaired emotional regulation and decision-making such as depression and SUD in adolescents and adulthood, and if the neurobiology of resilience to PTSD following severe maltreatment is a marker for healthier adulthood adaptations to childhood trauma.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)